A Few Numbers...

- About 2 million people acquire bacterial infections in U.S. hospitals each year
  - 90,000 die as a result
- About 70 percent are resistant to at least 1 drug
- Resistant pathogens lead to higher health care costs
  - Require more expensive drugs
  - Longer hospital length of stay
- Total cost to U.S. society ~ $5 billion annually

Disclosure

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

I am a member of the FSHP Educational Affairs Council.

Objectives

- Identify the barriers to timely antimicrobial administration
- Give examples of potential solutions to improve antimicrobial preparation and delivery to patients
- List the pros and cons of extended and continuous infusion antimicrobials

Time is of the Essence...

- Appropriate timing of antibiotics is critical to success for many hospitalized patients
- Surgery patients need antibiotics to be given within one hour of incision to prevent infection
- Patients with sepsis and other severe infections should receive antibiotics with one hour of presentation to the emergency room
- Many barriers exist to slow the process and delay appropriate therapy
Surgical Site Infections (SSI)

- 5-10% of all hospitalized patients develop a hospital-acquired infection (HAI)
- SSI are the 2nd most common cause of HAI
- Over 500,000 SSI occur annually in the U.S.

Patients who develop a SSI are:
- 60% more likely to spend time in the ICU
- 5 times more likely to be readmitted to the hospital
- Twice as likely to die than a patient without a SSI

Challenges with Surgery Patients

- Not all medications are available in the OR
- Several antibiotics are dosed based on weight
  - e.g. vancomycin, gentamicin, cefazolin
- Surgeries can occur 24 hours a day
- Handwritten orders may be incomplete and need clarification by the pharmacist
- Drug allergies can make regimens more complicated
- Who is in charge of infusing the drug?
  - Pre-op nurse versus anesthesiologist

SCIP Core Measures

- SCIP INF 1:
  - Prophylactic antibiotic received within 1 hr prior to surgical incision
- SCIP INF 2:
  - Prophylactic antibiotic selection for surgical patients
- SCIP INF 3:
  - Prophylactic antibiotics discontinued within 24 hours after surgery end time (48 hours for cardiac patients)
- SCIP INF 4:
  - Cardiac surgery patients with controlled 6 a.m. postoperative glucose
- SCIP INF 6:
  - Surgery patients with appropriate hair removal
- SCIP INF 7:
  - Colorectal surgery patients with immediate post-op normothermia

Types of Interventions

- Pre-built surgery order sets and/or order forms
- Right drug for right surgical procedure at right time
- Standard doses that can be batched ahead of time
  - Cefazolin 2 grams if < 120 kg, 3 grams if ≥ 120 kg
- Use of automated dispensing cabinets (ADT’s)
  - Pyxis, Accudose, Omnicell, etc
  - Preload standard doses in Pre-op area
- Clear communication between OR and Pharmacy
- OR pharmacy satellite with STAT hood

Surgical Prophylaxis

- Prophylactic antibiotics should be received within 1 hour of surgical incision

For Sepsis – Time is Life

- Time from hypotension onset (hours)
- Survival fraction and cumulative effective antimicrobial initiation

Crit Care Med 2006;34:1589-96
Antibiotic Timing in Sepsis

- Each hour of delay in antibiotic administration leads to an average decrease in survival of 7.6%
- Clinicians struggle with identifying the problem quickly and getting all the right resources in time
  - Fluids, vasopressors (norepinephrine), antibiotics, etc
- Pharmacy doesn’t have every antibiotic or dose preloaded in the emergency department or ICU
- Any delay in the process and can have major impacts on the patients chance of survival

Workflow for Orders

- Patient Arrives in ED
- MD Makes Diagnosis and Orders Medication
- RPh Enters/Verifies Order
- IV Room Label Prints
- RPhT Prepares Medication
- RPh Checks Medication
- Medication Sent Via Tube/Delivered to ED
- Nurse Receives Medication
- Patient Administered Drug

Optimal Infusion Time?

- Basic Definitions:
  - Intermittent IV administration:
    - 30 – 60 minutes
  - Extended IV administration:
    - 3 – 4 hours
  - Continuous IV administration:
    - 24 hours period at a fixed rate

Role of the Technician

- Prioritize antibiotics and vasopressors appropriately
  - STAT orders
  - Orders from the ECC and ICU
  - First dose versus batch label?
- Once the medication is prepared, get the RPh to check the drug now and send it
- If the ED nurse or pharmacist calls about a missing antibiotic or vasopressor, quickly resolve the problem

Intermittent vs Extended Infusion

- Graph showing concentration (mg/L) over time (h) for 30-minute and 4-hour infusions.
Which Antibiotics are Involved?

- **Penicillins:**
  - Penicillin G
  - Nafcillin/Oxacillin
  - Piperacillin/tazobactam
- **Cephalosporins:**
  - Cefazolin
  - Ceftazidime
  - Cefepime
- **Carbapenems:**
  - Meropenem
  - Doripenem
- **Vancomycin (rarely in US)**

Extended Infusion Pip/Tazo

- Most common antibiotic given as extended infusion
- Most clinical data to support use
- Usual: 3.375g IV every 8 hours infused over 4 hours
- Others:
  - 3.375g IV every 6 hours infused over 3 hours
  - 4.5g IV every 6 hours infused over 3 hours
- Frees up IV line for 12 hours
- Stable at room temp for up to 24 hours
- Continuous infusion may also used: 13.5-20.25g/day

Extended Infusion Carbapenems

- Meropenem
  - Usual: 1-2 grams IV every 8 hours infused over 3 hours
  - Stable at room temp for up to 4 hours
  - Usually reserved for severe infections and/or resistant pathogens
- Doripenem (less common)
  - Usual: 500mg IV every 8 hours infused over 4 hours
  - Stable at room temp for up to 12 hours

Continuous Infusion Cephalosporins

- Cefepime
  - Usual dose: 2 gram IV bolus, followed by continuous infusion of 4-6 grams every 24 hours (w/ cool packs)
  - Most will give 2 grams continuously every 8-12 hours
  - Stable at room temperature for up to 24 hours
- Ceftazidime
  - Usual dose: 2 gram IV bolus, followed by continuous infusion of 2 grams every 8 hours (6 grams/day)
  - Stable at room temperature for up to 12 hours

Pros and Cons of Extended/Continuous Infusion

- **Pros**
  - Better drug levels at the site of infection
  - Higher cure rates
  - Shorter length of stay in the hospital
  - Decreased mortality
- **Cons**
  - Ties up the intravenous line
  - Stability limitations
  - Drug incompatibility, especially with limited access
    - Admixture and Y-site limitations

Role of the Technician

- Know which extended and/or continuous infusion protocols are in place at your institution
- Always review the stability data of the product before mixing and don't mix too far ahead
- Some products have different stability data available based on the diluent used
  - Meropenem is stable at room temperature for 1 hour in D5W vs 4 hours in normal saline mini-bags
- Make sure the drug gets delivered on time to minimize delays in therapy and avoid waste
Inhaled Antibiotics for Respiratory Infections

Aerosolized Antibiotics
- Many of the antibiotics used to treat pneumonia do not penetrate well to the target site in the lungs
  - Vancomycin, tobramycin, beta-lactams, etc
- Clinicians have to use aggressive doses to treat these infections which can lead to toxicity
- Giving antibiotics via inhalation provides a unique alternative to IV or PO delivery
- Most common method of delivery is nebulizer

Antibiotic Used via Inhalation
- Tobramycin (FDA approved as Tobi nebs)
  - IV product commonly used in hospitals due to cost
  - Aztreonam (FDA approved as Cayston)
  - IV form should not be used, different salt form
  - Pentamidine (FDA approved as Nebupent)
  - Colistin (Colistimethate sodium)
  - Gentamicin
  - Amikacin
  - Amphotericin B

Inhaled Tobramycin (Tobi®)
- Indicated for management of Pseudomonas aeruginosa in patients with cystic fibrosis
- Nebulizer: 300 mg inhaled orally via nebulizer BID
- Powder for inhalation: 4 capsules (28 mg/capsule) inhaled PO BID
- Cost (AWP):
  - Tobi Brand: $8,012/28 day supply = $143/dose
  - Generic: $7211/28 day supply = $128/dose
  - 80 mg IV Vial: $1.55

Tobramycin IV as Inhalation
- Commonly used in hospitals for non-CF patients
- Used as adjunct for treatment of respiratory infections
- 80 – 160 mg via nebulizer twice daily
- Use preservative free formulation to minimize risk of adverse reactions
- Mix just prior to use since it is PF
- May cause wheezing or bronchospasm; consider pretreatment with albuterol

Colistin (Colistimethate)
- Polymyxin E - used to treat multi-drug resistant bacteria including Pseudomonas aeruginosa
- Available as colistimethate, an inactive prodrug
- Converts to active form colistin in the body
  - Also converts to active form when mixed in solution
- Given IV and/or via inhalation for serious respiratory infections, including pneumonia
- Inhalation dosing: 75 – 150 mg via nebulizer every 12 hours
Colistin FDA Warning

- Not FDA approved for use as a liquid to be inhaled via nebulizer
- Inhaling active form can injure lung tissue
- Premixing colistimethate into an aqueous solution and storing it for longer than 24 hours results in increased concentrations of colistin in solution, increasing the potential for lung toxicity
- To avoid this toxicity, it should be administered promptly after it is mixed

Not Always Good...

Disadvantages

- Most are not FDA approved for this route
- Drug stability data may be limited
- Who mixes the product? (pharmacy vs respiratory)
- Treatments can take 15-20 min to complete
- Cost of equipment, medications
- Risk for local side effects
  - Bronchospasm
  - Wheezing
  - Shortness of breath

Advantages

- Delivers the drug directly to the target site of the pathogen
- Higher local levels may minimize risk of resistance
- Less systemic drug levels may minimize toxicity
- May be given at home by patient or caregiver

Role of the Technician

- Double check with the pharmacist that the product ordered is safe to be given by this route
- Make sure the right product and dose are selected
- Tobi® nebs ≠ Tobramycin IV
- Identify the person who is mixing and administering the drug (respiratory therapist vs nurse vs patient)
- Do not mix too far in advance because of stability concerns with some of the products

Alternative Treatments for Clostridium difficile Infection
**Clostridium difficile**

- Gram-positive, spore-forming, anaerobic rod
- Transmission via fecal oral route
- Pathogenic strains produce exotoxins
  - Enterotoxin A, Cytotoxin B
- Most common cause of nosocomial diarrhea
- Resistant to most commonly used antibiotics
- Between 450K – 700K cases/year
- Overall recurrence rate around 25%

**Intracolonic Vancomycin**

- Given by enema or a foley catheter with a balloon
- Used as adjunctive therapy
- Optimal dosing and volume has not been established
- May benefit patients with severe or refractory cases
  - e.g. toxic megacolon, ileus, or toxic enterocolitis
- Commonly given as last line before surgery
- Usual dose: 500 mg in 100 mL NS every 6 hours

**Vancomycin**

- Activity: gram-positive aerobes and anaerobes
- First FDA-approved drug for C. difficile infection
- Not absorbed in the GI tract
  - Reaches high levels in the colon (site of infection)
- Usual Dose: 125 mg PO every 6 hours
- Comes in oral capsules as 125 mg and 250 mg
- Now available in generic (cost varies)
- AWP: $31/dose ~ $120/day

**Conclusion**

- Timing of first dose antibiotics can be very important
  - Especially in patients who present with sepsis or are undergoing a surgical procedure
- New approaches to older antibiotics can meet the needs of patients with resistant infections and few alternatives
- Pharmacy technicians play a key role in making sure the right drug is given at the right dose, to the right patient in a timely manner

**Oral Vancomycin Solution (Slurry)**

- Due to the high cost of oral capsules, many institutions compound an oral solution using the IV product
- Vancomycin 25 mg/mL or 50 mg/mL concentration
  - Vancomycin HCl 5 g or 10 g injection
  - Saccharin Sodium 0.4 g
  - Stevia 0.4 g
  - Glycerin 80 ml
  - Raspberry concentrate 0.2 ml
  - Distilled water qs 200 ml
- Stability = 14 days in refrigerator

**References**

References


Questions?

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