ADVERSE EFFECTS OF ANTIBIOTICS

PERFECTING MONITORING PLANS

Jolanta Piszczek, Pharm D
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OBJECTIVES

• To appreciate common and less common ADRs of select antibiotics
• To structure a reasonable monitoring plan
• To review strategies for management of ADRs
• To diminish the element of surprise
OUTLINE

• Background
• Drugs:
  • Beta-lactams
  • Daptomycin vs. Linezolid
  • Metronidazole
• Reporting
WHY ANTIBIOTICS?

- Well tolerated
- Short term
- Unpredictable...

Figure 1: ADRs by Drug Class

TERMINOLOGY

• Adverse Drug Reactions
  • Untoward event that occurs as a result of an inherent risk of the drug itself when drug is given as intended

• Adverse Event
  • Results from the use of the drug

• Medication Errors
  • Can encompass both

PREVENTABLE VS. NOT

• Medication Errors are always preventable
  • Goal is to minimize their occurrence
• ADRs and AEs can be unforeseen but many are predictable

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>Augmented, understood pharmacologic effects</td>
</tr>
<tr>
<td>Type B</td>
<td>Idiosyncratic</td>
</tr>
<tr>
<td>Type C</td>
<td>Chronic Effects</td>
</tr>
<tr>
<td>Type D</td>
<td>Delayed Effects (carcinogenic/ teratogenic)</td>
</tr>
<tr>
<td>Type E, etc.</td>
<td>End-of Treatment</td>
</tr>
</tbody>
</table>

• The goal is to:
  • Measure, Mitigate, Monitor, Minimize
• All of this starts with understanding AEs and putting together a deliberate follow-up plan
CHALLENGES WITH AE

- Most common adverse reactions are detected in premarketing clinical trials (landmark trial)
  - Short duration
  - Patient numbers are low compared to population
  - Extensive exclusion criteria
  - Bias
- Latent or rare ADRs often missed
- 3000 patients at risk is needed to detect with an incidence rate of 1/1000 with 95% certainty
- Additional ADRs are discovered once a drug enters the marketplace
  - Reported by people like you and I
  - Independent research
  - If serious enough – FDA or Health Canada Warning
Adverse Reactions Significant

>10%:

- Gastrointestinal: Diarrhea (5% to 12%), vomiting (3% to 12%), constipation (6% to 11%)
- Hematologic & oncologic: Anemia (2% to 13%)

1% to 10%:

- Cardiovascular: Chest pain (7%), peripheral edema (7%), hypertension (1% to 6%), hypotension (2% to 5%)
- Central nervous system: Insomnia (5% to 9%), headache (5% to 7%), dizziness (2% to 6%), anxiety (5%)
- Dermatologic: Skin rash (4% to 7%), pruritus (3% to 6%), diaphoresis (5%), erythema (5%)
- Endocrine & metabolic: Hypokalemia (9%), hyperkalemia (5%), hyperphosphatemia (3%)
- Gastrointestinal: Nausea (8% to 10%), abdominal pain (8%), dyspepsia (1% to 4%), loose stools (4%), gastrointestinal hemorrhage (2%)
- Genitourinary: Urinary tract infection (2% to 7%)
- Hematologic & oncologic: Eosinophilia (2%), increased INR (2%)
- Hepatic: Increased serum transaminases (2% to 3%), increased serum alkaline phosphatase (2%)
- Infection: Gram-negative organism infection (8%), bacteremia (5%), sepsis (5%), fungal infection (2% to 3%)
- Local: Injection site reaction (3% to 6%)
- Neuromuscular & skeletal: Increased creatine phosphokinase (3% to 9%), limb pain (2% to 9%), back pain (7%), osteomyelitis (6%), weakness (5%), arthralgia (1% to 3%)
- Renal: Renal failure (2% to 3%)
- Respiratory: Pharyngolaryngeal pain (8%), pleural effusion (6%), cough (3%), pneumonia (3%), dyspnea (2% to 3%)
- Miscellaneous: Fever (2% to 7%)

<1% (Limited to post-marketing data, not all cases are captured):

- Neurologic: Seizures, stroke, Guillain-Barré syndrome
- Other: Tachycardia, bradycardia, hypotension, hypertension, tachypnea, mental status changes, increased serum bicarbonate

Unusable Random
WHAT WE ACTUALLY NEED

• Absolute risk of AE vs. placebo
• Contributing risk factors
• Practical head-to-toe monitoring plan
  • Parameter
  • Degree of change
  • Frequency and duration of monitoring
  • Thresholds for changing therapy
  • Who is monitoring
• Management strategies
BETA-LACTAMS
BETA-LACTAMHS

• Most commonly prescribed class of antimicrobials
• Remain one of the safest antibiotic groups prescribed
• With experience
  • Identification of serious ADRs including hematological, renal and neurological
  • Well characterized ADRs
• Generally share AE
TYPE I ALLERGIC REACTIONS

• Important when eliciting history
• IgE mediated reactions
  • Incidence of anaphylaxis: 0.01-0.05%
  • Laryngeal edema, hypotension, angioedema, wheezing, urticaria, pruritus
  • Most occur within 4 hours; 1 hour in a sensitized host
  • Highly unusual to see a Type I reaction after 72 hours
    • Pruritus and hives 1-2 days later is a mild Type I reaction (1%)
    • 80% of patients lose their antibodies after 10 years

• For drug-naive patients:
  • Explain reaction
  • Reassure patient
  • Alert nursing staff
  • Treatment is IM epinephrine

Mayo Clin Proc 2005;80:405-10
JAMA 2001;285:2498-505
HEMATOLOGIC ADRS

<table>
<thead>
<tr>
<th></th>
<th>Type II reaction</th>
<th>Non-allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Formation of IgM and IgG Abs against blood cells causing cytotoxic effects</td>
<td>Direct toxic effects on myeloid precursors</td>
</tr>
<tr>
<td><strong>Most common</strong></td>
<td>Hemolytic anemia</td>
<td>Neutropenia</td>
</tr>
<tr>
<td><strong>manifestation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>1:1,000,000</td>
<td>1.5:100,000</td>
</tr>
<tr>
<td><strong>Main risk factor</strong></td>
<td>Dose</td>
<td>Duration</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Mean = 3 weeks</td>
<td></td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Asymptomatic, sudden drop of Hg</td>
<td>Generalized symptoms, can be more gradual</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Immediate d/c of drug, do not re-challenge, no cross-reactivity</td>
<td>Have a threshold for d/c, ? re-challenge</td>
</tr>
</tbody>
</table>

TYPE III ALLERGIC REACTIONS

- Antibody-antigen complexes precipitate in tissue, activate complement and cause tissue damage
- Late reaction occurring 7-10+ days post-exposure
- Most elusive
- Result in a variety of clinical syndromes that can affect any end organ
  - Most common: vasculitis (palpable purpura)
  - Serum-sickness
  - Drug fever (diagnosis of exclusion)
- Incidence is 4:10,000
- Self limiting upon discontinuation
NEUROLOGIC REACTIONS

- Penicillins are the most common drug cause of encephalopathy
  - “Toxic metabolic encephalopathy”
- Not just seizures
  - Change in consciousness
  - Somnolence
  - Stupor
  - Confusion
- Quite common (10%)
- Apparent within 1st week of therapy
- High doses, especially IV
  - Management is dose reduction if possible
- Risk factors: renal dysfunction, underlying CNS abnormalities

RENAL REACTIONS

- Can be Type III (serum-sickness)
- Acute interstitial nephritis
  - Type IV allergic reaction
    - Drug activates T-cells, then eosinophils
    - Inflammatory cellular infiltrate in the interstitium
  - Features:
    - Sudden and rapid increase in serum creatinine
    - Oligouria (50%)
    - Rash/fever/eosinophilia (25%)
    - Nausea, vomiting and malaise
  - Biopsy confirmed
  - Drug should be discontinued immediately; no re-challenge; careful with cross-reactivity
- Type IV reactions also include drug exanthems (2%)
  - Rarely dangerous and managed with antihistamines

*Kidney International (2010) 77, 956–961*
## MONITORING PLAN SUMMARY

<table>
<thead>
<tr>
<th>Organ</th>
<th>ADR</th>
<th>When/How long/Who/How</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>IgE-mediated</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; dose (4h)</td>
<td>IM Epinephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>First 72 hours Patient/Nurse</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Serum Sickness</td>
<td>7-10 days Ongoing</td>
<td>Stop drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Check for organ involvement, generalized sx and Complement</td>
</tr>
<tr>
<td>Type IV skin</td>
<td>reactions</td>
<td>Within days Ongoing</td>
<td>Ask to tolerate Antihistamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Mental status ∆s</td>
<td>Within days Ongoing</td>
<td>Dose decrease</td>
</tr>
<tr>
<td></td>
<td>Stupor</td>
<td></td>
<td>Check renal fx</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td></td>
<td>Re-challenge OK</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>Hemoglobin</td>
<td>Weekly</td>
<td>Have a threshold</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>Differentiate between sudden</td>
<td>Stop drug/no re-challenge if HA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>drops and gradual changes</td>
<td></td>
</tr>
<tr>
<td>CrCl</td>
<td>AIN</td>
<td>Weekly</td>
<td>Stop drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily if sudden drop, add</td>
<td>No re-challenge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>urinalysis</td>
<td></td>
</tr>
</tbody>
</table>
DAPTOMYCIN
LINEZOLID
A TALE OF TWO CITIES

Protein binding
Distribution
Use
MECHANISM OF ACTION AND ADRS

- Linezolid binds to the 50S ribosomal subunit
- Bacteriostatic

- Daptomycin disrupts the membrane by forming ion-conducting structures that cause the efflux of K+
- Bactericidal
DAPTOMYCIN PHARMACODYNAMICS

• MSK Effects:
  • High affinity for protein + intravascular drug
    • Ability to reach large muscles and attach to myocytes
    • Leakage of creatinine phosphokinase (CK) from cells
    • CK increases of 2X UNL occurs in ~7% of patients; Rhabdomyolysis 0.2%
  • Usually occurs with 1 week of use or longer
  • Risk factors include statin use and renal dysfunction
  • Time between doses has been shown to be protective

Pharmacology 2008;81:79–91
Clinical Infectious Diseases 2010; 50(11):63
DAPTOMYCIN PD CONT.

- **Respiratory ADRs**
  - Oligomerizes
    - Binds pulmonary surfactant
    - Accumulates in the lungs causing epithelial injury
    - Lung injury such as eosinophilic pneumonia and chronic pneumonitis have been described
    - Cough and sore throat quite common (8%)

- **Electrolyte disturbances**
  - Causes efflux of electrolytes, especially K+
    - Kidneys should compensate
    - Hyper AND hypokalemia is seen
    - Hyperphosphotemimia also reported

LINEZOLID PHARMACODYNAMICS

• Hematological adverse effects
  • Distributes to bone + mitochondrial toxicity
    • Direct marrow suppression: thrombocytopenia (Immune-mediated also), anemia, leukopenia
    • Thrombocytopenia occurs in 1/3 of patients treated with linezolid
      • Reports of bleeding and transfusions
    • Other blood dyscrasias also common but not as limiting
  • Occur as early as 7 days
  • Dose and duration related
  • Reversible, re-challenge OK
  • Report of treatment with B6

LINEZOLID PD CONT.

- Neuropathy
  - Also a manifestation of mitochondrial dysfunction
  - “Glove and Stocking” sensory impairment
  - Optic neuropathy
    - Decreased visual acuity
    - Floaties
    - Diminished color perception
  - Optic neuropathy tends to resolve
  - Peripheral neuropathy tends to be permanent
  - Associated with prolonged administration (30 days)

- Lactic acidosis can rarely occur
  - Thought to occur due to the same mechanism

## Monitoring Plans

<table>
<thead>
<tr>
<th>Dapto</th>
<th>ADR</th>
<th>When/How long/Who/How</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSK</td>
<td>Myalgia Rhabdomyolysis</td>
<td>Check baseline CK CK weekly</td>
<td>Have a threshold (usually 4X UNL) D/C or lower statins</td>
</tr>
<tr>
<td>‘Lytes</td>
<td>Hypo/hyperkalemia Hyperphosphotemia</td>
<td>Weekly K+ Other electrolytes if K abnormal</td>
<td>D/C other offenders Will not improve unless drug is stopped</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Linezolid</th>
<th>ADR</th>
<th>When/How long/Who/How</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Cytopenias</td>
<td>CBC weekly if using &gt;14d Ongoing</td>
<td>Have a threshold (usually 100 for platelets)</td>
</tr>
<tr>
<td>Neuro</td>
<td>Optic neuropathy Peripheral neuropathy</td>
<td>Ongoing Done by patient Ophthalmologist referral if suspected</td>
<td>Stop drug Vitamin B6 may be useful</td>
</tr>
<tr>
<td>General</td>
<td>Lactic acidosis</td>
<td>Lactate if general malaise, weakness, N&amp;V</td>
<td>Stop drug</td>
</tr>
</tbody>
</table>
METRONIDAZOLE
METRONIDAZOLE

- 2nd most frequently used antibiotic at IH after beta-lactams
- Well loved for its anaerobic coverage
- MoA: disrupts DNA of microbial cells by preventing nucleic acid synthesis
  - Molecule needs to be partially reduced for it to work
- Good safety profile
- Excellent tissue penetration
- Prototype of a GI upset drug
GASTROINTESTINAL ADRS

• GI issues are the most common ADRs of antibiotics
  • Diarrhea
  • Nausea and vomiting
• Diarrhea is related to quantitative and qualitative changes in the intestinal microflora
  • Unabsorbed or secreted antibiotics
  • Other mechanisms possible
• Independent risk factor for acquisition and infection with c. difficile
• Nausea and vomiting can have numerous etiologies
  • For antibiotics it is mainly chemically induced
    • Local effects
    • Direct effects

J Antimicrob Chemother 2001; 47:43–50
NAUSEA

- Quick onset, tolerance develops quickly
- Large psychosomatic component
  - Patient interview is important
- Bedtime administration
- Strategies to lessen degree of mucosal irritation
  - Food
  - Water
  - Dividing the dose
- Treatment trial is warranted (give regularly for 2-3 d)
  - Haloperidol 0.5-1 mg q12h
  - Prochlorperazine 5-10mg q8h
  - Ondansetron is potent and can be used pre-dose
  - Avoid pro-kinetics

Gastroenterolgy 2001; 120(1):263-286
AFP 2007;76;76-84.
**NON-CDI AAD**

- Tends to not improve
- If mild, can be tolerated
- Anti-motility agents such as loperamide are not recommended
  - If severe, drug has to be discontinued
  - 2-3 days for drug to be eliminated from the bowel
- Dietary tips
  - Hydration
  - Small, frequent meals
  - Cutting out irritating foods
  - Soluble fiber (oats and barley)
Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea
A Systematic Review and Meta-analysis

Hempel S et al. JAMA 2012; 307:1959-69
HEMPEL ET AL

- Objective: to evaluate the evidence for probiotic use in the prevention and treatment of AAD
- 82 RCTs evaluated
  - RR = 0.58 [95% CI 0.50-0.68]
  - Lactobacillus alone (N=17) RR=0.64 [95% CI 0.47-0.86]
  - Sacchromyces alone (N=15) RR = 0.48 [95% CI 0.35-0.65]
PROBIOTICS

- Largest systematic review/meta-analysis
  - 42% lower risk of developing ADD when given probiotics
    - NNT = 13
  - Insensitive to various subgroup analyses
  - Large enough to pool similar probiotics

- Limitations
  - Significant heterogeneity
  - External validity (who, how long, which antibiotic etc).

- Recommendations (if any)
  - Saccharomyces 250-500mg PO BID during and up to 2 weeks after
  - Lactobacillus sp. 1 billion CFUs TID
  - Plain yoghurt is not unreasonable

Hempel S et al. JAMA 2012; 307:1959-69
METRONIDAZOLE TIPS

• Is it necessary?
• Mask metallic taste
  • Capsules if available
• Dose
  • 500mg q12h may be sufficient
• PO vs. IV
  • For metronidazole there is no difference
## MONITORING PLAN GI ADRS

<table>
<thead>
<tr>
<th>ADR</th>
<th>When/How long/Who/How</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Nausea and vomiting</td>
<td>Psychological</td>
</tr>
<tr>
<td></td>
<td>First day, then daily x 3 days Patient interview is key</td>
<td>Dietary Medications</td>
</tr>
<tr>
<td>AAD</td>
<td>Ongoing Nursing staff to ↑ objectivity</td>
<td>Establish a baseline Have a threshold for d/c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Probiotics may be useful</td>
</tr>
</tbody>
</table>
REPORTING

• Health Canada online
  • 5 step process
• Enlist your pharmacist
• Manufacturer will be contacted by Health Canada and may contact you
• Write it up if it’s cool!
• Ideal
  • Nested case controls
  • Systematic review
SUMMARY

Pharmacokinetic Knowledge

Risk Assessment

Mitigation Strategies

Monitoring Plan

Team Approach (incl. patient)

Prevention and Minimization of Damage of ADRs
KEEP CALM AND BE AWESOME

THANK YOU!

QUESTIONS?