Adverse Drug Events and Trigger Tool Prototype

Barbara J. Zarowitz, PharmD, FCCP, BCPS, BCGP, FASCP
Senior Advisor and Affiliate Professor
Disclosures

Dr. Zarowitz is a Senior Strategic Advisor to Think Research, Toronto, Canada and participated in the development of the ADE prototype. Although unrelated to this presentation, Dr. Zarowitz has received research grant funding from Acadia Pharmaceuticals, Inc.
Objectives

At the completion of this session, participants will be able to:

1. select the top 5 most prevalent antibiotic-related adverse drug events;
2. identify the antibiotics commonly associated with adverse drug events; and
3. list the top 3 reasons antibiotic adverse events should be documented.
Tracking: Monitoring Antibiotic Prescribing, Use, and Resistance

Does your facility monitor one or more outcomes of antibiotic use?

− Rates of *C. difficile* infection
− Rates of antibiotic resistant organisms
− Rates of adverse drug events due to antibiotics

Adverse events due to use of medications in skilled nursing homes accounted for nearly 40% of harms identified in a recent report.\(^1\) Antibiotics are among the most frequently prescribed medications in LTCFs and have a high rate of adverse drug events.\(^2,3\)

20% of hospitalized adults have at least 1 ADE

Every 10 days of antibiotic therapy confers a 3% increased risk of ADE

GI (42%), Renal (24%), Blood (15%), Liver (7%), Neurologic (7%)

Sample Decision Algorithms for Antibiotic ADEs

This prototype remains in draft form, is subject to further development, and is being presented for educational purposes only. Healthcare practitioners should use their professional judgment in using the information provided. This is not a substitute for the care provided by licensed healthcare practitioners. We do not assume any responsibility for any aspect of healthcare administered with the aid of this tool, prototype, or information provided herein.
Antibiotic ADE: GI Event

- Diarrhea: > 3 loose stools per day; absence of laxatives
- Nausea and/or vomiting; nausea and vomiting associated with antibiotic; no other explanation
- Prevalence: 42%
- Median time to occurrence: 5 days (2 – 9)

**Antibiotics Implicated**
- Ampicillin
- Amoxicillin-clavulanate
- Ampicillin-sulbactam
- Oxacillin
- Piperacillin-tazobactam
- Ceftriaxone
- Cefpodoxime
- Ertapenem
- Cefepime
- Azithromycin
- Meropenem
- Doxycycline
- Clindamycin
- Metronidazole
- Fluoroquinolones
- Vancomycin
- Trimethoprim-SMZ

Non-infectious diarrhea, i.e., not *C. difficile* PCR positive

Possible Gastrointestinal Adverse Event

Contact Prescriber. Evaluate whether antibiotic can be taken with food to decrease nausea/vomiting.

Non-infectious diarrhea, i.e., not *C. difficile* PCR positive

Contact Prescriber. Obtain *C. difficile* PCR if not already known. Evaluate whether probiotic/prebiotic can be taken at least 2 hours prior to antibiotic to decrease diarrhea.

ADE: Renal Event

- Increase in Scr to > 1.5 times baseline; absence of precipitating renal factors (i.e., sepsis, other nephrotoxic drugs)
- Prevalence: 24%
- Median time to occurrence: 5 days (2 – 10)

ADE: Blood Disorder

- Anemia (hgb < 10 g/dL);
- Leukopenia (WBC < 4500 cells/μL);
- Thrombocytopenia (platelets < 150 x 10^3/μL);
- No bleeding or myelosuppressive therapy

- Prevalence: 15%
- Median time to occurrence: 12 days (6 – 24)

### Longer Term Antibiotic ADEs – up to 90 days

#### C. Difficile Infection – Infectious Diarrhea
- **Prevalence:**
  - 3.9 cases per 10,000 person days
  - 4% of study patients
- **Median time to occurrence:** 15 days (4 – 34)
- **Implicated antibiotics:** 3rd generation cephalosporins, cefepime, and fluoroquinolones

#### Infection with Multi-drug Resistant Organisms (MDRO)
- **Prevalence:**
  - 6.1 cases per 10,000 person days
  - 6% of study patients
- **Median time to occurrence:** within 90 days
- **Gm +ve resistance** (4.8/10,000 person days): VRE (67%)
- **Gm –ve resistance** (1.7/10,000 person days): extended spectrum β-lactamase production

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*C. difficile* and MDRO infections comprised 43% of all antibiotic-associated ADEs

Why Document Anti-infective ADEs?

• Protect the resident from future exposure to the ADE
• Communicate findings with other health care clinicians to avoid future occurrences
• Comply with standards of practice
• Adhere to regulatory and accreditation guidance
  • JCAHO
  • AMA Code of Ethics
  • CDC Core Principles of Antibiotic Stewardship
  • State Operations Manual: Appendix PP
Proposed Workflow

Where: EHR=electronic health record

1. Anti-infective started
   - Trigger 48-hour ADE assessment

2. 48-hour ADE assessment
   - Possible ADE Detected
     - Nurse Provides Signs and Symptoms in EHR
       - Infection Control Specialist Evaluates & Reports
       - MD/NP Evaluates and Intervenes, as needed
       - RPh Evaluates and Documents Outcome
       - Stop
   - No ADE Detected
     - Stop
Prototype Development

• In the spring, the Peter Lamy Center approached Think Research to assist in the development of a prototype of an electronic tool for documenting anti-infective associated ADEs

• Prototype requirements:
  • “Just-in-time” clinical content
  • Integrated into the electronic health record (EHR)
  • Complementary to existing facility workflow

• Pre-existing relationships between Think Research, Point Click Care (PCC) and MatrixCare were leveraged

• While the prototype is not a tool that can be used today, it provides a demonstration of the capabilities of such a tool integrated into the EHR
Prototype for Documenting Anti-infective ADEs in Long-term Care

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Think Research has partnered with expert advisory groups, EHR partners and other healthcare organizations to bring our clinical content and decision support software to the Long-Term, Post Acute Care Sector.

Founded in 2006 with a goal to improve clinical care by transitioning best practice and best evidence directly to the clinician. Today, our clinical content and decision support tools are used by over 1,100 health care organizations across Canada, the USA, and abroad.

Think Research has partnered with expert advisory groups, EHR partners and other healthcare organizations to bring our clinical content and decision support software to the Long-Term, Post Acute Care Sector.
BRIDGING THE KNOWLEDGE GAP BY PUTTING CURRENT EVIDENCE-BASED PRACTICES IN THE HANDS OF CLINICIANS AND UTILIZING REAL-TIME DATA TO INFORM KEY DECISIONS
THE DESIGN PROCESS

We adhere to a structured, iterative design approach to develop innovative solutions that meets the needs of all stakeholders.

1. UNDERSTAND
What are the user needs, business need and technology capacities?

2. STRATEGIZE
What is the key strategy and focus?

3. EXPLORE
How might we explore as many ideas as possible?

4. CONVERGE
Select the best ideas so far

5. PROTOTYPE
Create an artifact that allows to test the ideas with users

6. VALIDATE
Test the ideas with users, stakeholders, technical experts

CONTINUAL
ENHANCEMENT
Prototype Thoughts for Consideration

• Do you think the tool would be useful in supporting your staff to document and identify ADEs associated with antimicrobial stewardship?

• How does this compliment use of your electronic tools today?

• Who do you think should be primarily responsible for using the tool? To whom should the information go? Your consultant pharmacist? Infection control specialist? Prescriber?

• Regardless of the user, would this be useful in communication ADEs to other members of the care team and, avoiding them in the future?

• What barriers to adoption at your facility would exist? Existing workflows? Training of staff? Staff buy-in?

• Is this duplicative or complimentary of documentation you're doing today?

• What else would help your facility address and report on ADEs?
Next Steps

- Seek partnerships with facilities
- Better understand facility workflow
- Facilitate validation and adoption
## Contact Us

<table>
<thead>
<tr>
<th>Name</th>
<th>Title/Position</th>
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<tbody>
<tr>
<td><strong>Barbara Zarowitz</strong></td>
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<tr>
<td><strong>Brynne Eaton-Auva’a</strong></td>
<td>Vice President, Business Development, Think Research</td>
</tr>
<tr>
<td><strong>Christine Khouri</strong></td>
<td>Clinical Quality Specialist, Think Research</td>
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<tr>
<td><strong>Zainab Ali</strong></td>
<td>Engagement Manager, Think Research</td>
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Success is defined as partnerships to refine the tool and take the next steps!
Hidden Slides
Antibiotic ADE: Anaphylaxis

• Acute respiratory compromise, hypotension, or end-organ dysfunction within minutes after starting antibiotic; no alternate explanation

• Median time to occurrence: minutes (within an hour of administration)

Acute onset of SOB, difficulty breathing, ↑ RR, ↓ BP; preceded by angioedema, urticaria, rhinitis, bronchospasm & GI symptoms

Possible Anaphylaxis

HOLD ANTIBIOTIC & CONTACT PRESCRIBER

Evaluate other possible causes, i.e., sepsis, VTE, MI

Evaluate kidney, heart, lung, and liver function for acute damage, i.e., Scr, UO, HR, RR, LFTs

Evaluate need for Epinephrine IV, IV fluids, triage to emergency department

ADE: Skin Event

- Rash, hives, non-hive rashes, red man syndrome associated with antibiotic; resolution upon discontinuation
- Prevalence: 10%
- Median time to occurrence: minutes to days

Possible Skin Event

Typically non-immediate type allergic reactions. Typically self-limited without treatment. Rare cases can progress to more severe skin syndromes.

Notify Prescriber of possible skin/allergic reaction.

Antibiotics Implicated
- Penicillins, including Ampicillin
- Cephalosporins
- Fluoroquinolones
- Sulfonamides
- Trimethopim-SMZ
- Aminoglycosides
- Macrolides (rare)

ADE: Muscle Event

- Increase in creatine phosphokinase > 5 times baseline; absence of pre-existing myopathy or statin use
- Prevalence: 1%
- Median time to occurrence: days to weeks

ADE: Cardiac Event - Arrhythmia

• QTc > 440 ms in females
• QTc > 460 ms in males on two or more EKGs; absence of pre-existing arrhythmias
• Prevalence: 1%
• Median time to occurrence: 11 days (4-18)

↑QTc interval by 60 ms over baseline or
↑to > 440 ms in males;
↑to > 460 ms in females

Possible Arrhythmia

Evaluate HR and rhythm.
If HR > 140 or tachyarrhythmia,
HOLD ANTIBIOTIC & CONTACT PRESCRIBER

Anti-infective Implicated
Azithromycin
Ciprofloxacin
Erythromycin
Fluconazole
Levofloxacin
Moxifloxacin
Ketoconazole
Itraconazole;
Determine if other risk factors for TdP exist

Evaluate need for emergency triage, and potassium and magnesium replacement.

Credible Meds https://crediblemeds.org/
## Criteria for Antibiotic-associated ADEs

<table>
<thead>
<tr>
<th>Adverse Drug Event</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>&gt; 3 loose stools per day; no laxatives</td>
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<tr>
<td></td>
<td>Non-<em>C. difficile</em> and <em>C. difficile</em> (PCR)</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Nausea and vomiting associated with antibiotic; no other explanation</td>
</tr>
<tr>
<td>Blood Disorders</td>
<td>Anemia (hgb &lt; 10 g/dL); Leukopenia (WBC &lt; 4500 cells/μL); thrombocytopenia (platelets &lt; 150 x 10³/μL; no bleeding or myelosuppressive therapy</td>
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<tr>
<td>Liver Event</td>
<td>Total Bilirubin &gt; 3 mg/dL, ALT/AST &gt; 3 times baseline; absence of existing liver disease</td>
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<tr>
<td>Renal Event</td>
<td>Increase in Scr to &gt; 1.5 times baseline; absence of precipitating renal factors (i.e., sepsis, other nephrotoxic drugs)</td>
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<td>Adverse Drug Event</td>
<td>Definition</td>
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</tr>
<tr>
<td>Neurologic Event</td>
<td>Altered mental status, peripheral neuropathy, or seizures; absence of pre-existing conditions, substance-related toxic effects, or infectious syndromes</td>
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<tr>
<td>Skin Event</td>
<td>Rash, hives, non-hive rashes, red man syndrome associated with antibiotic; resolution upon discontinuation</td>
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<tr>
<td>Arrhythmia Event</td>
<td>QTc &gt; 440 ms in females on two or more EKGs; absence of pre-existing arrhythmias</td>
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<tr>
<td>Anaphylaxis</td>
<td>Acute respiratory compromise, hypotension, or end-organ dysfunction within minutes after starting antibiotic; no alternate explanation</td>
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<tr>
<td>Muscle Event</td>
<td>Increase in creatine phosphokinase &gt; 5 times baseline; absence of pre-existing myopathy or statin use</td>
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## Anticoagulant Interactions

<table>
<thead>
<tr>
<th>Anti-infective Medication</th>
<th>Dabigatran (Pradaxa)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Savaysa)</th>
<th>Rivaroxaban (Xarelto)</th>
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<tbody>
<tr>
<td><strong>Increased Risk of Bleeding</strong></td>
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<tr>
<td>Clarithromycin</td>
<td>15-20% ↑ in anticoagulant effect</td>
<td>60% ↑ anticoagulant effect</td>
<td>90% ↑ anticoagulant effect</td>
<td>54% (Clarithromycin)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>No Dosage Change</td>
<td>Avoid coadministration</td>
<td>Avoid coadministration</td>
<td>34% (Erythromycin) ↑ anticoagulant effect. Avoid coadministration.</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Not studied</td>
<td>Not studied</td>
<td>Not studied</td>
<td>42% ↑ anticoagulant effect. Avoid coadministration.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>140-150% ↑ anticoagulant effect. Avoid coadministration.</td>
<td>100% ↑ anticoagulant effect. Avoid coadministration.</td>
<td>87-95% ↑ anticoagulant effect. Reduce dose by 50%.</td>
<td>Up to 160% ↑ anticoagulant effect. Avoid coadministration.</td>
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<tr>
<td>Ketoconazole</td>
<td>Voriconazole</td>
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<tr>
<td><strong>Decreased Anticoagulant Effectiveness</strong></td>
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<tr>
<td>Rifampicin</td>
<td>66% ↓ in anticoagulant effect. Avoid coadministration.</td>
<td>54% ↓ in anticoagulant effect. Avoid coadministration.</td>
<td>35% ↓ in anticoagulant but compensatory ↑ in active metabolites.</td>
<td>Up to 50% ↓ in anticoagulant effect. Avoid coadministration.</td>
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</table>
ADE: Anticoagulant Drug Interactions

- Anti-infective drug interactions with the oral antithrombotic drugs is due primarily to $P$-gp (glycoprotein) competition and strong CYP3A4 inhibition or induction.
- Given that dosage reduction is not often possible, avoidance of the interacting drug is recommended.

Resident receiving direct oral anticoagulant (DOAC) who is started on an anti-infective

Anti-infective/DOAC Interaction at Risk of Supratherapeutic Anticoagulation
- Clarithromycin
- Erythromycin
- Fluconazole
- Itraconazole
- Ketoconazole
- Voriconazole

Anti-infective/DOAC Interaction at Moderate Risk of Subtherapeutic Anticoagulation
- Rifampin

CONTACT PRESCRIBER and recommend discontinuation of anti-infective. Consider a replacement with a non-interacting antibiotic if anti-infective therapy is necessary.

doi:10.1093/eurheartj/ehy136
ADE: Anticoagulant Drug Interactions

**Anti-infective/Warfarin Interaction at High Risk of Supratherapeutic Anticoagulation**
- Azithromycin
- Chloramphenicol
- Clarithromycin
- Fluconazole
- Ketoconazole
- Metronidazole
- Moxifloxacin
- Ofloxacin
- Sulfisoxazole
- Tinidazole

**Anti-infective/Warfarin Interaction at Moderate Risk of Supratherapeutic Anticoagulation**
- Amoxicillin
- Ampicillin
- Cefazolin
- Ceftriaxone
- Doxycycline
- Penicillin G
- Penicillin G Benz
- Piperacillin-tazo
- Ticarcillin-clavulanate

**Anti-infective/Warfarin Interaction at Moderate Risk of Subtherapeutic Anticoagulation**
- Dicloxacillin
- Griseofulvin
- Nafcillin
- Rifabutin
- Rifampin
- Rifapentine

**Resident receiving warfarin who is started on an antibiotic**

**CONTACT PRESCRIBER and recommend lowering warfarin dosage by 30%/week and monitoring INR every 3 days until 12 days after stopping anti-infective**

**CONTACT PRESCRIBER and recommend monitoring INR at least weekly until 2 weeks following anti-infective discontinuation**

ADE: Neurologic Event

• Altered mental status, peripheral neuropathy, or seizures; absence of pre-existing conditions, substance-related toxic effects, or infectious syndromes
• Prevalence: 7%
• Median time to occurrence: 3 days (2 – 4)

Contact prescriber to evaluate symptoms and order laboratory and radiologic tests. Determine if antibiotic places resident at risk of neurological event.

ADE: Liver Event

- Total Bilirubin > 3 mg/dL, ALT/AST > 3 times baseline; absence of existing liver disease
- Prevalence: 7%
- Median time to occurrence: 8 days (4 – 12)