UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY
THE PETER LAMY CENTER
ON DRUG THERAPY AND AGING

Adverse Drug Events and Trigger Tool Prototype

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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

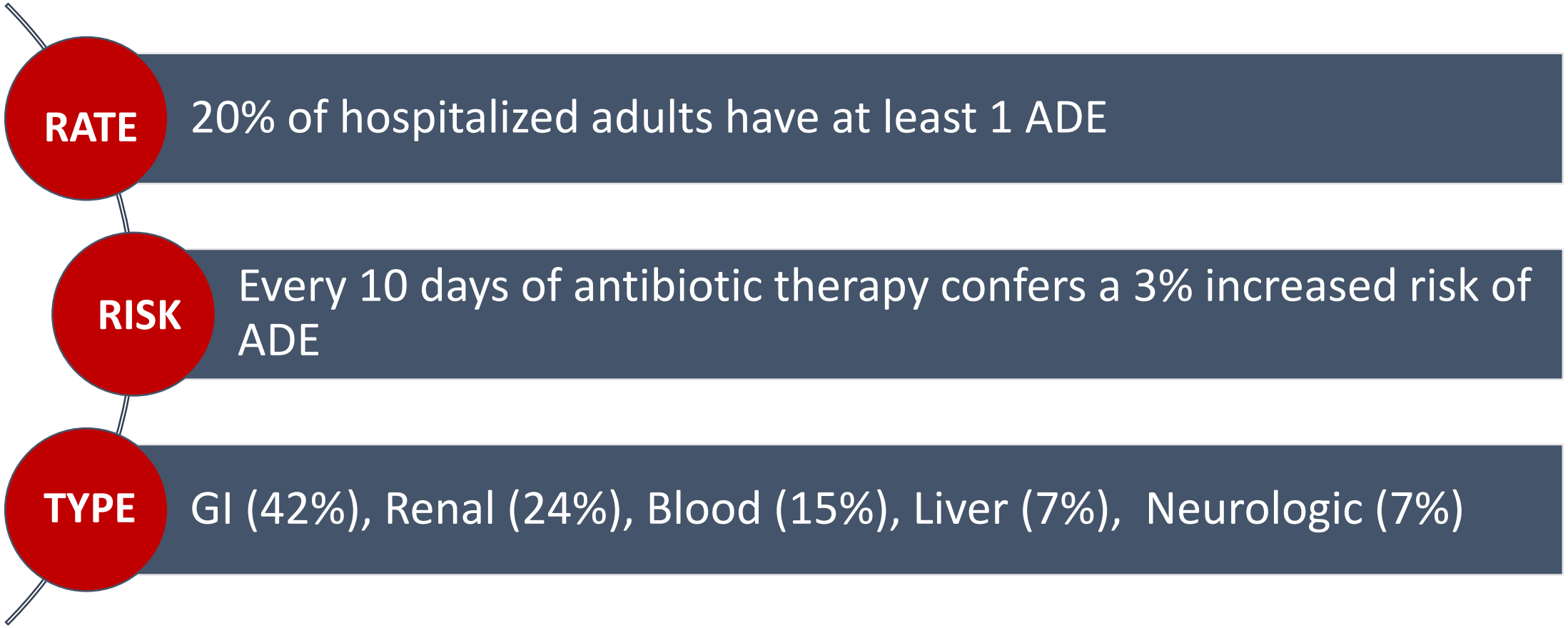
Does your facility monitor one or more outcomes of antibiotic use?

- 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]

1.Office of the Inspector General. Adverse Events in Skilled Nursing Facilities: National Incidence Among Medicare Beneficiaries (OEI-06-11-00370), February 2014.
2. Nicolle LE, Bentley D, Garibaldi R, et al. Antimicrobial use in long-term care facilities. Infect Control Hosp Epidemiol 2000; 21:537–45.
3. Gurwitz JH, Field TS, Avorn J et al. Incidence and preventability of adverse drug events in nursing homes. Am J Med. 2000;109:87–94.

Antibiotic-associated Adverse Drug Events



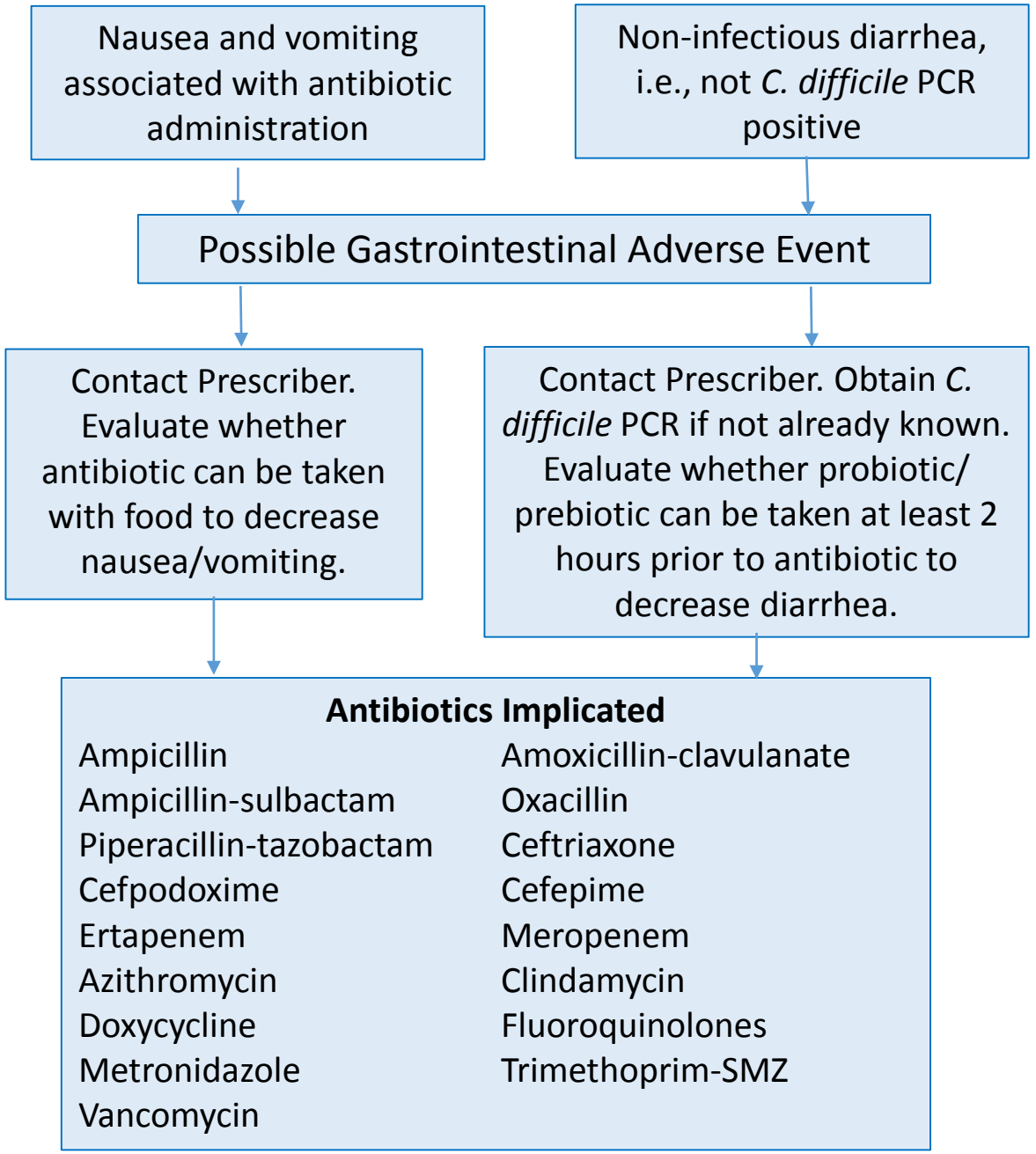
Tamma PD, et al. Association of adverse events with antibiotic use in hospitalized patients. JAMA Int Med 2017;177:1308-15.

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)



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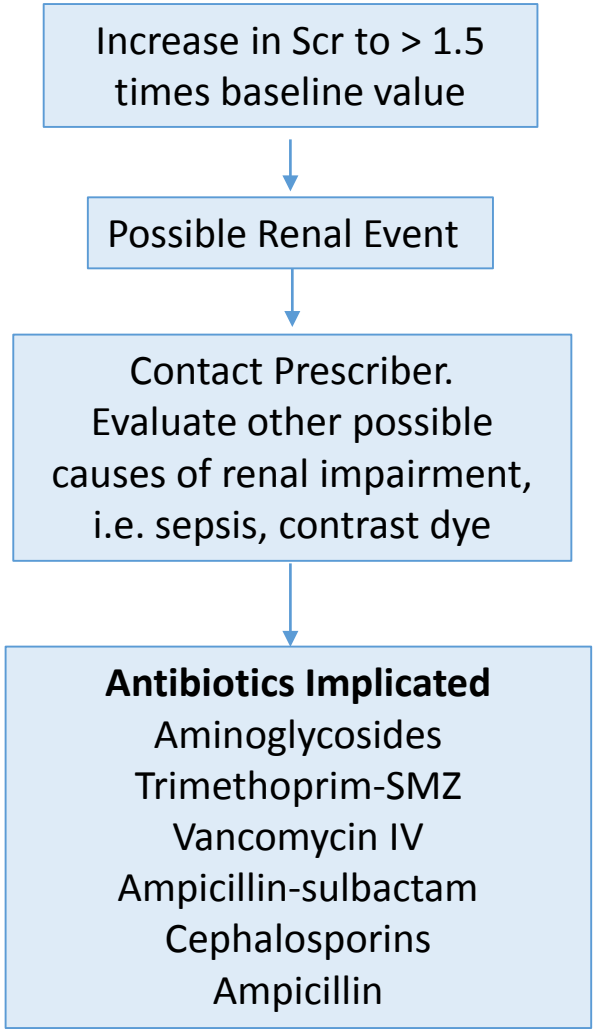
ADE: Renal Event

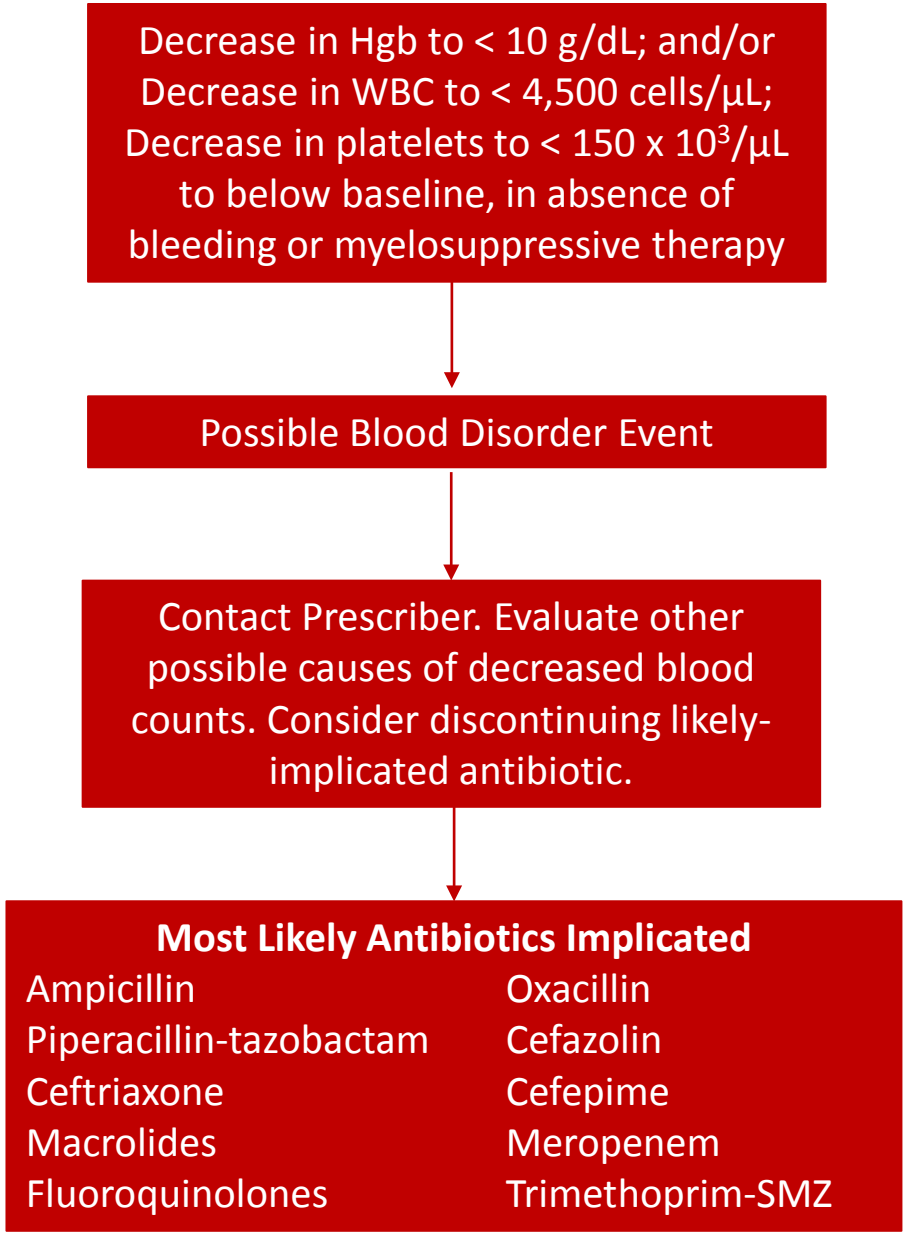
- Increase in Scr to > 1.5 times baseline; absence of precipitating renal factors (i.e., sepsis, other nephrotoxic drugs)
- Prevalence: 24%
- Median time to occurrence: 5 days (2 – 10)



Tamma PD, et al. Association of adverse events with antibiotic use in hospitalized patients. JAMA Int Med 2017;177:1308-15.

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)



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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

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

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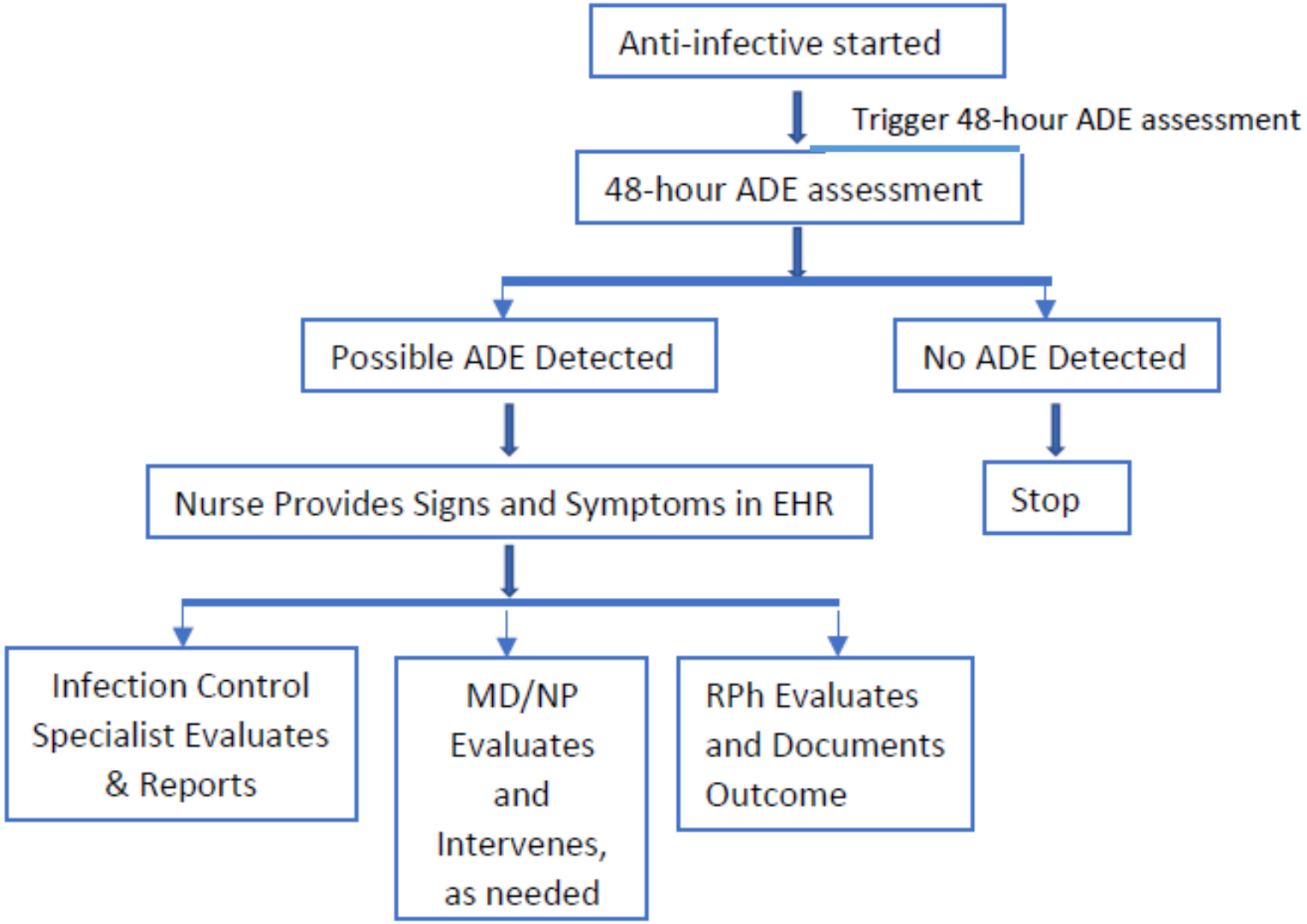
Why Document Anti-infective ADEs?

- 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

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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200+

FULL TIME EMPLOYEES

1,100+

FACILITIES IN NETWORK

PROVIDER OF CLINICAL SUPPORT TOOLS SPANNING THE CONTINUUM

THINK RESEARCH

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.

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BRIDGING THE KNOWLEDGE GAP BY PUTTING CURRENT EVIDENCE-BASED PRACTICES IN THE HANDS OF CLINICIANS AND UTILIZING REAL-TIME DATA TO INFORM KEY DECISIONS

EVIDENCE-BASED KNOWLEDGE AT THE POINT OF CARE

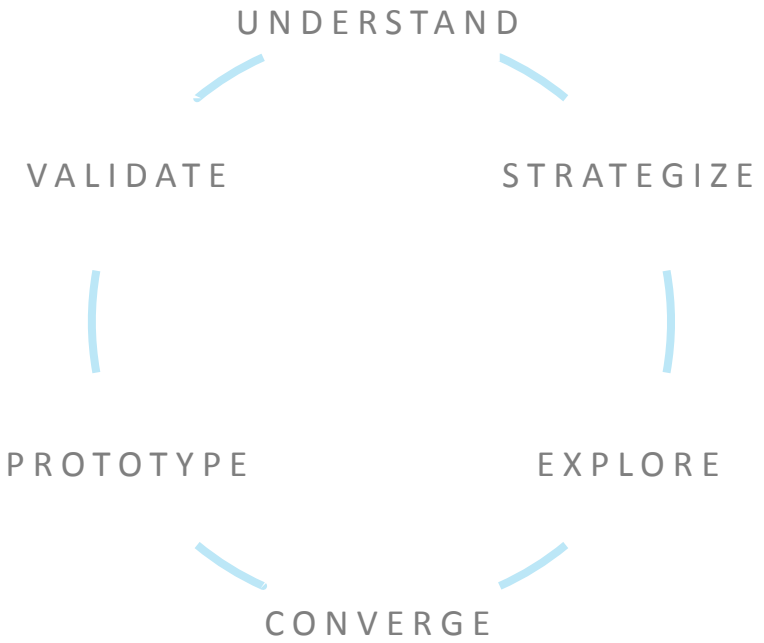
American HealthTech

MatrixCare®
Integrated Care. Better Outcomes.

PointClickCare®

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?

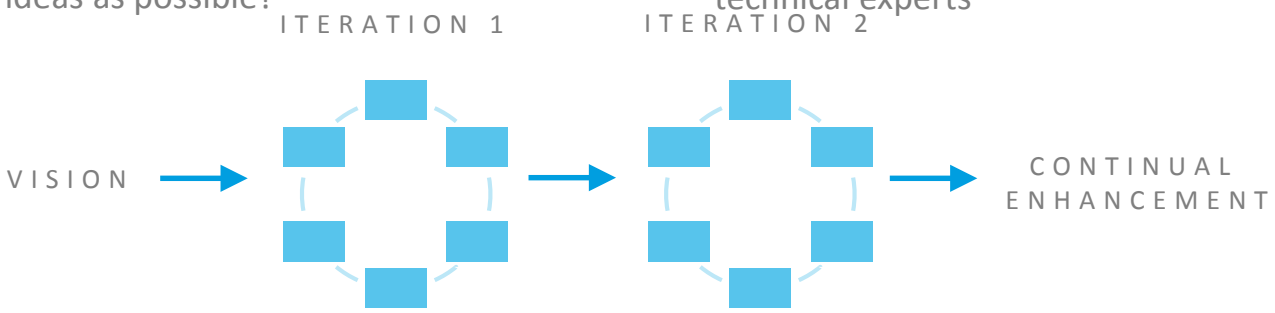
2. STRATEGIZE
What is the key strategy and focus?

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



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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

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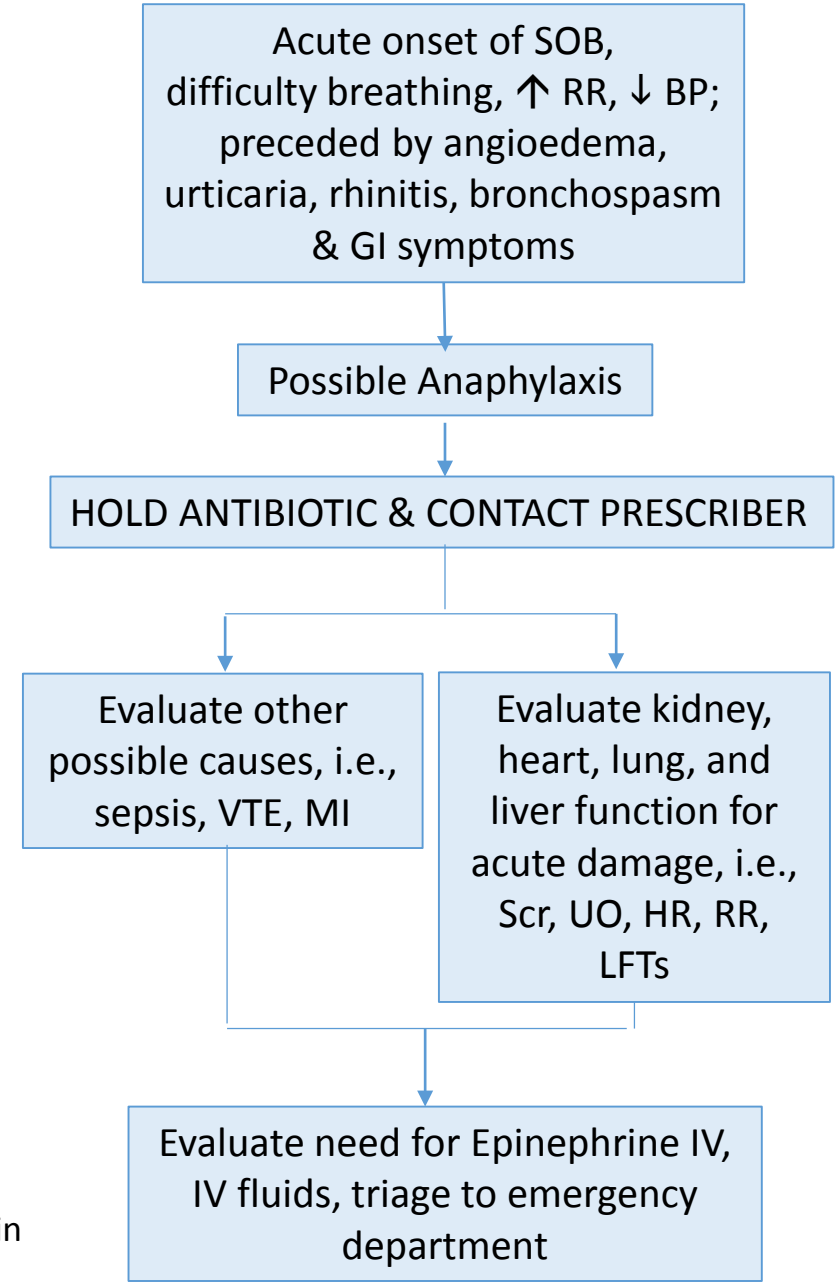
Success is defined as partnerships to refine the tool and take the next steps!

THANK YOU

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)



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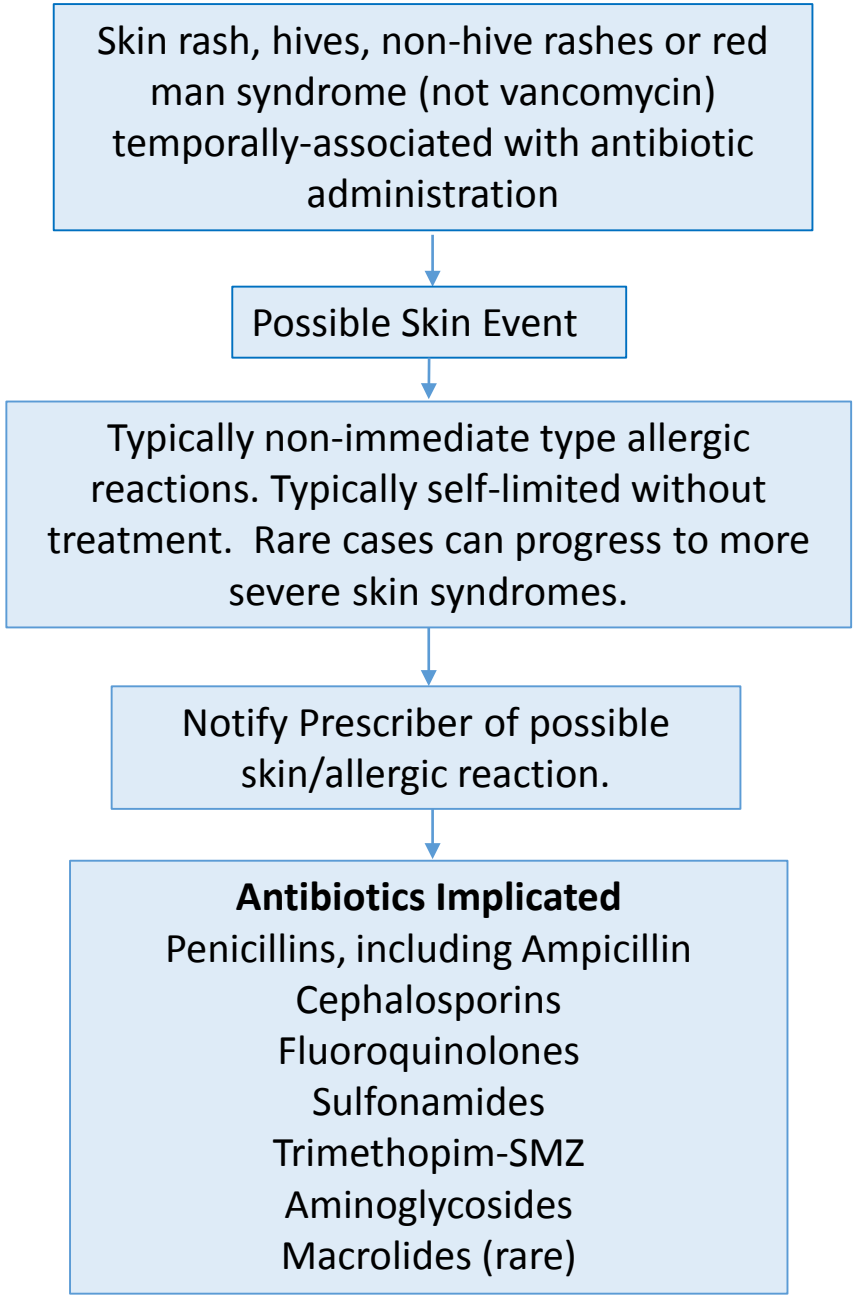
Romano A, Caubet J-C. Antibiotic allergies in children and adults: From clinical symptoms to skin testing diagnosis. J Allergy Clin Immunol Pract 2014;2:3-12. doi: 10.1016.j.jaip.2013.11.006

ADE: Skin Event

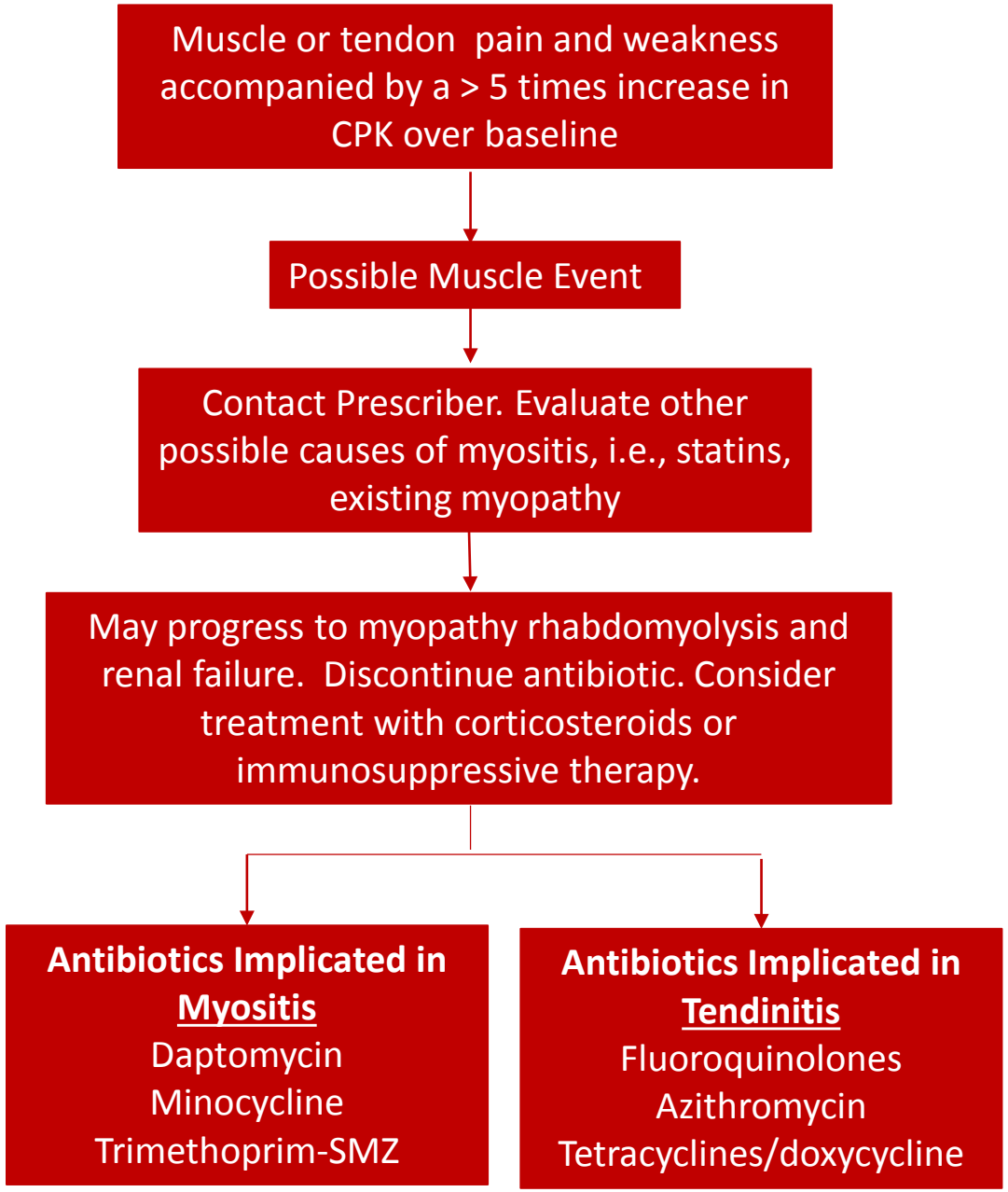
- Rash, hives, non-hive rashes, red man syndrome associated with antibiotic; resolution upon discontinuation
- Prevalence: 10%
- Median time to occurrence: minutes to days



Romano A, Caubet J-C. Antibiotic allergies in children and adults: From clinical symptoms to skin testing diagnosis. J Allergy Clin Immunol Pract 2014;2:3-12. doi: 10.1016.j.jaip.2013.11.006

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



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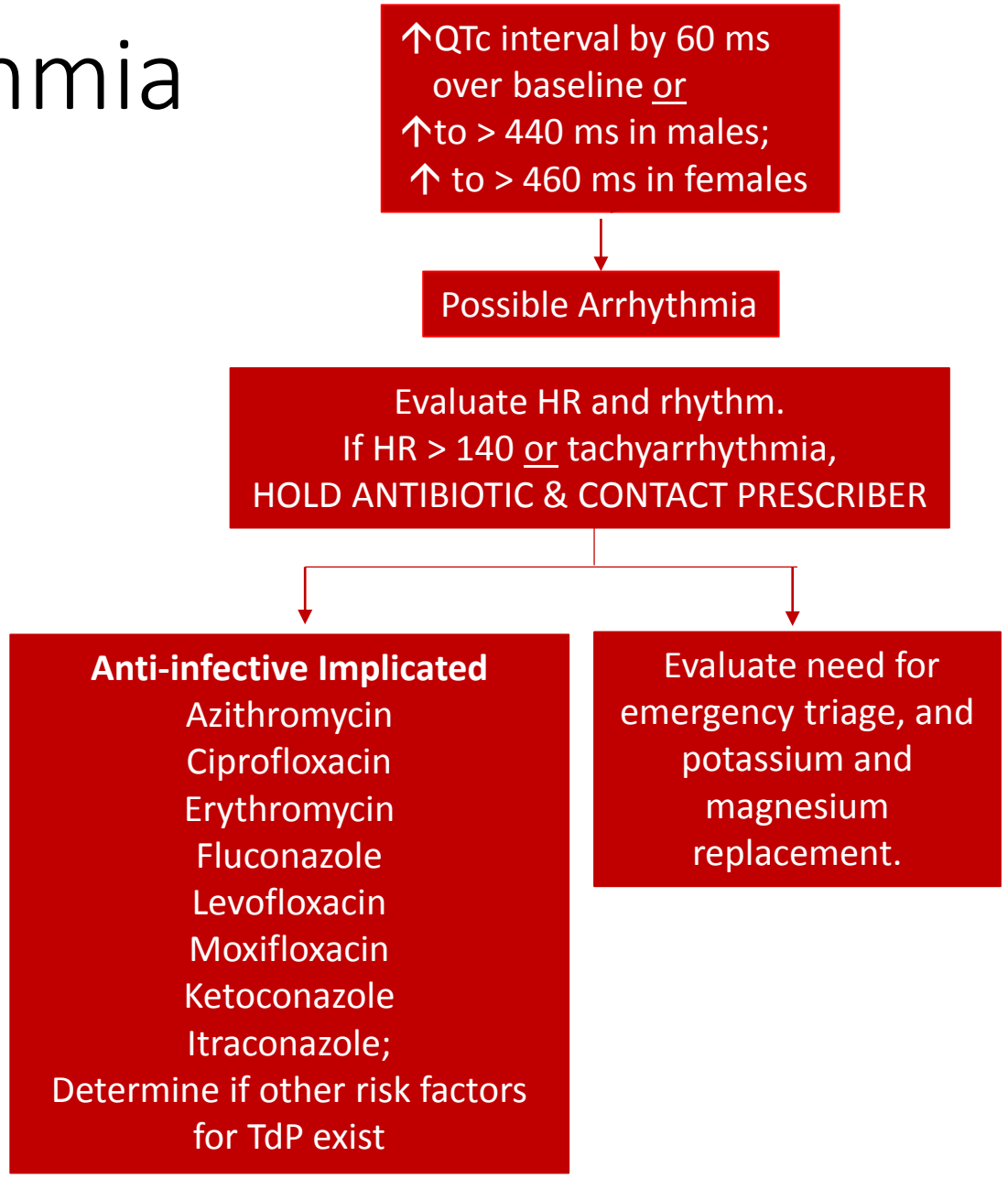
ADE: Cardiac Event - Arrhythmia

- 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)



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Credible Meds https://crediblemeds.org/

Criteria for Antibiotic-associated ADEs

Adverse Drug Event	Definition
Diarrhea	> 3 loose stools per day; no laxatives Non-*C. difficile* and *C. difficile* (PCR)
Nausea and Vomiting	Nausea and vomiting associated with antibiotic; no other explanation
Blood Disorders	Anemia (hgb < 10 g/dL); Leukopenia (WBC < 4500 cells/µL); thrombocytopenia (platelets < 150 x 10^3/µL; no bleeding or myelosuppressive therapy
Liver Event	Total Bilirubin > 3 mg/dL, ALT/AST > 3 times baseline; absence of existing liver disease
Renal Event	Increase in Scr to > 1.5 times baseline; absence of precipitating renal factors (i.e., sepsis, other nephrotoxic drugs)

Criteria for Antibiotic-associated ADEs, continued

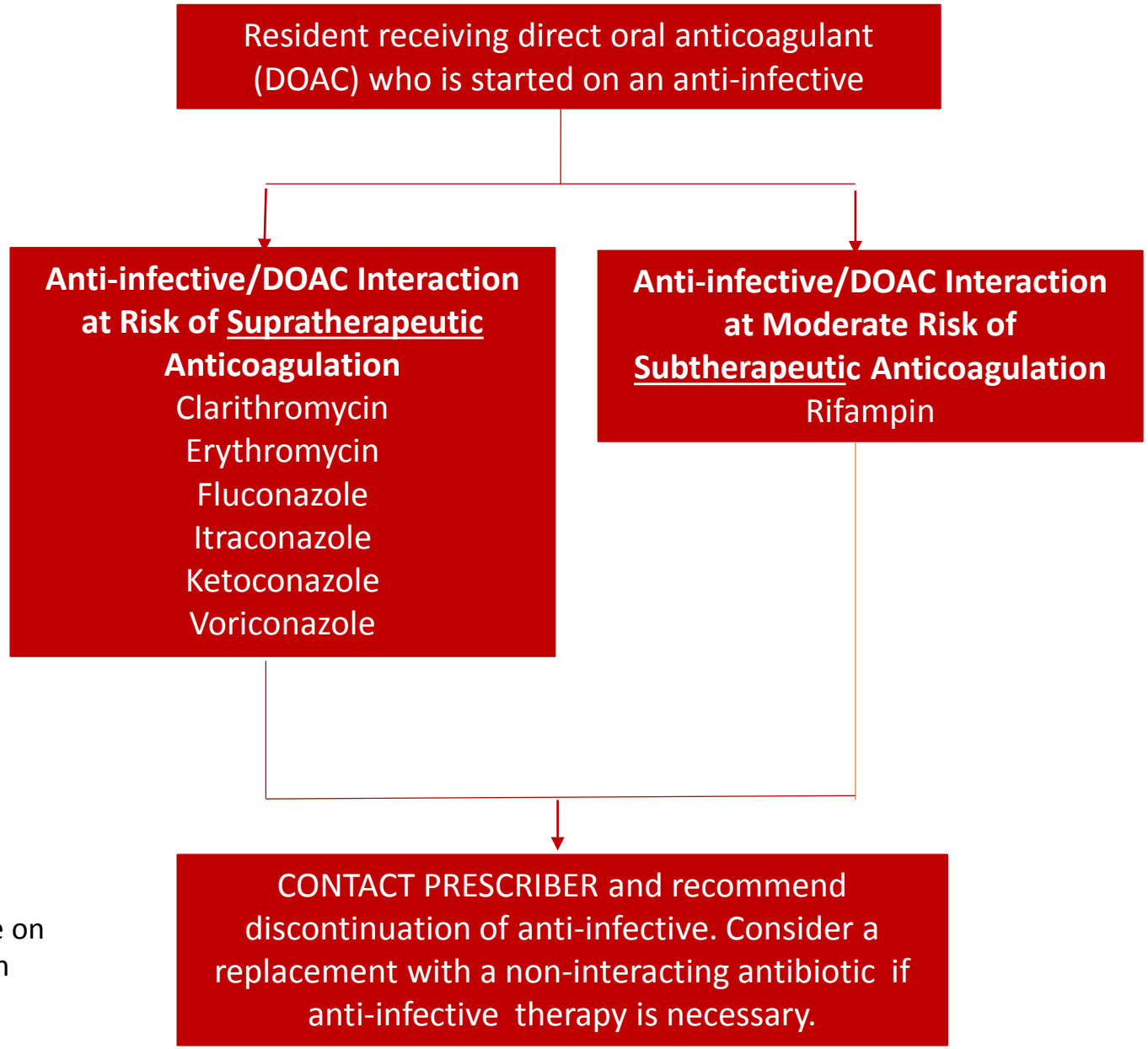
Adverse Drug Event	Definition
Neurologic Event	Altered mental status, peripheral neuropathy, or seizures; absence of pre-existing conditions, substance-related toxic effects, or infectious syndromes
Skin Event	Rash, hives, non-hive rashes, red man syndrome associated with antibiotic; resolution upon discontinuation
Arrhythmia Event	QTc > 440 ms in females on two or more EKGs; absence of pre-existing arrhythmias
Anaphylaxis	Acute respiratory compromise, hypotension, or end-organ dysfunction within minutes after starting antibiotic; no alternate explanation
Muscle Event	Increase in creatine phosphokinase > 5 times baseline; absence of pre-existing myopathy or statin use

ADE: Anticoagulant Interactions

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

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.



Steffel J, et al. 2018 European Heart Rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330-93 doi:10.1093/eurheartj/ehy136

ADE: Anticoagulant Drug Interactions

Resident receiving warfarin who is started on an antibiotic

Anti-infective/Warfarin Interaction at High Risk of Supratherapeutic Anticoagulation

Azithromycin	Cefotetan
Chloramphenicol	Ciprofloxacin
Clarithromycin	Erythromycin
Fluconazole	Itraconazole
Ketoconazole	Levofloxacin
Metronidazole	Miconazole
Moxifloxacin	Norfloxacin
Ofloxacin	Trimethoprim-SMZ
Sulfisoxazole	Telithromycin
Tinidazole	Voriconazole

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

Anti-infective/Warfarin Interaction at Moderate Risk of Supratherapeutic Anticoagulation

Amoxicillin	Amoxicillin-clavulanate
Ampicillin	Ampicillin-sulbactam
Cefazolin	Cefotetan
Ceftriaxone	Demeclocycline
Doxycycline	Minocycline
Penicillin G	Penicillin G Procaine
Penicillin G Benz	Piperacillin
Piperacillin-tazo	Tetracycline
Ticarcillin-clavulanate	

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

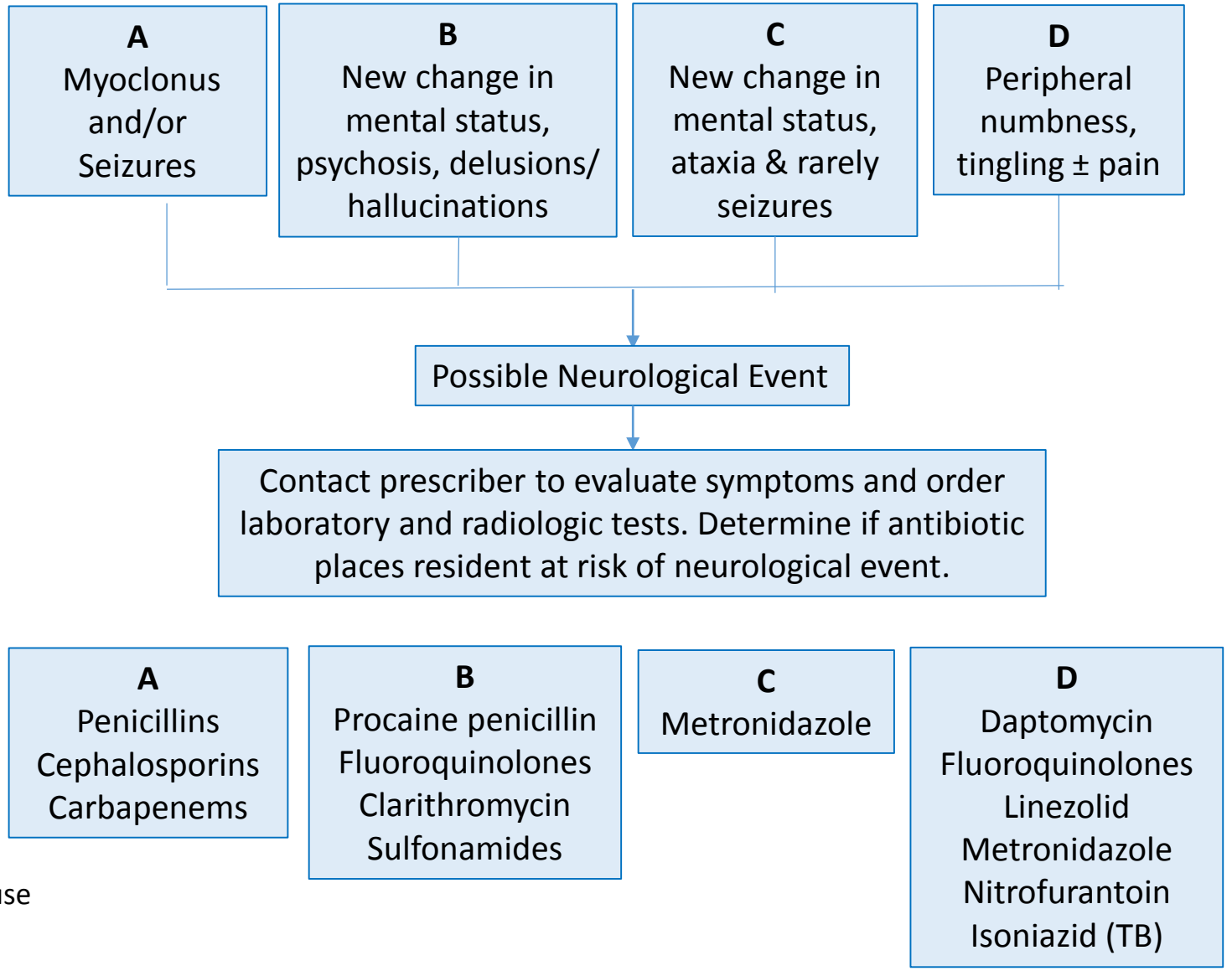
Anti-infective/Warfarin Interaction at Moderate Risk of Subtherapeutic Anticoagulation

Dicloxacillin
Griseofulvin
Nafcillin
Rifabutin
Rifampin
Rifapentine

Anticoagulation Forum http://www.anticoagulationtoolkit.org/sites/default/files/toolkit_pdfs/toolkitfull.pdf

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)



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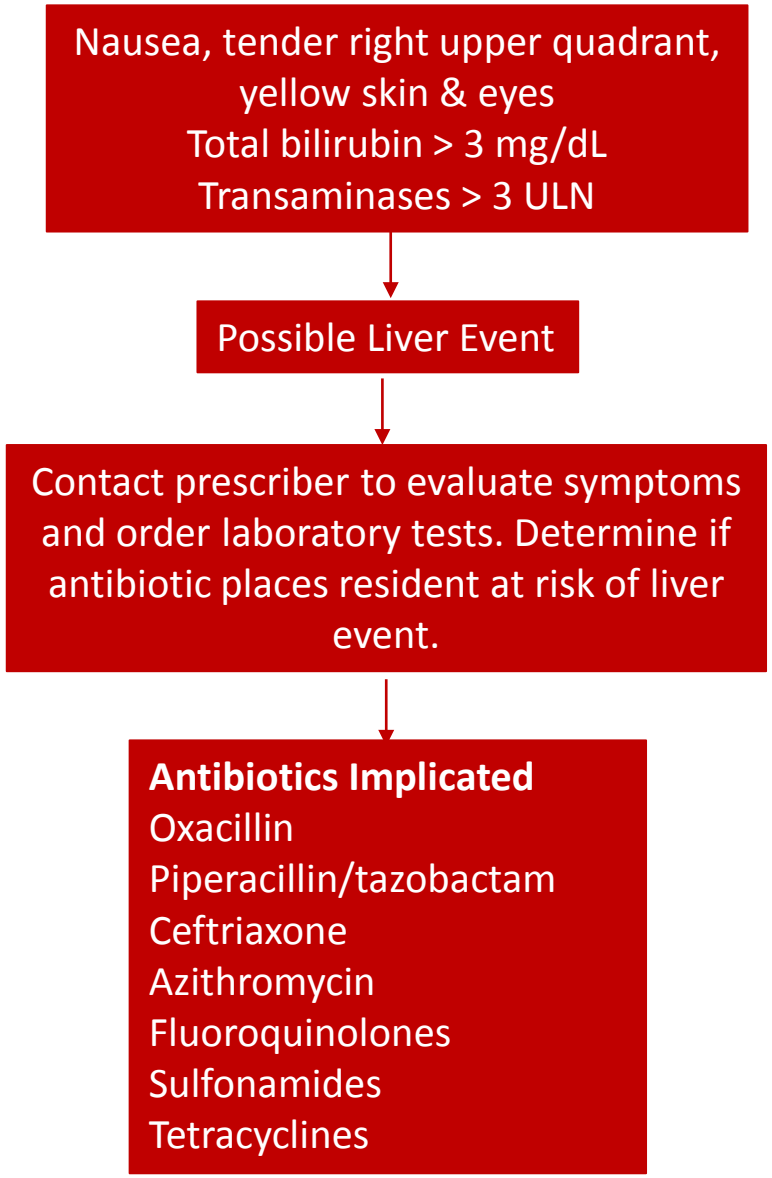
ADE: Liver Event

- 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)



Where ULN=upper limit of normal

Tamma PD, et al. Association of adverse events with antibiotic use in hospitalized patients. JAMA Int Med 2017;177:1308-15.