ANTIBIOTIC ADVERSE DRUG EVENTS (ADE) TEMPLATE

2018 Guidance for the Post-Acute Long-Term Care Team

Abstract

Nearly half of adverse drug events (ADEs) are preventable and account for about 11% of hospital admissions. ADEs are more likely to occur in adults older than 65 years, recently started on a new medication, and receiving 5 or more chronic medications. About 40% of harm noted in skilled nursing facilities is associated with ADEs. Antibiotics are used frequently in post-acute and long-term care settings and cause a high rate of ADEs.

This guidance document outlines recommendations for using the antibiotic ADE template to improve identification, reporting, and documentation of antibiotic ADEs. The application of this approach to antibiotic monitoring is fundamental to improving antimicrobial stewardship in post-acute and long-term care facilities as ADEs relate directly to patient safety.

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Find more information at: https://www.pharmacy.umaryland.edu/centers/lamy/antimicrobial-stewardship/

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INTRODUCTION

Background

The Centers for Disease Control and Prevention (CDC) identified the opportunity to improve the safe and effective use of antibiotics in a variety of healthcare settings.[1] Initial efforts focused on acute care hospitals where significant improvements have been made in antibiotic stewardship.

In 2015, antibiotic stewardship became a focus in post-acute and long-term care (PALTC) facilities leading to the release of:

- Core Elements for Antibiotic Stewardship in Long-term Care Facilities;[2]
- Appendix A: Policy and practice actions to improve antibiotic use;[3] and
- Appendix B: Measures of antibiotic prescribing, use and outcomes.[4]

Together, these documents inspired an increase in education and activities designed to improve antibiotic use by PALTC clinicians and nursing staff.

At approximately the same time, the Centers for Medicare & Medicaid Services (CMS) updated their regulatory requirements for skilled nursing facilities expanding the infection control responsibilities to embrace tenets of antibiotic stewardship.[5] With the release of these regulations in November 2017, skilled nursing facilities (§ 483.80 Infection Control) are required to have an antibiotic stewardship program as part of their Infection Prevention and Control Program (IPCP). The intent of this regulation is to ensure that the facility:

- develops and implements protocols to optimize the treatment of infections by ensuring that residents who require an antibiotic, are prescribed the appropriate antibiotic;
- reduces the risk of adverse events, including the development of antibiotic-resistant organisms, from unnecessary or inappropriate antibiotic use; and
- develops, promotes, and implements a facility-wide system to monitor the use of antibiotics.

The requirements for an infection preventionist (IP), with specialized training in infection prevention and control in skilled nursing facilities, began in November 2017 but financial penalties are not associated with failure to comply until 2019.

Antibiotics are used frequently in PALTC facilities and have led to the development of adverse drug reactions, drug interactions, and antibiotic resistance.[6-9] In addition to the public health concern of resistance of microorganisms to available antibiotics and emerging multi-resistant strains of bacteria, nursing home residents are at risk for adverse outcomes associated with antibiotics that may include but are not limited to the following:

- increased adverse drug events and drug interactions (e.g., allergic rash, anaphylaxis or death);
- serious diarrheal infections from *C. difficile*;
- disruption of normal flora (e.g., this can result in overgrowth of Candida such as oral thrush); and/or
- colonization and/or infection with antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and multidrug-resistant gram-negative bacteria (GNB).[5]

For these reasons, the CDC suggests monitoring adverse drug events as appropriate outcome measures in facilities' infection control and prevention programs.[4]

Characteristics of PALTC residents that increase their risk of antibiotic ADEs include:

- age older than 65 years;
- multiple underlying conditions that can predispose to ADEs (i.e., immunosuppression, renal or liver impairment);
- polypharmacy (i.e., > 5 active medications leading to drug-drug interactions); and
- recent exposure to previous antibiotic therapy.[7,9-12]

Barriers exist to documenting ADEs.[13] There are inconsistent workflow models for identifying and documenting antibiotic-related ADEs and because attempts to minimize blood draws in PALTC have reduced laboratory monitoring, there are limited data available to confirm that residents' presenting signs and symptoms are related to antibiotic ADEs. We suspect a significant under-recognition and thus under-reporting of ADEs in this care environment.

Despite having limited laboratory confirmation of ADEs, PALTC clinicians are urged to identify and investigate possible signs and symptoms that may be related to antibiotics. The premise is that through increased attention and tracking ADEs, antibiotic resistance can be reduced, thereby improving medication safety for LTC residents and decreasing the emergence of antibiotic resistant microorganisms.

Clinicians often inquire why there is a need to document antibiotic ADEs.[13] The most important reason is that by documenting an antibiotic-related ADE in an individual resident, future exposure to the antibiotic can be avoided and thus subsequent ADEs prevented. When antibiotic ADEs become part of the medical record, communication between clinicians is improved and steps can be taken to avoid future occurrences. There are regulatory and accreditation standards that outline reporting requirements as a part of medication safety and quality assurance (i.e., Joint Commission on Accreditation of Health-system Organizations, Centers for Disease Control and Prevention, and CMS).[2-5,14]

As a result of the ongoing risks associated with antibiotic treatment, and knowledge that as much as 75% of antibiotics may be prescribed unnecessarily for other than true infections, several dedicated groups began working together to improve antimicrobial stewardship in PALTC residents in Maryland.[8]

A commitment was made to enhance skills and knowledge to improve practices found to contribute to inappropriate antibiotic use. At an Antimicrobial Stewardship Kick-off Summit, nursing home staff (nurses, infection control experts), pharmacists and physicians received information on the CDC antibiotic stewardship initiative, appropriate use of antibiograms, and antibiotic effectiveness, spectrum of activity, and adverse effects.[15] Quality improvement processes and implementation strategies were applied during an afternoon workshop. Follow-up online case discussions, "office hours" for consultation, and general information will be hosted by the University of Maryland, School of Pharmacy faculty with infectious diseases and geriatrics expertise. The development and implementation of a tool for documenting and reporting antibiotic ADEs was the third area of focus in antimicrobial stewardship.

Purpose of the Antibiotic Adverse Drug Event Tool

In 2016, the Maryland Department of Health Infectious Disease Epidemiology and Outbreak Response Bureau undertook the goal of improving antibiotic stewardship across healthcare settings throughout the state. In the long-term care environment, the University of Maryland was asked to partner in the dissemination of education and resources to PALTC facilities across the State.

As a part of the development of resources, the Peter Lamy Center on Drug Therapy and Aging at the University of Maryland has focused on the provision of a tool to improve identification and tracking of antibiotic ADEs. Current practice for ADE monitoring is highly variable across facilities.

This guidance document outlines recommendations for using the antibiotic ADE template to improve identification, reporting, and documentation of antibiotic ADEs. The purpose of incorporating the ADE tool into facility workflow is to:

- educate clinicians about antibiotic ADEs, their frequency, timing, manifestations and outcomes;
- provide an algorithmic approach for evaluation of possible antibiotic ADEs;
- develop a consistent workflow for evaluating antibiotic therapy to determine if ADEs have occurred;
- accurately document and report antibiotic ADEs;
- assist nursing personnel in triaging possible antibiotic ADEs to prescribers for further evaluation and development of a treatment plan;
- enhance the management of antibiotic ADEs; and
- document associated outcomes.

The application of this approach to antibiotic monitoring is fundamental to improving antimicrobial stewardship in post-acute and long-term care facilities as ADEs relate directly to patient safety.

Participants

The work product related to the Antibiotic ADE Tool evolved through the cooperative effort of several individuals and organizations that worked together to improve antimicrobial stewardship in Maryland for PALTC residents.

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ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)

Outside of *C. difficile* diarrhea, and multi-resistant organisms, little is known about the prevalence, timing, clinical presentations, and outcomes of antibiotic-related ADEs in PALTC residents. The absence of consistent approaches to identify and document ADEs, as well as the limited availability of confirmatory laboratory evidence gives rise to uncertainty about characteristics of antibiotic ADEs in this population. Information garnered in other populations is applied to nursing home residents as "best available" evidence. With the implementation of the ADE Tool, facilities will have the ability to track ADEs more efficiently and learn more about the characteristics of antibiotic adverse effects in older adults.

In a recent publication a retrospective review of antibiotic therapy in 1,488 hospitalized adults (mean age 59 years, 51% female) provides insights regarding the prevalence and timing of antibiotic ADEs.[15]

Prevalence

Twenty percent of antibiotic-treated patients experienced at least one ADE. For every additional 10 antibiotic days of therapy an additional 3% increased risk of an ADE was conferred. The prevalence and timing of each ADE category is shown in Table 1.

Timing

The median time to development of an ADE was 5 days (range, 3 – 8 days). Most (73%) ADEs occurred during the hospital stay; 27% were identified after hospital discharge.

Table 1: Prevalence, Timing, and Criteria for Antibiotic-Related ADEs in Hospitalized Adults

Classification	Prevalence	Median Time (days)	Time Interquartile Range (days)	Criteria
Gastrointestinal	78 (42%)	5	2 - 9	Diarrhea: > 3 loose stools /day N/V: associated with antibiotic
Renal	45 (24%)	5	2 - 10	Increase Scr to > 1.5 x baseline
Hematologic (Blood)	28 (15%)	12	6 - 24	Anemia: Hgb < 10 g/dL Leukopenia: WBC < 4500 cells/µL Thrombocytopenia: platelets < 150 x 10^3/µL
Hepatobiliary (Liver)	13 (7%)	8	4 - 12	Total bilirubin > 3 mg/dL, ALT/AST > 3 x baseline
Neurologic	13 (7%)	3	2 - 4	Altered mental status, peripheral neuropathy, or seizures
Cardiac (Arrhythmia)	2 (1%)	11	4 - 18	QTc > 440 msec in females QTc > 460 msec in males
Myositis (Muscle)	2 (1%)	NA	NA	Increase in creatine phosphokinase > 5 x baseline
Dermatologic (Skin)	2 (1%)	minutes to days	NA	Rash, hives, non-hive rashes, red man syndrome associated with non-vancomycin antibiotic
Anaphylaxis	1 (0.007%)	minutes	NA	Acute respiratory compromise, hypotension, or end-organ dysfunction within minutes of starting antibiotic

Among ADEs that occurred post-discharge, 11 (20%) were *C. difficile* infections and 44 (52%) were multi-drug resistant organism (MDRO) infections. The median time to development of these post-discharge ADEs was 15 days (4 – 34 days)

Manifestations and Outcomes

ADEs associated classically with recognizable signs and symptoms are gastrointestinal, skin, neurological, and anaphylaxis while some of the others, such as renal, hematological, and liver, are more dependent on observing laboratory abnormalities as a sign of the ADE. Irrespective of the presence or absence of underlying signs and symptoms, most ADEs produce mildly to moderately severe adverse effects that resolve in a few days to weeks after antibiotic discontinuation.

The presentation of signs and symptoms is often a predictable effect of a given medication class (i.e., nausea, vomiting or diarrhea with beta lactam antibiotics (e.g., ampicillin, amoxicillin-clavulanate, cephalosporins, carbapenems)) (Table 1). However, some ADEs occur unpredictably and are considered idiopathic (i.e., linezolid peripheral neuropathy).[16]

The antibiotic ADE tool provides the opportunity for the healthcare team to document the ADE and subsequently report residents' outcomes.

Table 1: Frequency of Commonly-Prescribed Antibiotic ADEs for Hospitalized Adults

Rate/ 10,000 PD	Ampicillin	Amox-clav	Amp-sulb	Oxacillin	Pip-tazo	Cefazolin	Ceftriaxone	Cefpodoxime	Cefepime	Ertapenem	Meropenem	Amino	Azithromycin	Clindamycin	Daptomycin	Doxycycline	Fluoro	Linezolid	Metronidazole	TMP-SMX	IV Vancomycin	Overall Rates
Receiving Agent	63	102	52	33	315	79	607	89	414	85	80	32	400	193	9	57	394	23	175	155	544	1488
Cardiac	0	0	0	0	0	0	0	0	0	0	0	0	0.8	0	0	0	0.9	0	0	0	0	0.4
Gastrointestinal	12	13	7.2	37.1	14.8	0	8	7.7	8.5	12.1	18	0	0.8	5.4	0	12	4.4	0	2	11.2	1.3	18.2
Hematologic	5.6	0	0	10.8	4.3	4.4	6.2	0	5	0	13	0	0	0	0	0	0.9	0	0	0	0	6.4
Hepatobiliary	0	0	0	21.6	1.1	0	2.1	0	0	0	0	0	3.4	0	0	0	2.6	0	0	0	0	2.9
Renal	5.6	0	14	0	1.1	8.2	2.8	0	5	0	0	21	0	0	0	0	0.9	0	0	13.2	12.1	10.6
Neurologic	0	0	0	0	1.1	0	0.6	0	6.7	0	4.4	0	0	0	0	0	0.9	16	2	0	0	2.9
Other event	0	0	0	0	1.1	0	0	0	0.8	0	0	0	0	0	44.8*	0	0.9	0	0	2.1	1.3	1.6
Total Rate/ 10,000 PD	23	13	21	69.5	23.5	12.6	19.7	7.7	26	12.1	35	21	5	5.4	0	12	11.5	16	4	26.5	14.7	43

where: amox-clav=amoxicillin-clavulanate; amp-sulb=ampicillin-sulbactam; pip-tazo=piperacilllin-tazobactam; amino=aminoglycosides; fluoro=fluoroquinolones; TMP-SMX=trimethoprim-sulfamethoxazole
*=myositis

Table 1 shows the rate of occurrence per 10,000 patient days for each of the prevalent ADE categories for the antibiotics reported by Tamma et al in hospitalized adults.[15]

Figure 1: Antibiotic Rate of ADEs/10,000 Patient Days

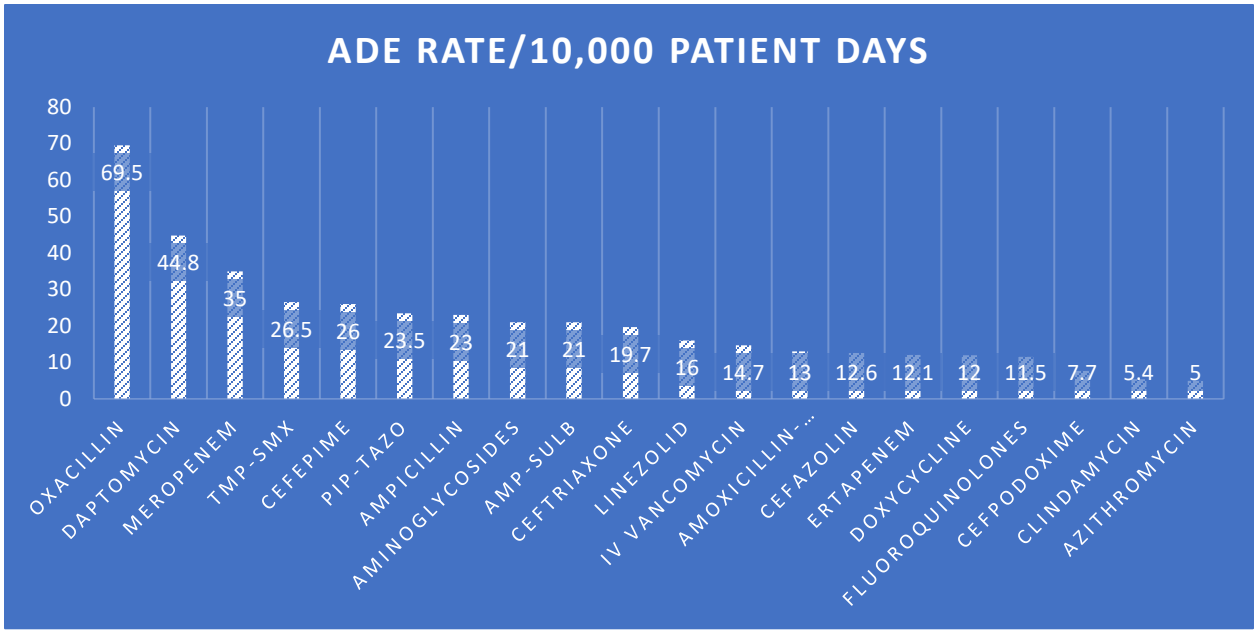


Figure 1 compares the rate of antibiotic ADEs per 10,000 patient days for the antibiotics prescribed to hospitalized adults.[15] The data are shown from the highest rate (oxacillin, 69.5) to the lowest (azithromycin, 5). While some of the ADE are mild to moderate in severity (i.e., nausea or diarrhea from beta lactam antibiotics) others are severe requiring new hospitalization (3%), prolonged hospitalization (9%), additional clinic or emergency department visits (9%), and additional laboratory tests, electrocardiograms or imaging (61%). There were no deaths attributable to any antibiotic-associated ADE in this report.

Longer-term antibiotic ADEs occurring within 90 days accounted for 43% of all ADEs in this report. The rate of *C. difficile* infection was 3.9/10,000 patient days corresponding to 4% of hospitalized adults developing *C. difficile* infection within 90 days of antibiotic initiation. The antibiotics most frequently associated with causing *C. difficile* infection were third generation cephalosporins, cefepime, and fluoroquinolones. Emergence of MDRO infections was 6.1/10,000 patient days corresponding to 6% of study patients.

Organ System Approach

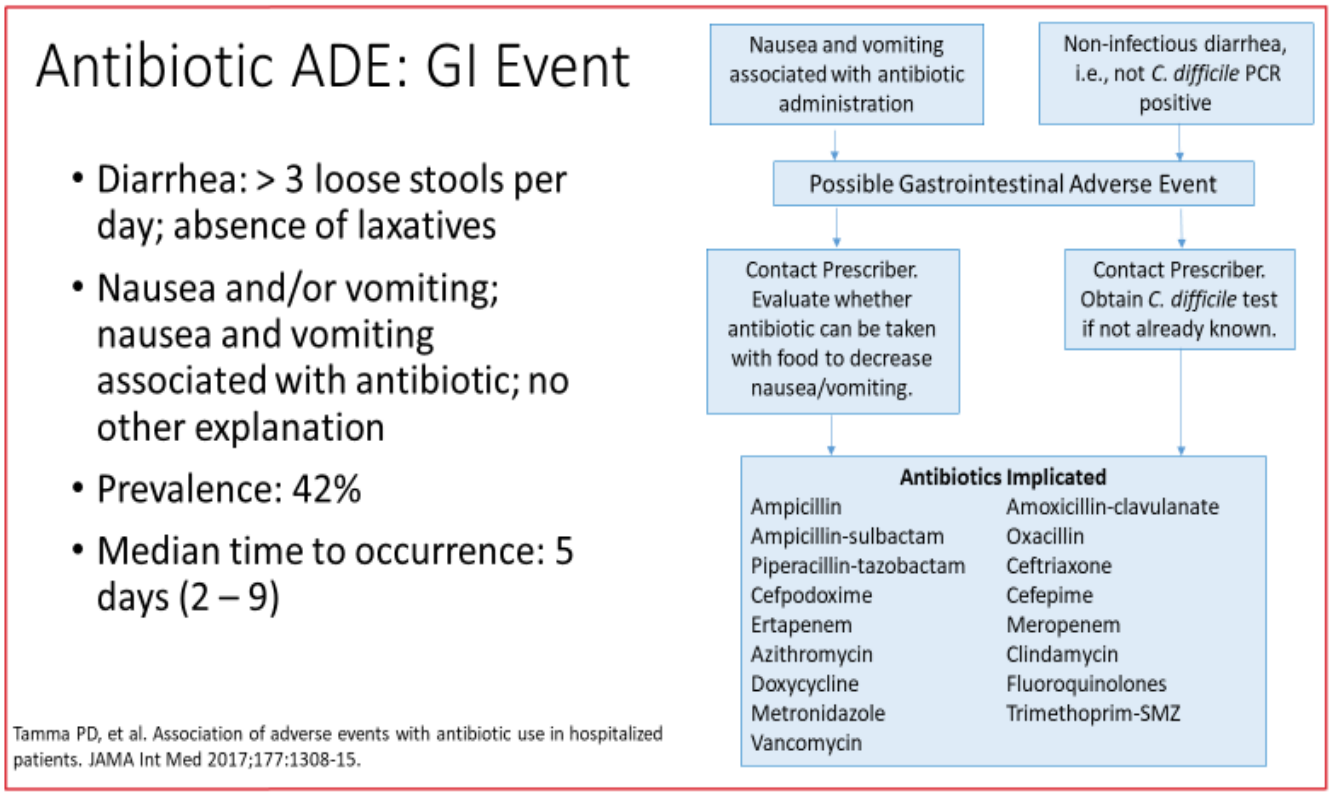
The antibiotic ADE Tool follows an organ system approach from the most prevalent to the least prevalent ADEs, beginning with gastrointestinal. For each organ system, common signs and symptoms associated with antibiotic ADEs are listed. The prevalence, timing and antibiotics associated with each ADE category are summarized with an algorithm for evaluating the resident. Nursing staff can select the signs and symptoms they identified in the resident and collect relevant information before they contact the prescriber for follow-up instructions or new orders.

COMMON ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs) BY ORGAN SYSTEM APPROACH

- **GASTROINTESTINAL**
- **RENAL**
- **HEMATOLOGICAL (BLOOD)**
- **HEPATOBILIARY (LIVER)**
- **NEUROLOGICAL**
- **MYOSITIS OR TENDINITIS**
- **CARDIOVASCULAR (ARRHYTHMIA)**
- **DERMATOLOGICAL (SKIN)**
- **ANAPHYLAXIS**
- **ANTICOAGULANT-ANTIBIOTIC INTERACTION**
- ***C. DIFFICILE* INFECTION**
- **MDRO INFECTION**

The signs and symptoms presented in the ADE tool guidance represent those most commonly associated with the specific adverse event for each relevant organ system. The antimicrobial agents implicated in causing the adverse event represent those most likely associated with causing the ADE but should not be considered a comprehensive list of all antimicrobials that could cause adverse signs and symptoms. Individual patient responses and clinical characteristics can vary and may predispose to alternative signs and symptoms. Administration of antimicrobial medications should be assumed capable of producing any adverse event in any given patient.

GASTROINTESTINAL ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)



Assessment of possible anti-infective related adverse event observed (select all that apply):

☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Abdominal tenderness/pain
☐ Distended abdomen ☐ Increased bowel sounds ☐ Infectious diarrhea (*C. difficile)*
☐ Other

1. Possible Gastrointestinal Event

Provide details:

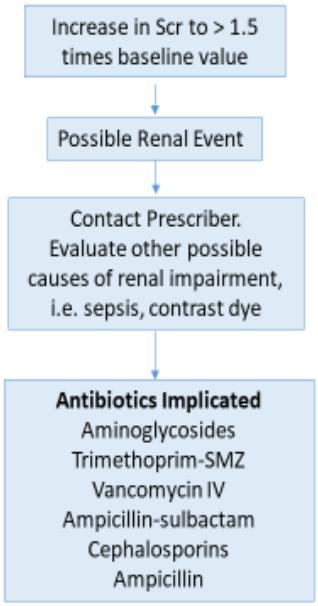
Date Observed _____

Nursing staff observes and/or asks resident about the presence of any gastrointestinal signs and symptoms and selects all that apply. Details can be provided in free text (i.e., 3 bouts of loose stool/diarrhea and nausea today). The date of observation should be recorded.

RENAL ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)

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.

Assessment of possible anti-infective related adverse event observed (select all that apply):

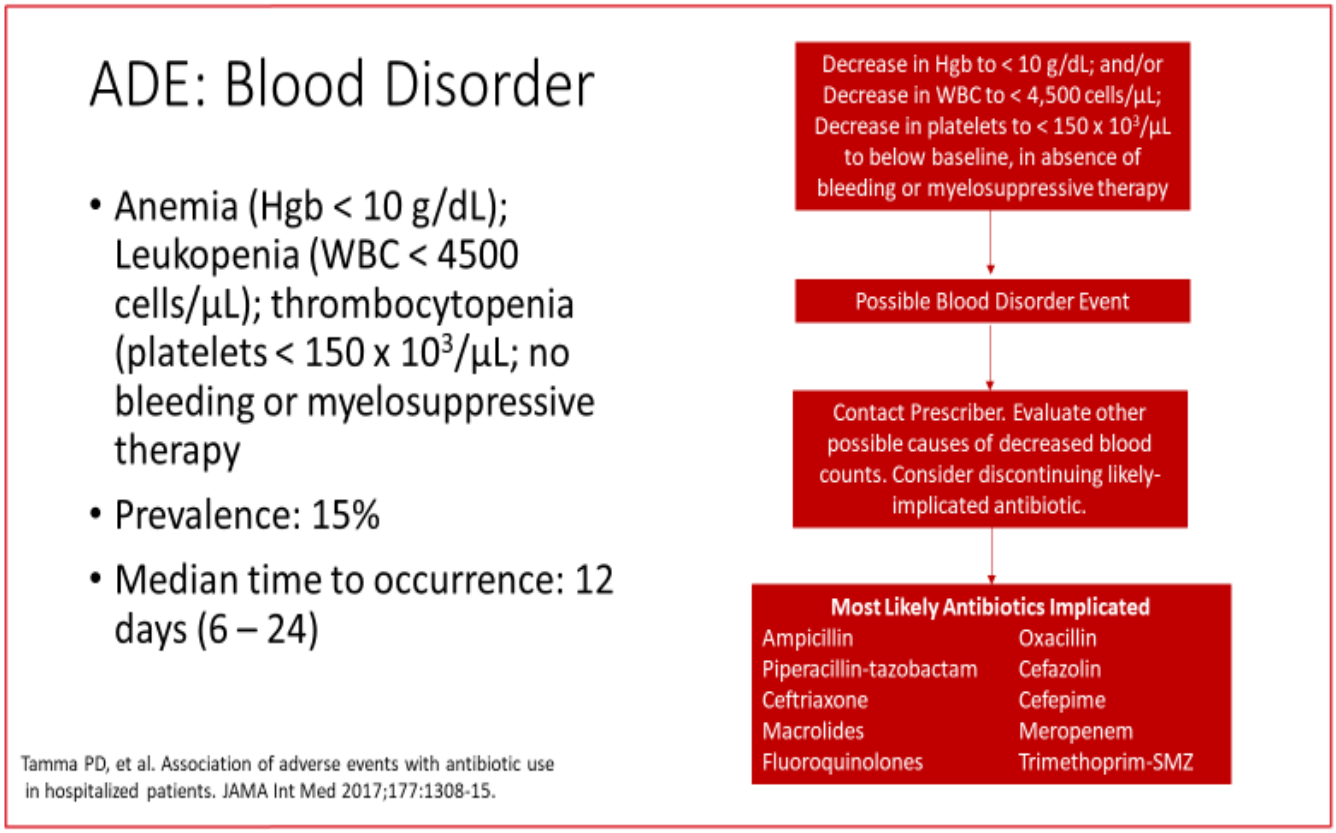
☐ Decreased urine output ☐ Painful urination ☐ Blood in urine ☐ Other

2. Possible Renal Event
Provide details:

Date Observed _____

The resident may not report these signs and symptoms prior to a significant increase in the serum creatinine value. For the antibiotics noted above, serum creatinine should be monitored at least weekly while the resident receives the antibiotic.

HEMATOLOGICAL (BLOOD) ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)



Assessment of possible anti-infective related adverse event observed (select all that apply):

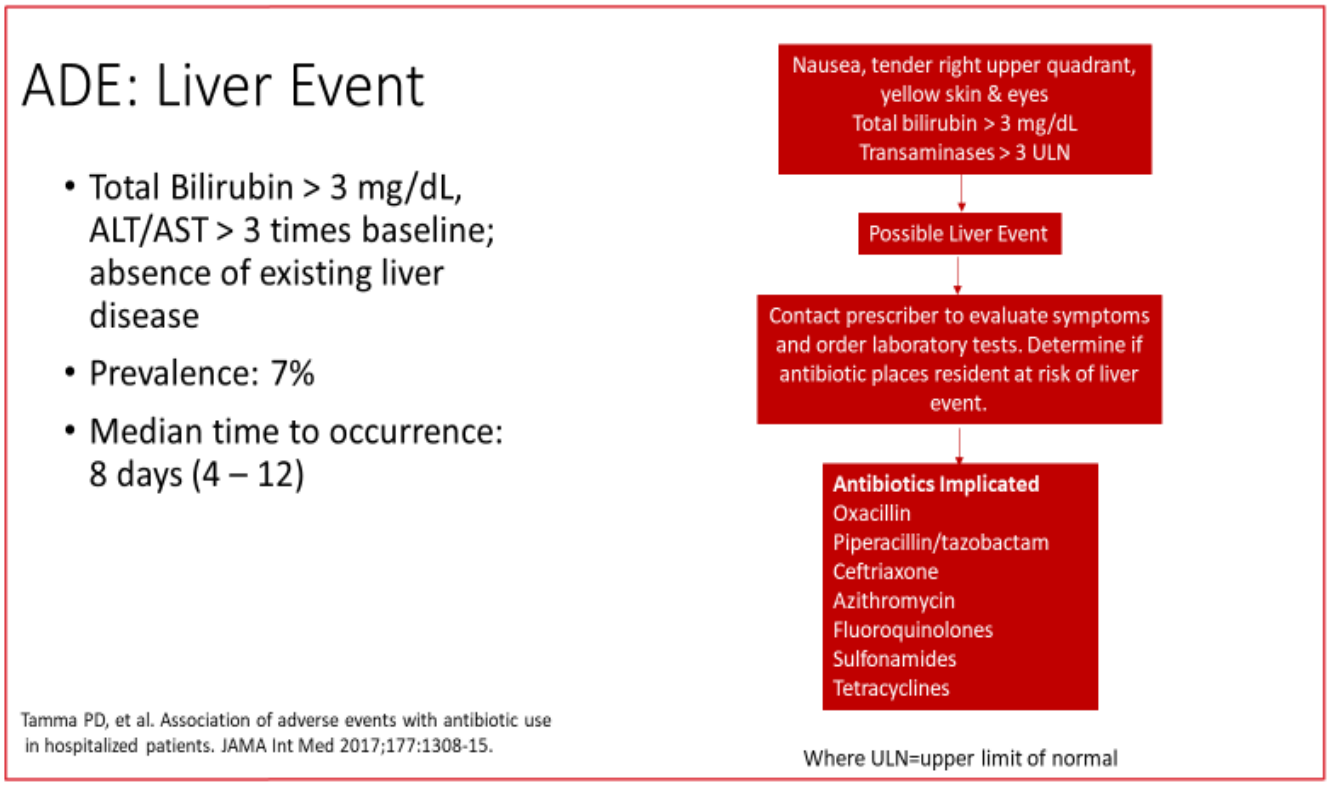
☐ Fatigue ☐ Bleeding ☐ Delayed clotting ☐ Bruising ☐ Other

3. Possible Blood Event
Provide details:

Date Observed _____

Adverse hematological effects are generally detected by laboratory abnormalities. Signs and symptoms may occur at the same time or later. Residents receiving the antibiotics noted above should have a complete blood count obtained weekly.

HEPATOBILIARY (LIVER) ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)



Assessment of possible anti-infective related adverse event observed (select all that apply):

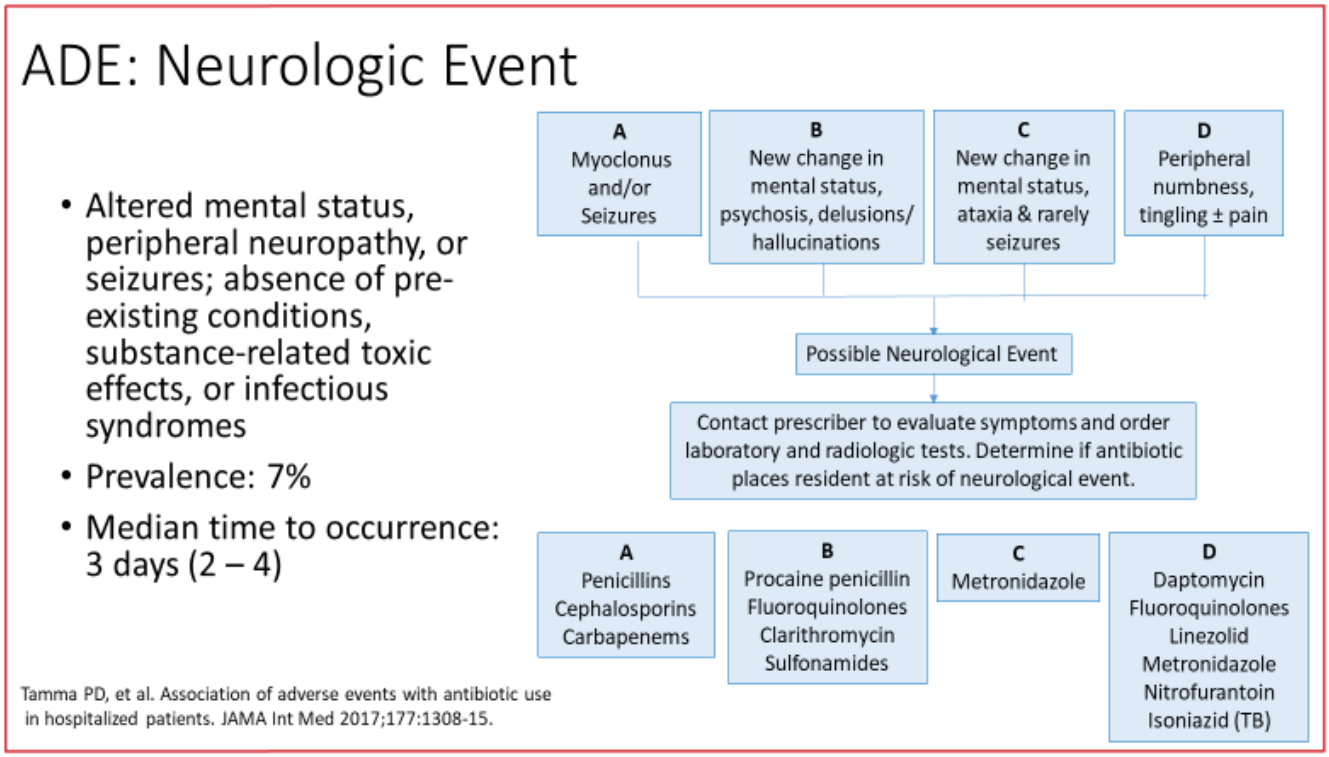
☐ Abdominal tenderness/pain ☐ Nausea/vomiting ☐ Decreased appetite
☐ Yellow skin or eyes ☐ Other

4. Possible Liver Event
Provide details:

Date Observed _____

Nursing staff should observe residents and ask about signs and symptoms of liver ADEs. Total serum bilirubin, ALT and AST should be obtained weekly for residents receiving antibiotics noted above.

NEUROLOGICAL ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)



Assessment of possible anti-infective related adverse event observed (select all that apply):

☐ Dizziness ☐ Confusion ☐ Hypoactive, difficulty arousing ☐ Delirium ☐ Delusions
☐ Hallucinations ☐ Spasmodic jerky muscle movements (myoclonus) ☐ Peripheral numbness & tingling
☐ Seizure(s) ☐ Other

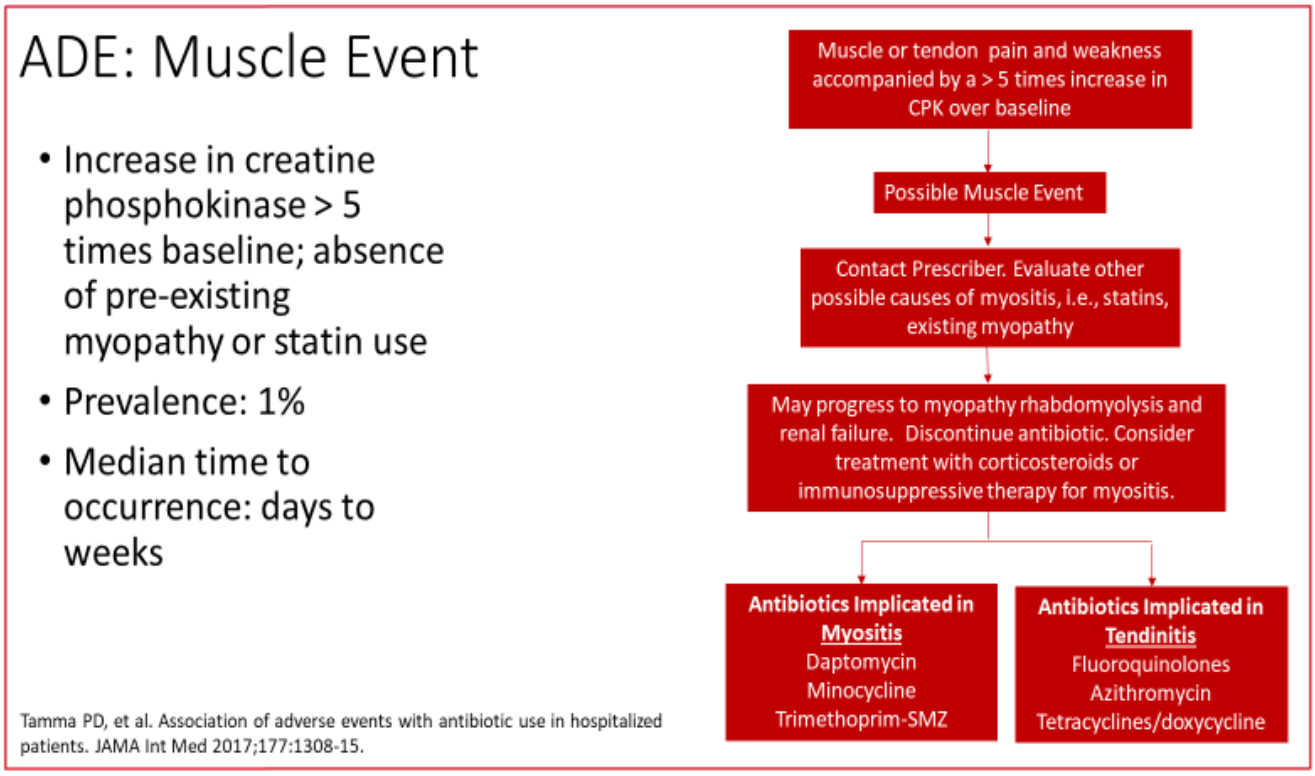
5. Possible Neurological Event
Provide details:

Hallucinations are a sensory experience without a stimulus.
Delusions are fixed false beliefs held despite evidence to the contrary.

Date Observed _____

There are 4 primary patterns (A, B, C, and D) of neurological toxicity associated with antibiotics. Nursing staff should record the observed signs and symptoms and contact the prescriber to order appropriate interventions.

MYOSITIS (MUSCLE) ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)



Assessment of possible anti-infective related adverse event observed (select all that apply):

☐ Muscle pain ☐ Muscle weakness ☐ Tendon pain (e.g. Achilles tendon) ☐ Other

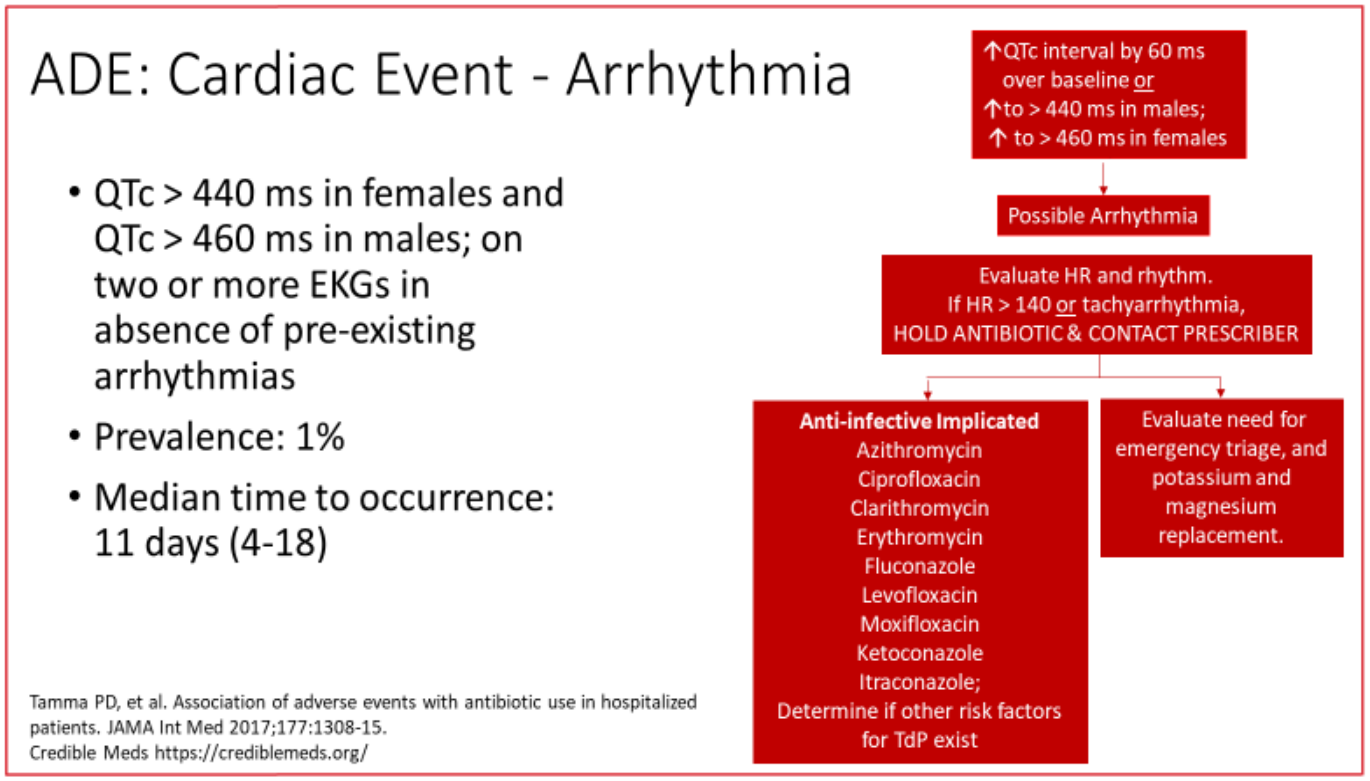
6. Possible Muscle Pain/Muscle Weakness/Myositis

Provide details:

Date Observed _____

For residents receiving the antibiotics listed above, nurses should ask about muscle pain and weakness and contact the prescriber to evaluate for possible myositis. This can be a very serious adverse effect.

CARDIOVASCULAR (ARRHYTHMIA) ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)



Assessment of possible anti-infective related adverse event observed (select all that apply):

☐ Fast heart rate ☐ Low blood pressure ☐ QTc interval > 500 msec
☐ Palpitations ☐ Dizziness ☐ Syncope (fainting) ☐ Other

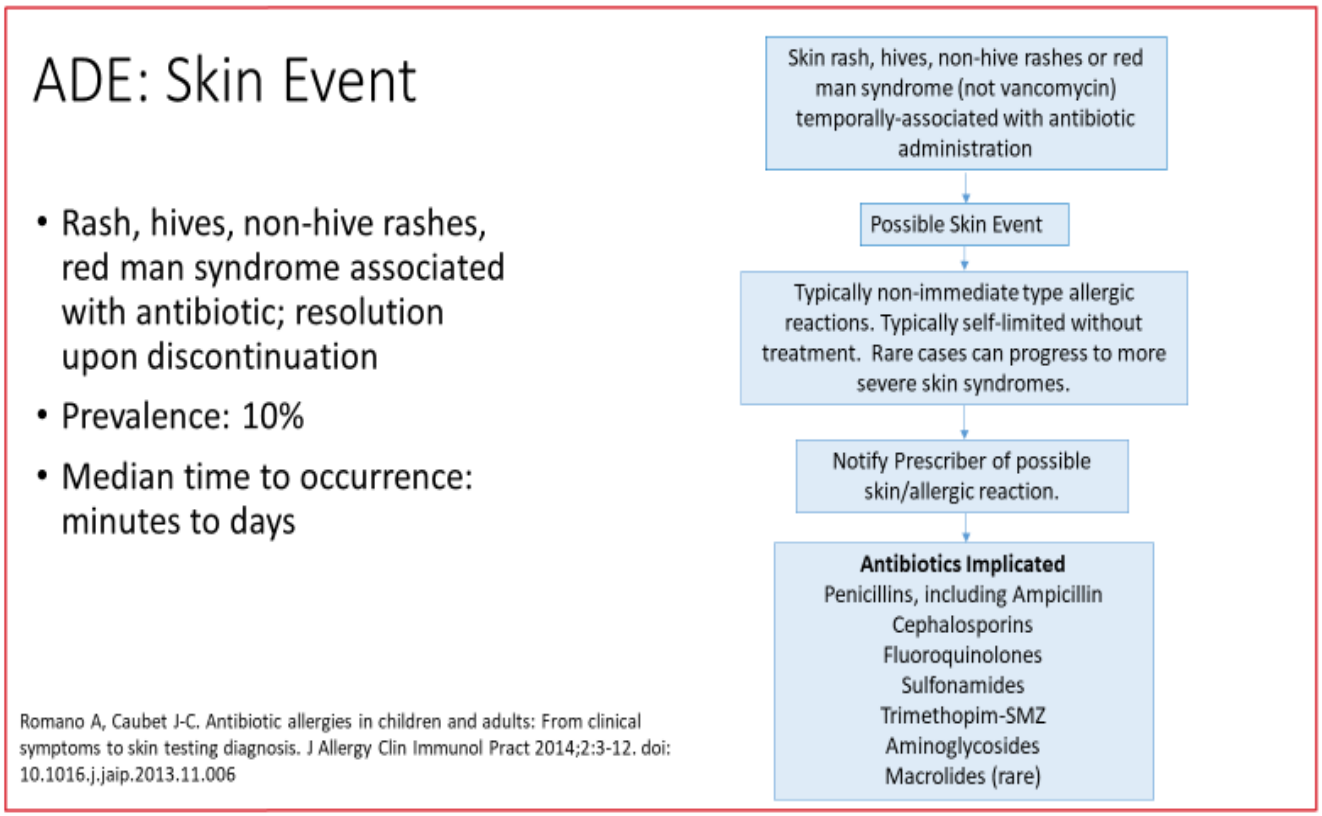
7. Possible Arrhythmia Event

Provide details (including onset of ADE relative to drug administration, actions taken):

Date Observed _____

While the diagnosis of QTc interval prolongation requires an electrocardiogram, residents experiencing this ADE can present with a fast heart rate, low blood pressure, palpitations, dizziness and fainting. This ADE should be triaged as a medical emergency.

DERMATOLOGICAL (SKIN) ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)



Assessment of possible anti-infective related adverse event observed (select all that apply):

☐ Rash ☐ Hives/wheal/flare ☐ Erythema (skin redness) ☐ Pruritis (itchiness) ☐ Other

8. Skin/Dermatological Event

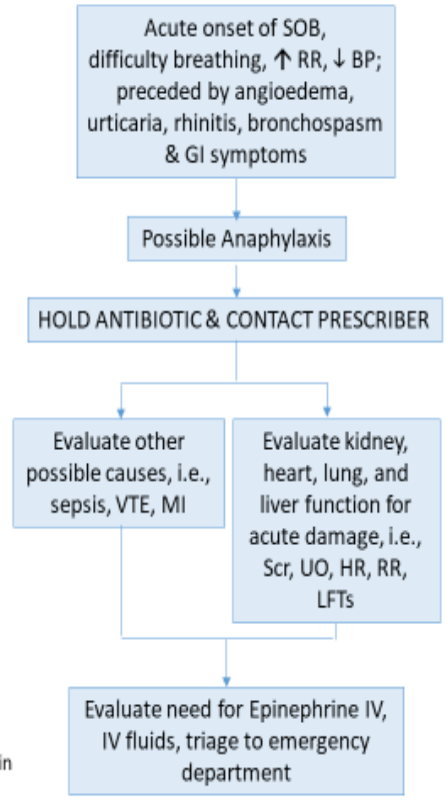
Provide details:

Date Observed _____

ANAPHYLAXIS (SEVERE ALLERGY) ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)

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)



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

Assessment of possible anti-infective related adverse event observed (select all that apply):

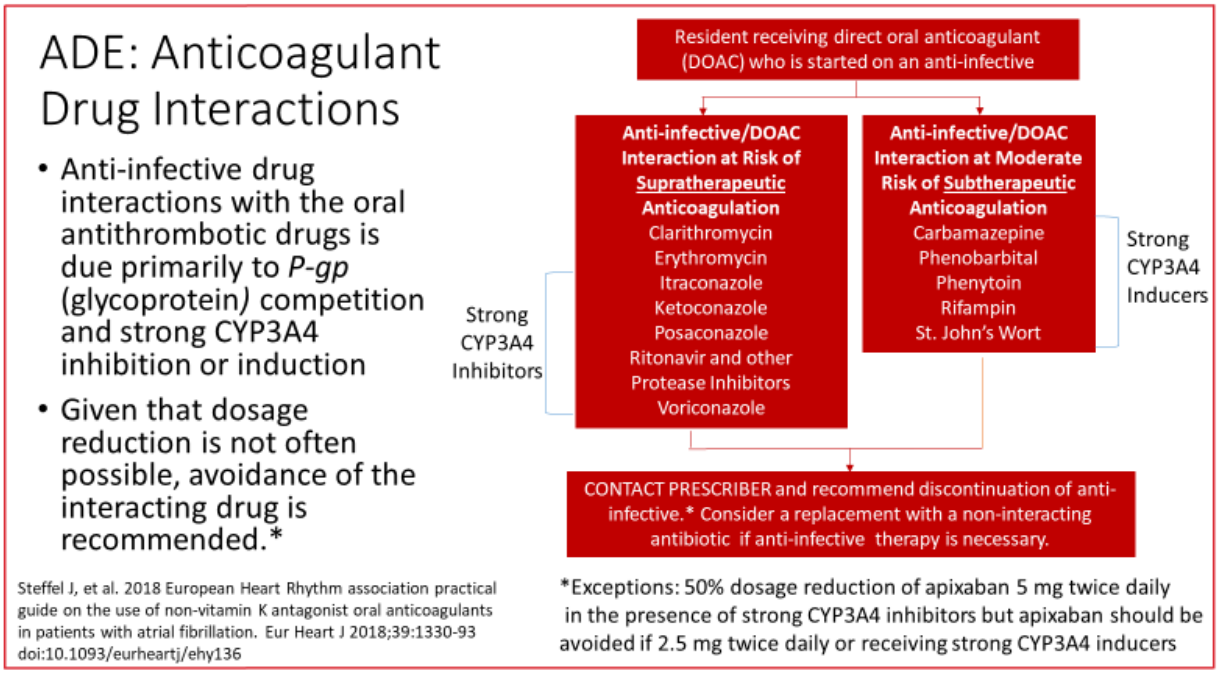
☐ Hives, wheal and flare ☐ Labored breathing
☐ Systolic BP < 90 mm Hg

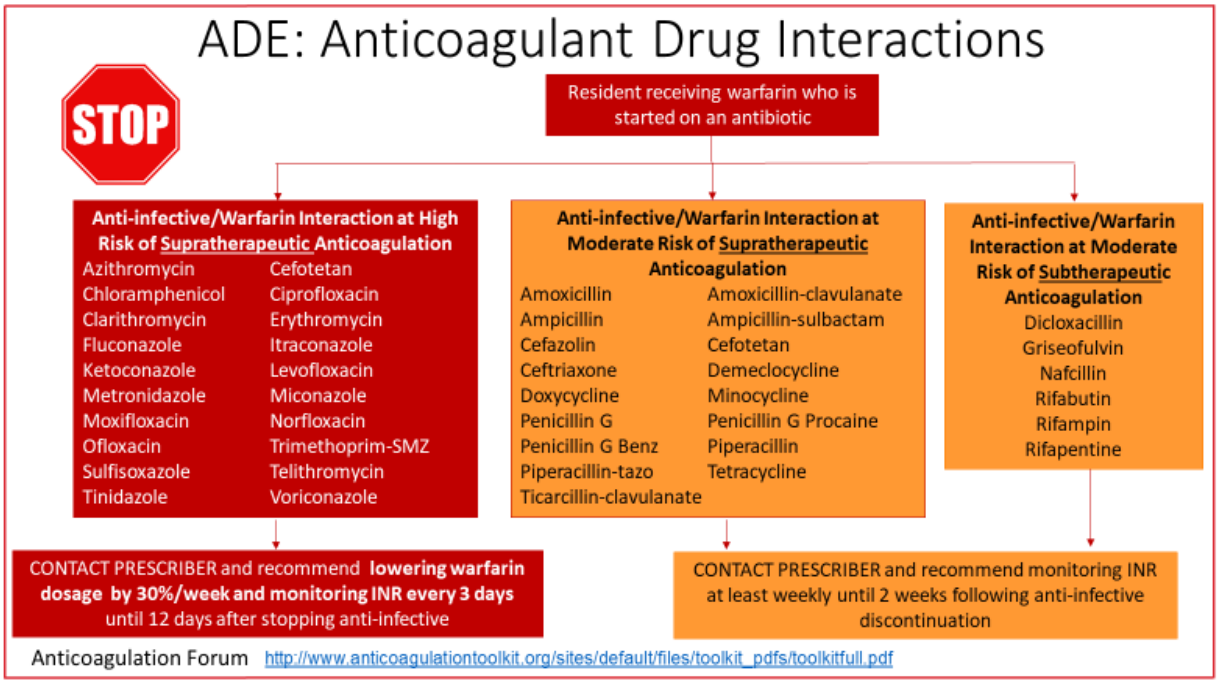
9. Possible Anaphylaxis
Provide details (including onset of ADE relative to drug administration, actions taken):

Residents presenting with these signs and symptoms within a few minutes to an hour after administration of the first dose of the antibiotic may be experiencing an anaphylactic reaction. They should be triaged immediately by dialing 911.

Date Observed _____

ANTICOAGULANT ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)





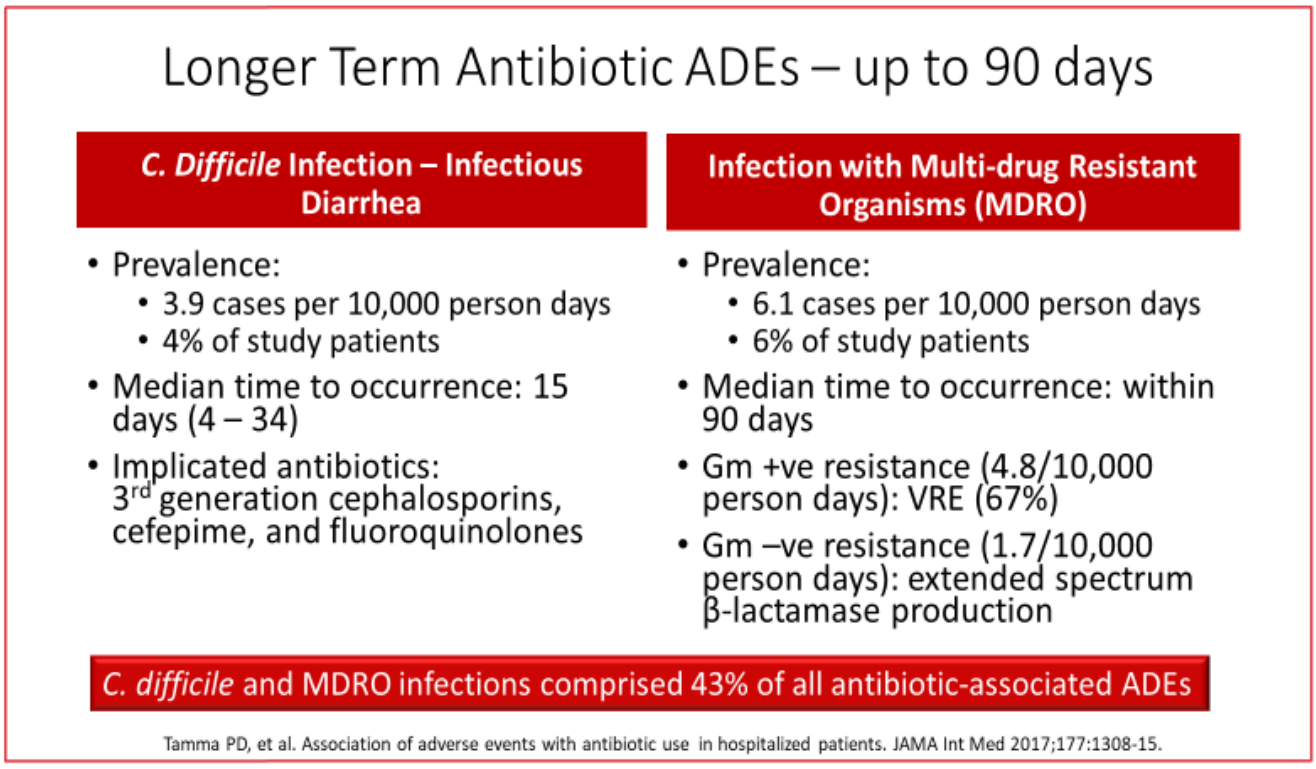
ANTICOAGULANT ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)

1. Anti-infective-anticoagulant drug interaction

Document interacting anti-infective(s) and if appropriate action(s) have been taken to address interaction:

Active anticoagulant (select all that apply):

- ☐ warfarin (Coumadin)
- ☐ rivaroxaban (Xarelto)
- ☐ apixaban (Eliquis)
- ☐ edoxaban (Savaysa)
- ☐ dabigatran (Pradaxa)



C. DIFFICILE INFECTION: ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)

2. *C. difficile* Infectious Diarrhea

(Compared to baseline; check all that you observe.)

☐ Diarrhea ☐ Abdominal pain ☐ Increased bowel sounds ☐ Other
☐ *C. difficile* test_____ date _____
Provide details:

Date Observed _____

MULTI-DRUG RESISTANT ORGANISM INFECTIONS: ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs)

3. Multi-drug resistant organism (MDRO) infection(s)

Identify type of multi-drug resistant (MDRO) infection(s):

- ☐ methicillin-resistant *S. aureus* (MRSA)
- ☐ vancomycin-resistant *Enterococci* (VRE)
- ☐ carbapenem-resistant *Enterobacteriaceae* (CRE)
- ☐ MDR *Acinetobacter*
- ☐ MDR *Pseudomonas*
- ☐ Extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*
- ☐ other _____

How many anti-infectives has the resident received in the last 90 days?

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ other

Provide details of anti-infectives (i.e., dose, duration, frequency, indication, start and end dates):

Date Observed _____

OPTIMIZING MEDICATION SAFETY THROUGH THE USE OF AN ANTIBIOTIC ADVERSE DRUG EVENTS (ADEs) TOOL

The Antibiotic ADE Tool is annotated on the next several pages to demonstrate the recommended use of the tool. For the purposes of illustration, the following case has been created. Appendix 1 contains a blank, non-annotated version of the ADE Tool for your use.

CASE

Ms. MK is a 92 year old female who was sent from her long-term care facility to the hospital for completion of treatment for a complicated urinary tract infection (UTI). In addition to the UTI she has a history of heart failure, dementia, and chronic obstructive pulmonary disease (COPD). Her medications are listed in the table below.

Medications

Medication	Dose
Digoxin	0.125 mg p.o. every other day
Furosemide (Lasix)	40 mg p.o. daily
Lisinopril	10 mg p.o. daily
Metoprolol Succinate (Toprol XL)	50 mg p.o. daily
Donepezil (Aricept)	10 mg p.o. daily
Vitamin D_3	2,000 iu p.o. once daily
Tiotropium Handihaler (Spiriva)	18 mcg (2 puffs) once daily by inhalation
Albuterol Inhaler (ProAir HFA)	180 mcg (2 puffs) by inhalation as needed for shortness of breath
Ciprofloxacin (Cipro)	500 mg p.o. every 12 hours x 10 days

She received 7 days of ciprofloxacin I.V. in the hospital and then was transferred back to the nursing home on all of the same medications, but the ciprofloxacin was changed from intravenous to oral administration.

On day 7 of ciprofloxacin (Cipro) therapy her nurse observes new, extensive watery diarrhea. The diarrhea occurs every couple of hours causing abdominal pain. The only new medication she started was the ciprofloxacin. The nurse looks back 7 days at her laboratory results and finds a positive test for *C. difficile.* He/she begins to complete an antibiotic ADE and calls her doctor for instructions.

The Antibiotic ADE is completed with annotations on the next several pages.

Sample Annotated ADE Tool

Optimizing Medication Safety 4.0 Annotated 11/23/2018

Client:_____ Location:_____

A. ASSESSMENT

1. Demographics

a. Allergies

Known allergies should be documented before administration of any new medication, particularly antibiotics.

b. Active Diagnoses (from most recent history/physical)

Active diagnoses are helpful to prevent confusing new signs and symptoms with a change in an underlying condition. These should be taken from the most recent history and physical

Basic demographic information is needed to calculate creatinine clearance and determine if the antibiotic dose is correct.

Date of Birth: 07/06/1926 (DD/MM/YYYY) Age 92

Most Recent Weight: 49 kg Scale:_____ Date: 10/1/2018

Most Recent Height: 5'2" Method:_____ Date:_____

Creatinine Clearance: 30.9 mL/min Date of Creatinine: 10/18/2018

New or Change in Signs and Symptoms

Emergencies should be handled first as emergencies.

A. If this is an emergency, take immediate action and notify **PRESCRIBER**.

B. Assessment of possible anti-infective related adverse event observed (select all that apply):

In all of section B, the nurse should identify any new, relevant signs and symptoms, provide details of the ADE(s) and the date observed and take appropriate follow-up action. The focus is on a change that occurred after starting the antibiotic(s).

☐ Nausea ☐ Vomiting ☑ Diarrhea ☑ Abdominal tenderness/pain
☐ Distended abdomen ☑ Increased bowel sounds ☑ Infectious diarrhea (*C. difficile*)
☐ Other

1. Possible Gastrointestinal Event

Provide details:

C. difficile suspected based on watery diarrhea and presence of positive *C. diff* test.

Date Observed _____

☐ Decreased urine output ☐ Painful urination ☐ Blood in urine ☐ Other

2. Possible Renal Event

Provide details:

Date Observed _____

Sample Annotated ADE Tool

Optimizing Medication Safety 4.0 Annotated 11/23/2018

Client:_____ Location:_____

In all of section B, the nurse should identify any new relevant signs and symptoms, provide details of the ADE(s) and the date observed and take appropriate follow-up action. The focus is on changes from baseline that occurred after starting the antibiotic(s).

☐ Fatigue ☐ Bleeding ☐ Delayed clotting ☐ Bruising ☐ Other

3. Possible Blood Event

Provide details:

Date Observed _____

☐ Abdominal tenderness/pain ☐ Nausea/vomiting ☐ Decreased appetite

☐ Yellow skin or eyes ☐ Other

4. Possible Liver Event

Provide details:

Date Observed _____

☐ Dizziness ☐ Confusion ☐ Hypoactive, difficulty arousing ☐ Delirium ☐ Delusions

☐ Hallucinations ☐ Spasmodic jerky muscle movements (myoclonus) ☐ Peripheral numbness & tingling

☐ Seizure(s) ☐ Other

5. Possible Neurological Event

Provide details:

Hallucinations are a sensory experience without a stimulus.
Delusions are fixed false beliefs held despite evidence to the contrary.

Date Observed _____

☐ Muscle pain ☐ Muscle weakness ☐ Tendon pain ☐ Other

6. Possible Muscle Pain/Muscle Weakness/Myositis

Provide details:

Tendon pain – for example, Achilles tendon.

Date Observed _____

Sample Annotated ADE Tool

Optimizing Medication Safety 4.0 Annotated 11/23/2018

Client:_____ Location:_____

In all of section B, the nurse should identify any new relevant signs and symptoms, provide details of the ADE(s) and the date observed and take appropriate follow-up action. The focus is on changes from baseline that occurred after starting the antibiotic(s).

☐ Fast heart rate ☐ Low blood pressure ☐ QTc interval > 500 msec
☐ Palpitations ☐ Dizziness ☐ Syncope (fainting) ☐ Other

7. Possible Arrhythmia Event

Provide details (including onset of ADE relative to drug administration, actions taken):

Date Observed _____

☐ Rash ☐ Hives/wheal/flare ☐ Erythema (skin redness) ☐ Pruritis (itchiness) ☐ Other

8. Skin/Dermatological Event

Provide details:

Date Observed _____

☐ Hives, wheel and flare ☐ Labored breathing
☐ Systolic BP < 90 mm Hg ☐ Other

9. Possible Anaphylaxis

Provide details (including onset of ADE relative to drug administration, actions taken):

Date Observed _____

10. Other Event

Provide signs and symptoms noted:

Date Observed _____

Sample Annotated ADE Tool

Optimizing Medication Safety 4.0 Annotated 11/23/2018

Client:_____ Location:_____

3. Laboratory Values

A. Current (within the past 14 days) laboratory values (related to ADE):

Renal Event	☐ 1. Serum creatinine	Date Obtained _____
Blood Event	☐ 2. WBC	Date Obtained _____
	☐ 3. Hemoglobin	Date Obtained _____
	☐ 4. Platelets	Date Obtained _____
Liver Event	☐ 5. Total bilirubin	Date Obtained _____
	☐ 6. AST/ALT	Date Obtained _____
Muscle Event	☐ 7. Creatinine phosphokinase (CPK)	Date Obtained _____
C. difficile Infection	☑ 8. *C. difficile* test	Date Obtained 10/18/2018
	☐ 9. Other	Date Obtained _____

Renal, blood, liver, and muscle ADEs and *C. difficile* infections are likely to have laboratory values available that will help make the diagnosis. If they are not available, it is likely that the prescriber will order the relevant laboratory test(s) corresponding to the suspected ADE event.

4. Current anti-infectives resident is receiving (anti-infective may have been started in the hospital):

Brand Name	Generic Name	Start Date	Stop Date
Cipro	ciprofloxacin	10/18/2018	10/28/2018

It is common for residents to receive two or more antibiotics at the same time. All antibiotics, and their start and planned stop dates, should be recorded.

5. Discussion with Prescriber

Recommendation to the Prescriber:

☑ Discontinue suspected anti-infective ☐ Replace with alternative medication ☐ Change dose/ frequency/route of administration ☐ Other

☐ No further action at this time

Provide details, including follow-up plan (if applicable):

Has had 7 days of ciprofloxacin. Should another antibiotic be used instead to complete the 10 day course?

While the nurse is not making the diagnosis, he/she can use their professional knowledge and experience to assess the severity of the ADE and suggest a plan to the prescriber.

B. INTERVENTION

1. Suspected Anti-infective Ciprofloxacin

2. Course of Action and Follow-up

☑ Discontinue suspected medication _____
☐ Replace with alternative medication _____
☐ Change dose/frequency/route of administration _____
☐ Other _____
☐ No further action at this time

This section is generally completed by the prescriber or by the nurse following discussion with the prescriber.

Provide details, including follow-up plan (if applicable):

Rehydrated, supportive measures instituted.

Sample Annotated ADE Tool

Optimizing Medication Safety 4.0 Annotated 11/23/2018

Client:_____ Location:_____

C. ADDITIONAL REVIEW AND EVALUATION

This section is generally completed by the pharmacist or infection preventionist following the course of antibiotic therapy.

1. Estimated Creatinine Clearance _____ mL/min Date _____

2. Other Possible Adverse Anti-infective Events

A. Evaluate if the resident has experienced an anti-infective related ADE:

1. Anti-infective-anticoagulant drug interaction

Document interacting anti-infective(s) and if appropriate action(s) have been taken to address interaction:

Active anticoagulant (select all that apply):

- ☐ warfarin (Coumadin)
- ☐ rivaroxaban (Xarelto)
- ☐ apixaban (Eliquis)
- ☐ edoxaban (Savaysa)
- ☐ dabigatran (Pradaxa)

2. Multi-drug resistant organism (MDRO) infection(s)

Infection with an MDRO generally occurs later after the first course of antibiotics is finished.

Identify type of MDRO infection(s):

- ☐ methicillin-resistant *S. aureus* (MRSA)
- ☐ vancomycin-resistant *Enterococci* (VRE)
- ☐ carbapenem-resistant *Enterobacteriaceae* (CRE)
- ☐ MDR *Acinetobacter*
- ☐ MDR *Pseudomonas*
- ☐ Extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*
- ☐ Other _____

How many anti-infectives has the resident received in the last 90 days?

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ other

Provide details of anti-infectives (i.e., dose, duration, frequency, indication, start and end dates):

Date Observed _____

Sample Annotated ADE Tool

Optimizing Medication Safety 4.0 Annotated 11/23/2018

Client:_____ Location:_____

3. *C. difficile* infectious diarrhea (Compared to baseline; check all that you observe.)

☐ Diarrhea ☐ Abdominal pain ☐ Increased bowel sounds ☐ Other

☐ *C. difficile* test_____ date _____

Provide details:

Date Observed _____

Infection with *C. difficile* generally occurs later and may occur after the first course of antibiotics is finished.

4. Other

Provide details:

Date Observed _____ Suspected Anti-infective _____

This section is available to record any other antibiotic ADE(s) that may be detected by the pharmacist or infection preventionist.

3. Category of Possible Anti-infective Adverse Drug Event

Predictable Preventable ADEs

☐ Allergy

☑ Anticipated/Expected/Dose-related

☐ Idiosyncratic/Unanticipated/Unpredictable

The pharmacist or infection preventionist should choose the category of antibiotic ADE. Subsequently, root cause analysis can be performed to identify strategies to minimize allergic reactions and predictable/preventable ADEs.

4. Event Outcome (Hartwig Severity Assessment Scale)[1]

The Hartwig scale is a reliable and valid way to categorize event outcomes. This section should be completed by the pharmacist or infection preventionist following the ADE.

☐ Level 1. Resolved, no residual harm. No change in treatment was needed.

☐ Level 2. Resolved with suspected anti-infective held, discontinued or otherwise changed.

☑ Level 3. Resolved with suspected anti-infective held, discontinued or otherwise changed AND/OR an antidote or other treatment was required.

☐ Level 4. Any Level 3 ADE which causes hospitalization or increases length of stay by at least 1 day.

☐ Level 5. Any Level 4 ADE which requires intensive medical care.

☐ Level 6. The ADE caused permanent harm to the resident.

☐ Level 7. The ADE either directly or indirectly led to the death of the resident.

Resulting Severity of the ADE

☐ A. Mild Event: Levels 1 and 2

☑ B. Moderate Event: Levels 3 and 4

☐ C. Severe Event: Levels 5, 6 and 7

The severity of the ADE is determined by the numerical Level.

5. EMR Documentation

☑ This adverse event should be documented in the resident's medical record to help avoid future exposure and adverse events.

1.Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reac

Unless the ADE Tool is a permanent part of the resident's medical record, this box should be checked to assure that that ADE is transcribed into the EMR.

ASSESSING AND DOCUMENTING OUTCOMES OF ANTIBIOTIC ADVERSE DRUG EVENTS (ADEs)

The Hartwig Severity Assessment Scale is useful to document outcomes associated with the ADE.[17] Outcomes can range from no permanent sequelae to permanent damage or death. The Hartwig Scale allows the evaluator to quantify the severity of the ADE by documenting whether or not hospitalization was required and for residents hospitalized, whether they were admitted to an intensive care unit. In PALTC, evaluators may be unable to obtain details on what occurred during a hospitalization, but they can document whether hospitalization was required.

Table 2: The Hartwig Severity Assessment Scale – Event Outcome

Severity	Description
Level 1	Resolved; no residual harm. No change in treatment was needed.
Level 2	Resolved with suspected antimicrobial held, discontinued or otherwise changed.
Level 3	Resolved with suspected antimicrobial held, discontinued or otherwise changed AND/OR an antidote or other treatment was required.
Level 4	Any Level 3 ADE which causes hospitalization or increases length of stay by at least one (1) day.
Level 5	Any Level 4 ADE which requires intensive medical care.
Level 6	The ADE caused permanent harm to the resident.
Level 7	The ADE either directly or indirectly led to the death of the resident.

Table 3: Resulting Severity of the ADE

Mild Event	Levels 1 and 2
Moderate Event	Levels 3 and 4
Severe Event	Levels 5, 6, and 7

Events are rated mild, moderate or severe, based on the corresponding Level of severity in Table 2.

For the case study depicted on the annotated ADE tool, because the resident was sent back to the hospital by the physician, the severity Level is 4 and the ADE is considered **a moderate event** (Table 3).

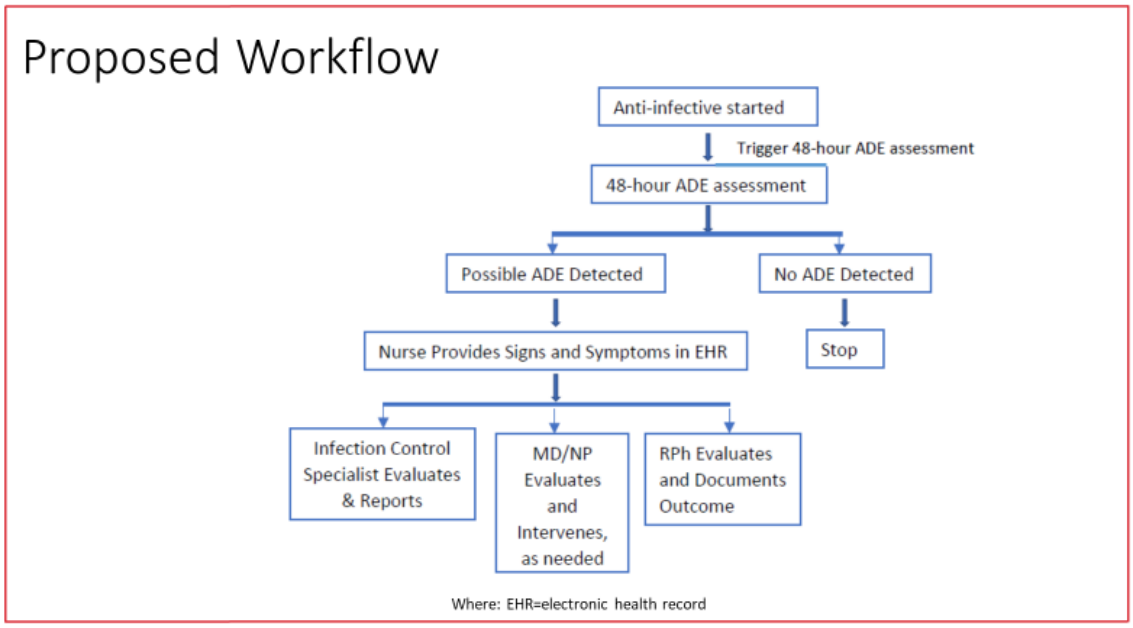
SUGGESTED ANTIBIOTIC-RELATED ADVERSE DRUG EVENTS (ADEs) MONITORING WORKFLOW

Documentation of ADEs may be occurring several ways in nursing homes. They may be recorded as a part of the permanent medical record, a quality web site, or by using the INTERACT SBAR form to notify the prescriber of a possible ADE.[18] In order to capture information about ADEs so future events can be prevented, it is important to collect information such as:

- name, dose, route of administration and frequency of drug administration;
- the date the antibiotic was started and how many days of therapy the resident has received;
- signs and symptoms associated with the ADE;
- abnormal laboratory values associated with the ADE;
- action(s) taken following identification of the ADE;
- date on which the ADE was first observed; and
- name and title of the healthcare worker that observed and documented the ADE.

This information is generally noted by the nurse at the bedside. When a resident has a change in condition (i.e., an infection) that requires starting an antibiotic, the resident's care plan generally outlines follow-up monitoring to assess whether the resident is responding to the antibiotic and the infection is getting better. It is during this assessment, that monitoring for a possible antibiotic-related adverse events should be performed. Care plans may outline follow-up monitoring at 48 – 72 hours, which provides sufficient time for most antibiotics to begin taking effect and for the resident to show a response to therapy, (i.e., defervesce if febrile, etc.), or possible toxicity.[19]

Figure 2: Proposed ADE Monitoring Workflow



After the nurse has documented the ADE and contacted the prescriber for follow-up instruction(s) and new orders as may be necessary, either the infection preventionist or the consultant pharmacist can be alerted to evaluate the severity of the infection, calculate creatinine clearance, and review the resident's chart for any other ADEs that may be occurring, such as an antibiotic-anticoagulant drug interaction, or infection with *C. difficile* or a MDRO.

Creatinine clearance is a valuable way to assess renal function for assessment of antibiotic doses. Many antibiotics are excreted from the body by the kidneys and thus creatinine clearance provides the best way to assess when dosing reductions may be necessary. Many antibiotic ADEs are dose-related and can be avoided when appropriate dose reductions are made for residents with renal impairment. Examples of dose-related ADEs include:

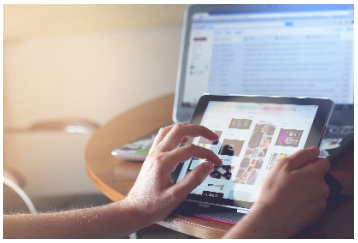
- renal impairment caused by aminoglycosides (gentamicin, tobramycin, amikacin);
- seizures caused by penicillins;
- arrhythmia (QTc interval prolongation) caused by fluoroquinolones (ciprofloxacin, levofloxacin moxifloxacin) and macrolides (erythromycin, clarithromycin, azithromycin); and
- mental status changes, delusions, and hallucinations caused by fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and penicillins.

Documentation of ADEs in the medical chart is important to inform the entire healthcare team such that future exposure to the offending antibiotic can be avoided by selecting a different antibiotic and/or using a lower, but therapeutic dose of the antibiotic.

As part of antimicrobial stewardship, the CDC has recommended documenting ADEs, including occurrences of *C. difficile* and MDRO infections. Through ongoing monitoring, the healthcare community can identify ways to lower ADE risk and reduce resident harm.

Sample reports or clinical dashboards could include trended information, such as:

- the number of ADE/10,000 patient days;
- % of antibiotic-treated residents that experience an ADE;
- % of ADEs that are mild, moderate or severe;
- occurrence of ADEs per antibiotic class; and
- ADE outcomes, such as % ADEs resulting in transfer to the hospital.



This information can inform strategies to improve antibiotic stewardship, reduce resident harm, and perhaps avoid unnecessary hospitalizations.

SUMMARY

In PALTC facilities there may be an infection preventionist and/or other infection control person, whose primary responsibility is implementation and monitoring of the facility's efforts to improve antimicrobial stewardship. However, everyone in the facility plays an important role in improving the effective and safe use of antibiotics, whether it is observance of proper hand-washing techniques, rigorous prevention of food-borne illnesses by the dietary staff, avoidance of unnecessary antibiotic use, or selection of the best antibiotic at the correct dose for a given infection in a specific resident based on his/her clinical situation. Antimicrobial stewardship is everyone's responsibility and care initiatives must be aligned to be successful.[19]

Similarly, everyone plays an important role in the identification of possible antibiotic-related ADEs. It may be the nurse's aide who notes a new rash while bathing a resident, or the LPN when administering the antibiotic who sees the resident is suddenly confused, delusional and having hallucinations. These initial alerts brought to the attention of the nurse can be the trigger to use the ADE tool to describe and document the ADE. Some facilities have expanded their antibiotic care plans to include ADE monitoring and the request for certain laboratory tests that may help to confirm an ADE.

It is hopeful, that electronic versions of the ADE tool can be embedded into electronic health records (EHRs) to improve the efficiency of identification and documentation. Clinical decision support tools have been shown to improve quality outcomes. Until then, the ADE tool is available in the public domain to be used manually to organize the approach to ADE documentation and monitoring in PALTC facilities.

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