

August 2018

Volume 25 Number 2

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Changes to Formulary

Deletions

1. Nitroglycerin 2% ointment

- Discontinued by manufacturer
- Formulary Alternatives: Nitroglycerin patch; Isosorbide Dinitrate tablets

Table 1. Nitroglycerin Approximate Dose Equivalence¹

Nitroglycerin 2% ointment	1 inch (2.5 cm) Q6H
Nitroglycerin patch	0.4 mg/hr
Isosorbide Dinitrate tablets	15 to 20 mg TID
Isosorbide Mononitrate ² Sustained-Release tablets	30 mg/day

¹ Nitrates Comparison Chart, University Health Network, Jan 2015

² Non formulary

Policy Updates

1. VALSARTAN GENERIC RECALL

Several generic formulations of valsartan have been recalled due to contamination with N-nitrosodimethylamine (NDMA), a potential human carcinogen. The Diovan[®] brand name product is not affected. Alternatively, clinicians may opt to switch patients to another aldosterone receptor blocker (ARB).

1. BORTEZOMIB CONCENTRATION CHANGE

As of June 6, 2018, bortezomib (Velcade[®]) subcutaneous (SUBCUT) doses are now prepared as a 2.5 mg/mL concentration, instead of the previous 1 mg/mL concentration. The 2.5 mg/mL formulation will minimize the number of injections required per dose; this concentration is intended for SUBCUT administration only.

2. ERTAPENEM TO MEROPENEM THERAPEUTIC INTERCHANGE POLICY

Ertapenem is restricted to outpatient use only. For inpatient use, all orders for ertapenem will be interchanged to meropenem based on renal function (see Table 2) unless ertapenem is prescribed 1) on the day of discharge to the home IV therapy or outpatient antimicrobial program, or 2) for IM use until IV access is established.

Table 2. Ertapenem to Meropenem Therapeutic Interchange

Ertapenem 0.5 to 1 g IV daily to be converted to:	
CrCl (mL/min)	Meropenem Dose Dispensed
Above 50	500 mg IV Q6H
26-50	500 mg IV Q8H
10 to 25	500 mg IV Q12H
Below 10	500 mg IV Q24H

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3. CEFAZOLIN FOR SURGICAL PROPHYLAXIS IN PATIENTS WITH PENICILLIN ALLERGY

Karen Shalansky, Pharm.D., Tim Lau, Pharm.D., Cesilia Nishii, Pharm.D., Jennifer Grant, MDCM, Raymond Mak, M.D.

New VA Practice for Surgical Prophylaxis

The VA Medical Advisory Committee (MAC) has approved the use of cefazolin for surgical prophylaxis in patients with a documented Type I hypersensitivity reaction to penicillins in perioperative areas at VGH and UBCH. As of **Sept 17, 2018**, all surgical pre-printed orders will be updated with the following statement:

Cefazolin can be safely administered to patients with history of allergy to penicillins including anaphylaxis, **EXCEPT** in those with severe delayed skin reactions - e.g. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS).

Background

Cefazolin is the drug of choice for prophylaxis in most surgical procedures. Selecting an alternate antibiotic may be less efficacious or have greater toxicities.¹ Historically, there has been a reluctance to administer any beta-lactam antibiotic (e.g. penicillins, cephalosporins) to patients with a penicillin-type allergy due to concerns of cross-reactivity. Cross-reactivity between penicillins and cephalosporins is due to similarities in the side chain structure, not the beta-lactam ring. Since cefazolin does not share similar side chains with any other beta-lactam antibiotic, it should not cross-react with penicillins (ie. penicillin, amoxicillin, ampicillin, cloxacillin, piperacillin-tazobactam).²⁻⁴

Classification of Hypersensitivity Reactions

Type	Description	Mediator	Onset	Clinical Reaction	Skin Test Useful	Comments For Beta-Lactam Related Hypersensitivities
I	Immediate	IgE	< 1 hr (1 to 24 hr)	Anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor	Yes	Avoid the offending agent and side-chain related agents.
II	Cytotoxic	IgG, IgM	> 72 hr	Hemolytic anemia, thrombocytopenia, neutropenia	No	Drug specific. Avoid the offending agent.
III	Antibody-complex	Immune complexes	> 72 hr	Serum sickness, drug-induced lupus, small vessel vasculitis	No	Tissue lodging of antibody-antigen complexes and may affect any end organ; drug fever. Avoid the offending agent.
IV	Delayed	Cell mediated	> 72 hr	Benign: Contact dermatitis, morbilliform rash, fixed drug eruption Severe: SJS, TEN, DRESS	No	Benign rashes are not a contraindication to future beta-lactam use. Severe rashes are rare. Avoid all beta-lactam antibiotics.

Type I (Immediate Hypersensitivity) Reactions

Type I reactions are IgE mediated, occur rapidly, and are associated with anaphylaxis. The frequency of anaphylactic reactions to penicillins is 0.01-0.05% and cephalosporins 0.0001-0.1%.

- ⇒ In patients who report a penicillin allergy, cross-reactivity to a cephalosporin is estimated to be 1-2.6%. However, risk of cross-reactivity is only significant in cephalosporins with similar side chains to penicillins. **Cefazolin is NOT expected to cross-react with any penicillin-related antibiotic** as it does not have similar side chains to any beta-lactam antibiotic.
- ⇒ Penicillin skin testing should be considered in patients with a history suggestive of a Type I hypersensitivity reaction. If a patient has a positive penicillin skin test (or until skin testing is done), penicillins and other beta-lactams with similar side chains should be avoided. Alternatively, desensitization may be considered.

Type II-IV Reactions (SJS, TEN, DRESS)

Type II to IV reactions are non-IgE mediated and tend to occur greater than 72 hours after exposure.

- ⇒ Type II and III reactions are drug specific and the offending agent should be avoided.^{2,3}
- ⇒ Severe delayed Type IV skin reactions (SJS, TEN, DRESS) are rare with beta-lactams, but because these reactions are life-threatening, all beta-lactam antibiotics (including cefazolin) should be avoided.

Cefazolin for Surgical Prophylaxis in Patients with Penicillin Allergy at VA

Even though cefazolin is not expected to cross-react with penicillins, there is limited literature on the use of cefazolin for perioperative prophylaxis in patients with a documented penicillin allergy. In addition, studies that support the use of cefazolin in patients who report a penicillin-type allergy are of poor quality and retrospective in design. Thus this initiative will be implemented in the highly monitored perioperative environment.⁶ In the future, this policy may be expanded to include other clinical areas where cefazolin is indicated.

Implementation Plan

- 1) Update pre-printed orders (PPOs): All surgical PPOs will be updated to allow cefazolin use in patients with penicillin allergies (including anaphylaxis) other than severe delayed skin reactions.
- 2) Provide Education/Resources: Over the next month, VCH Antimicrobial Stewardship Programme (ASPIRES) will provide educational sessions to pharmacists, nurses, surgeons and anesthesiologists on this practice change. ASPIRES will evaluate the safety and efficacy of this practice.

The VA "Parenteral Antibiotic Allergy Cross-sensitivity Chart" has also been revised to reflect this change (page 4). This chart is located on-line at www.vhpharmsci.com website. Click on: *Formulary*, then *Prescribing Tools*, then *Antibiotic Cross Sensitivity Chart*.

- 3) Implementation Date: **Sept 17, 2018**.

References

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5. Baldo BA, Pharm NH. Classification and description of allergic reactions to drugs. In *Drug Allergy: clinical aspects, diagnosis, mechanisms, structure activity relationships*, 2013. Springer, p1-13.
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 PARENTERAL ANTIBIOTIC ALLERGY CROSS-SENSITIVITY CHART

	Amikacin	Ampicillin	Azithromycin	Cefazolin	Cefotaxime	Cefoxitin	Ceftazidime	Ceftriaxone	Cefuroxime	Chloramphenicol	Ciprofloxacin	Clindamycin	Cloxacillin	Cotrimoxazole (Sulfa)	Daptomycin	Ertapenem	Erythromycin	Gentamicin	Imipenem	Levofloxacin	Meropenem	Metronidazole	Moxifloxacin	Penicillin	Piperacillin/Tazobactam	Streptomycin	Tigecycline	Tobramycin	Vancomycin
Amikacin																	X								X		X		
Ampicillin				a	b	b	b	b	b			X				c		c		c				X	X				
Azithromycin																	X												
Cefazolin		a			X	X	X	X	X			a			a			a		a			a	a					
Cefotaxime		b		X		X	X	X	X			b			c			c		c			b	b					
Cefoxitin		b		X	X		X	X	X			b			c			c		c			b	b					
Ceftazidime		b		X	X	X		X	X			b			c			c		c			b	b					
Ceftriaxone		b		X	X	X	X		X			b			c			c		c			b	b					
Cefuroxime		b		X	X	X	X	X				b			c			c		c			b	b					
Chloramphenicol																													
Ciprofloxacin																				X			X						
Clindamycin																													
Cloxacillin		X		a	b	b	b	b	b									c		c			X	X					
Cotrimoxazole (Sulfa)																													
Daptomycin																													
Ertapenem		c		a	c	c	c	c	c			c						X		X			c	c					
Erythromycin			X																										
Gentamicin	X																									X		X	
Imipenem		c		a	c	c	c	c	c			c			X					X			c	c					
Levofloxacin											X												X						
Meropenem		c		a	c	c	c	c	c			c			X				X				c	c					
Metronidazole																													
Moxifloxacin											X									X									
Penicillin		X		a	b	b	b	b	b			X			c			c		c			X						
Piperacillin/Tazobactam		X		a	b	b	b	b	b			X			c			c		c			X						
Streptomycin	X																X											X	
Tigecycline																													
Tobramycin	X																X								X				
Vancomycin																													

a = Cefazolin may be safely administered to patients with history of allergy to penicillins including anaphylaxis, EXCEPT in those with severe delayed skin reactions - e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS).
 b = May consider using if non-anaphylactic reaction to the penicillin or cephalosporin; monitor closely
 c = There is little potential for cross-reactivity between penicillin/cephalosporins and carbapenems; however, monitor closely if previous anaphylactic reaction to penicillins or cephalosporins
 X = Potential for cross-sensitivity
 Blank = Not cross-sensitive

Updated: Aug 2018 ASPIRES/PHARMACY