BAPTIST HEALTH

Antimicrobial Stewardship Sub-Committee
Antibiotic Graded Dose Challenge and Desensitization Guideline

Background

IgE-mediated allergies

Antibiotic allergies are commonly reported by patients, with a variety of reactions cited ranging from IgE-mediated reactions (e.g. anaphylaxis, angioedema, or hives) to adverse effects (e.g. nausea, vomiting). Deciphering true allergies (IgE-mediated reactions) from non-allergic reactions is challenging. Among patients with a reported allergy to penicillin, ≤10% are truly allergic.[1] Identifying patients at high risk for allergic reactions is vital when making antibiotic recommendations, especially for life-threatening infections. Clinical manifestations of IgE-mediated reactions include urticaria, pruritic rash, angioedema, wheezing, laryngeal edema, hypotension, and/or anaphylaxis. The onset of symptoms occurs approximately within the first hour of administration in patients previously sensitized.[3] The purpose of this document is to provide guidance on obtaining an allergy history from a patient, evaluate risk of allergic reactions, and provide recommendations on challenging or desensitizing allergies.

Dose challenges vs Desensitization

A dose challenge cautiously administers antibiotics to patients with low probability of an immediate allergic reaction. It does not modify an IgE-mediated response. It can be performed using either a graded (multiple) dose or single test dose of the intended beta-lactam. Both methods are evidence based. [12] A dose challenge can be quickly and easily completed while still mitigating risk of an IgE mediated reaction. While graded-dose challenges are performed using multiple reduced doses that are titrated to the full desired dose, a test dose is a single reduced dose of the desired antimicrobial, which ranges from 10-50% reduction of the desired dose. [12-14] Desensitization protocols are for patients with a high probability of experiencing a serious allergic reaction. Desensitization creates a “temporary state” of antibiotic tolerance following slow induction of the antibiotic. This will allow the patient to safely receive treatment. However, if the patient is not exposed to the antibiotic for > 24 hours, the desensitization must be repeated to create the “temporary state” of tolerance. Patients not eligible for graded dose challenge or de-sensitization include patients with a history of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hepatitis, hemolytic anemia, angioedema, or interstitial nephritis.[1]

How to Obtain a Thorough Allergy History

Direct questioning of the patient or family is necessary to clarify antibiotic allergy histories. Ask open ended questions to prevent leading the patient. Update the allergy record in the EMR after interviewing patient.

The following questions are necessary to clarify the allergy:

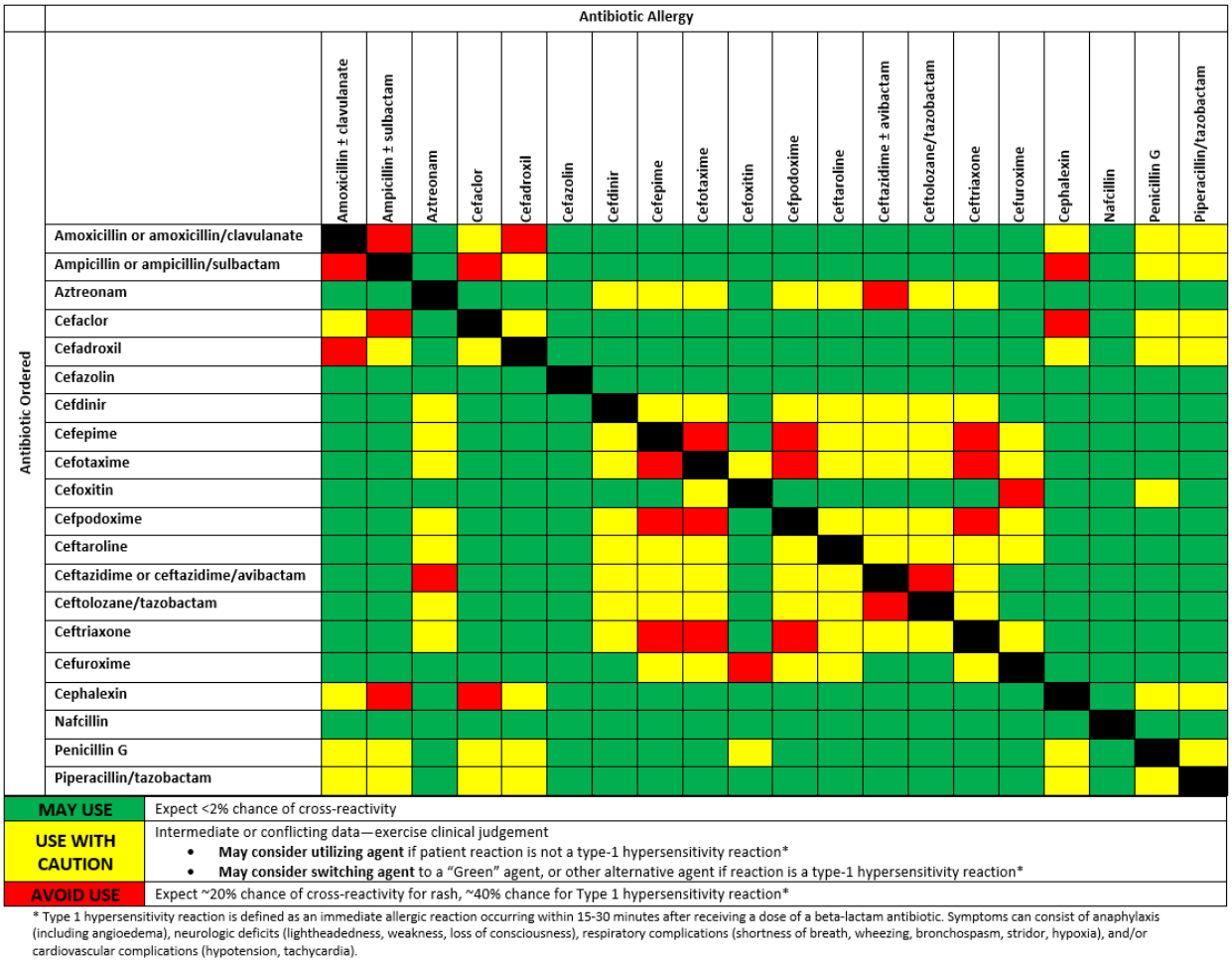
- What happened when you received the antibiotic and how old were you when it happened?
  - **The why**: Patients do not forget true anaphylaxis; the sterility of penicillin has changed over time resulting in a reduction in ADRs; allergies also change approximately every 5-10 years.
- How long after taking the antibiotic did the reaction occur?
  - **The why**: Differentiating a side effect from anaphylaxis; true anaphylaxis typically occurs with 15-60 minutes following contact with the antibiotic. Viral exanthem (or rash) is also typically another cause of inaccurate allergies frequently observed 3-4 days after taking the antibiotic.
- Did you have to receive an injection following the reaction and did you respond to the treatment?
  - **The why**: Identifying epinephrine administration; differentiating a side effect from anaphylaxis.
- What other antibiotics have you taken recently?
  - **The why**: the cross reactivity can be evaluated to help determine tolerability of first-line pre-op antibiotics.

Questions to ask:

1. What happened when you received the antibiotic?
2. How old were you when it happened?
3. How long after taking the antibiotic did the reaction occur (minutes vs days)?
4. What was the antibiotic prescribed for?
5. Did you have to receive an injection (epinephrine) to treat the reaction and did you respond to the treatment?
6. What other antibiotics have you taken recently [e.g. amoxicillin/clavulanate (Augmentin), amoxicillin, cephalexin (Keflex)]?

If an alternative antibiotic is available but still within the beta-lactam class (ie. penicillin allergy with a cephalosporin as an alternative), **refer to cross-reactivity chart below**. This chart can aid in evaluating whether side chains are similar, which has been most commonly associated with cross-reactivity. If side chains are dissimilar, a graded dose challenge or desensitization is not needed.

Cross Reactivity Chart



* Type 1 hypersensitivity reaction is defined as an immediate allergic reaction occurring within 15-30 minutes after receiving a dose of a beta-lactam antibiotic. Symptoms can consist of anaphylaxis (including angioedema), neurologic deficits (lightheadedness, weakness, loss of consciousness), respiratory complications (shortness of breath, wheezing, bronchospasm, stridor, hypoxia), and/or cardiovascular complications (hypotension, tachycardia).

Single or Graded Dose Challenge Protocol(s)

1) Patient eligibility
   a) Patients are not eligible for dose challenges if the documented or stated allergic reaction is anaphylaxis, angioedema, or the patient can recall being hospitalized for the allergic reaction.
   b) Recommended for patients with low probability of a severe immediate allergic reaction:
      i) Cannot recall allergy, does not recall being hospitalized for reaction
      ii) "Allergy" is a minor, non-IgE-mediated reaction – ex: rash, nausea, vomiting, diarrhea
      iii) Index allergy occurred >10yrs ago

2) Administration Instructions
   a) Increased level of care is not needed and can be performed on any floor
   b) Do not give any premedication
   c) Oral/IV single dose challenge – Give a single reduced dose of agent being considered for treatment

i) Administer a 10-50% of final dose desired
   (1) Choose a dose reduction that will work for available products (i.e. if 1,000 mg amoxicillin is desired, use a dose reduction that will be feasible to make with dosage form available).
ii) Administer the full final dose desired

d) Oral/IV graded dose challenge - Give 3 total doses every 60 minutes
   i) 1% of final dose desired
   ii) 10% of final dose desired
   iii) Full final dose desired
   iv) Total procedure time is 180 minutes
   v) 4 vitals checks

3) Monitoring Instructions
   a) Vital signs monitoring
      i) Vitals include: heart rate, respiratory rate, blood pressure, presence or lack of wheezing on physical exam
      ii) Check vitals prior to first dose and every 60 minutes until completed
   b) Patient education
      i) Instruct patient to use call light to alert nurse or provider if the following reaction occurs: Itching, hives, full body flushing, chest pain, wheezing, confusion, shortness of breath, or hypotension
   c) When to call the physician
      i) If the patient has signs and/or symptoms of an allergic reaction
         (1) Reactions listed above
         (2) Blood pressure decreases by 20% from baseline
         (3) Increase in wheezing from baseline
         (4) Heart rate increases by 20% from baseline
      ii) If the patient experiences a severe IgE-mediated reaction and it is determined that the patient needs this antibiotic, refer to antibiotic desensitization
   d) Rescue medications
      i) Will be provided on patient's MAR prior to procedure
         (1) Epinephrine 0.3 mg (1:1000) IM or 3 mL (1:10,000) IV
            (a) Can repeat every 5 minutes (up to 3 times) if necessary
         (2) Diphenhydramine 50 mg IV
      ii) Available in the unit ADS
      iii) If rescue medications are required, stop the graded dose challenge

4) Symptom Management
   a) Mild symptoms such as new onset runny nose, itching, congestion, mild nausea/discomfort or a few scattered hives require that the patient be monitored closely. These symptoms may signify impending anaphylaxis and desensitization may be required.

i) DO NOT give premedications to prevent mild symptoms as this may mask an impending reaction

b) Systemic symptoms indicative of anaphylaxis include full body flushing, hives, severe nausea, vomiting, diarrhea, chest pain, shortness of breath, wheezing, or hypotension and will require rescue medications. If these medications are required, immediately STOP the protocol.
   i) Epinephrine 0.3 mg (1:1000) IM as needed
   ii) For profound hypotension (SBP < 80): epinephrine 0.3 mg IV push as needed
   iii) Methylprednisolone 125 mg IV push as needed

5) Compounding instructions - **Appendix A**: Preparation and administration instructions for common graded dose challenges

6) Documentation instructions - The results of the graded dose challenge should be documented in EPIC

Desensitization Protocol

1) Patient eligibility
   a) Patients are not eligible for a desensitization protocol if the documented or stated allergic reaction is mild or non-IgE-mediated, refer to graded dose challenge
   b) Desensitization is recommended for patients with a high probability of an immediate allergic reaction:
      i) Describes anaphylaxis or recalls being hospitalized for reaction

2) Administration instructions
   a) Increased level of care is not needed and can be performed on any floor. However, due to the time intensive nature of desensitization protocols, a higher level of care may be needed for lower nurse to patient ratios.
   b) Do not give any premedication
   c) Pharmacist instructions
      i) Preparation: **See appendix B**
         (1) Number of infusions can range from 12-20 with increasing doses
         (2) Patient may require repeat doses if one is not tolerated
            (a) I.e. Patient is on infusion #6 and starts to experience itching. The nurse will re-infuse #5 and proceed to #6 once tolerated. Infusion #5 will need to be remade in the instance.

3) Monitoring instructions
   a) Vital sign monitoring
      i) Complete vital sign monitoring at baseline then every 30 minutes through completion of desensitization protocol
      ii) Heart rate, respiratory rate, blood pressure, presence or lack of wheezing on physical exam
   b) Patient education

i) Instruct patient to use call light to alert nurse or provider if the following reaction occurs: Itching, hives, full body flushing, chest pain, wheezing, confusion, shortness of breath, or hypotension
ii) If the patient begins to experience a reaction (i.e. itching, hives, flushing), stop the current infusion and repeat the previous (Example: patient is on infusion #6 and starts to experience itching. The nurse will re-infuse #5 and proceed to #6 once tolerated. Coordination with pharmacy will be necessary.)

c) When to call the physician
i) If the patient has signs and/or symptoms of an allergic reaction
(1) Reactions listed above
(2) Blood pressure decreases by 20% from baseline
(3) Increase in wheezing from baseline
(4) Heart rate increases by 20% from baseline

d) Rescue medications
i) Will be provided on patient's MAR prior to procedure
(1) Epinephrine 0.3 mg (1:1000) IM or 3 mL (1:10,000) IV
(a) Can repeat every 5 minutes (up to 3 times) if necessary
(2) Diphenhydramine 50 mg IV
ii) Available in the unit ADS
iii) If rescue medications are required, stop the desensitization

4) Symptom Management
a) Mild symptoms such as new onset runny nose, itching, congestion, mild nausea/discomfort or a few scattered hives require that the patient be monitored closely. These symptoms may signify impending anaphylaxis.
i) Give diphenhydramine 50 mg IV push as needed if patient experiences reaction as described. If these reactions do occur, as described above, stop the current infusion and repeat the previous to continue desensitization.

b) Systemic symptoms indicative of anaphylaxis include full body flushing, hives, severe nausea, vomiting, diarrhea, chest pain, shortness of breath, wheezing, or hypotension and will require rescue medications. If these medications are required, immediately STOP the protocol.
i) Epinephrine 0.3 mg (1:1000) IM as needed
ii) For profound hypotension (SBP < 80): epinephrine 0.3 mg IV push as needed
iii) Methylprednisolone 125 mg IV push as needed

5) Compounding instructions - **See Appendix B**: Preparation and administration instructions for common desensitization protocols

6) Documentation instructions - The results of the desensitization should be documented in EPIC

Appendix

Appendix A. Preparation and administration instructions for common graded dose challenges

1) Oral Graded Dose Challenge Preparation: attach label printed from EPIC
   a) 1% dose (syringe 1)
      i) Take the stock suspension at the concentration given below in table 2 and withdraw the volume for 1% of drug dose into an oral syringe
   b) 10% dose (syringe 2)
      i) Take the stock suspension at the concentration given below in table 2 and withdraw the volume for 10% of drug dose into an oral syringe
   c) 89% dose (syringe 3)
      i) Take the stock suspension at the concentration given below in table 2 and withdraw the volume for 89% of drug dose into an oral syringe

Table 2: Common antibiotics and concentrations for oral graded dose challenge

Antibiotic	Concentration	100% Dose		1% Dose	10% Dose	89% Dose
		Dose (mg)	Dose (mL)	Dose (mL)	Dose (mL)	Dose (mL)
PCN V/K	50 mg/mL	500	10	0.1	1.0	8.9
Amoxicillin	50 mg/mL	500	10	0.1	1.0	8.9
Amox/Clav	120 mg/mL	875	7.3	0.07	0.7	6.5
Cephalexin	50 mg/mL	500	10	0.1	1.0	8.9
Cefdinir	50 mg/mL	300	6	0.06	0.6	5.4

2) Intravenous Graded Dose Challenge Preparation: attach label printed from EPIC
   a) 1% dose (Infusion bag 1)
      i) Take the fully reconstituted product at 100% of the dose and concentration (stock solution) stated below in table 3, withdraw the volume given, and add to the volume for the diluent given above for 1% of dose
   b) 10% dose (Infusion bag 2)
      i) Take the previous stock solution and withdraw the volume stated below in table 3, and add to the volume for the diluent given for 10% of dose
   c) 89% dose (Infusion bag 3)
      i) Take the previous stock solution to use as 89% of dose
   d) Ensure adequate **flush** following each dose due to small volume administered.

Table 3: Common antibiotics and concentrations for intravenous graded dose challenge

Antibiotic	Concentration (mg/mL)	Diluent	100% Dose (mg)	1% Dose		10% Dose		89% Dose	
				Drug (mL)	Diluent (mL)	Drug (mL)	Diluent (mL)	Drug (mL)	Diluent (mL)
Ampicillin	20	NS	2000	1	99	10	90	89	11
Amp/Sulb	15	NS	1500	1	99	10	90	89	11
Cefazolin	20	D5W	2000	1	99	10	90	89	11
Cefepime	20	D5W	1000	0.5	49.5	5	45	44.5	5.5
Cefotaxime	10	D5W	1000	1	99	10	90	89	11
Cefoxitin	20	D5W	1000	0.5	49.5	5	45	44.5	5.5
Ceftazidime	10	NS	1000	1	99	10	90	89	11
Ceftriaxone	10	D5W	1000	1	99	10	90	89	11
Cefuroxime	15	D5W	750	0.5	49.5	5	45	44.5	5.5
Ertapenem	20	NS	1000	0.5	49.5	5	45	44.5	5.5
Meropenem	5	NS	500	1	99	10	90	89	11
Oxacillin	20	D5W	1000	0.5	49.5	5	45	44.5	5.5
Nafcillin	40	D5W	2000	0.5	49.5	5	45	44.5	5.5
PCN G	25,000 U/mL	D5W	2.5 million U	1	99	10	90	89	11
Pip/Tazo	67.5	D5W	3375	0.5	49.5	5	45	44.5	5.5

Appendix B. Preparation and administration instructions for desensitization

INTRAVENOUS DESENSITIZATION PROTOCOLS

1) Intravenous Penicillin desensitization protocol[4-5]

a) Preparation: See table 4
   - Reconstitute penicillin G 1,000,000 units in 50mL of D5W for a final approximate concentration of 20,000units/mL.
   - Prepare the following 10 fold serial dilutions:
     - SOLUTION #1: Above dilution (Final concentration = 20,000units/mL)
     - SOLUTION #2: Withdrawal 20 mL from SOLUTION #1 and add to 180 mL of D5W (Final Concentration = 2,000units/mL)
     - SOLUTION #3: Withdrawal 20 mL from SOLUTION #2 and add to 180 mL of D5W (Final Concentration = 200units/mL)
     - SOLUTION #4: Withdrawal 20 mL from SOLUTION #3 and add to 180 mL of D5W (Final Concentration = 20units/mL)
     - **Doses 1 to 5**: Prepared from SOLUTION #4
     - **Doses 6 to 9**: Prepared from SOLUTION #3
     - **Doses 10 to 12**: Prepared from SOLUTION #2
     - **Doses 13 and 14**: Prepared from SOLUTION #1

b) Administer each dose over **15 minutes** followed immediately by the next scheduled dose

c) Following final dose, observe patient for 15-30 minutes
   - If patient tolerates the final dose, administer full therapeutic dose

d) Ensure adequate **flush** following each dose due to small volume administered.

Table 4. IV Penicillin Desensitization Protocol

Dose Number	Concentration (units/mL)	Dose (units)	Dose (mL)	Cumulative Dose (units)
1	20	50	2.5	50
2	20	100	5	150
3	20	200	10	350
4	20	400	20	750
5	20	800	40	1,550
6	200	1,500	7.5	3,050
7	200	3,000	15	6,050
8	200	6,000	30	12,050
9	200	12,000	60	24,050
10	2,000	25,000	12.5	49,050
11	2,000	50,000	25	99,050
12	2,000	100,000	50	199,050
13	20,000	200,000	10	399,050
14	20,000	400,000	20	799,050

2) Intravenous Ampicillin desensitization protocol[6]

a) Preparation: See table 5
- Dilute 1000 mg of ampicillin to 1,000 mL of 0.9% sodium chloride (NS) to achieve the 1mg/mL solution (expiration = 12 hours)
  - **Dose 1**: take 0.1 mL of the 1 mg/mL solution and add to 200mL of NS (concentration = 0.0005 mg/mL)
  - **Dose 2**: Take 1 mL of the 1 mg/mL solution an add to 200mL of NS (0.005 mg/mL)
  - **Dose 3 and 4**: Take 1 mL of the 1 mg/mL solution and QS with NS to 10mL (0.1 mg/mL)
  - **Doses 5 to 11**: Withdraw appropriate volume from 1 mg/mL solution to make doses
  - **Doses 12 to 18**: Dispense a sufficient number of 1 gram vials (3 vials should be adequate); do not reconstitute all due to short (1 hour) stability of 100 mg/mL concentration, reconstitute prior to administration
    - Dilute each vial with 9.4 mL of sterile water to provide 10 mL of volume (100mg/mL)
    - Sufficient volume should be withdrawn from each vial to make the respective dose

b) Administer each dose over **15 minutes** followed immediately by the next scheduled dose

c) Following final dose, observe patient for 15-30 minutes
- If patient tolerates the final dose, administer full therapeutic dose

d) Ensure adequate **flush** following each dose due to small volume administered.

Table 5. IV Ampicillin Desensitization Protocol

Dose Number	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	0.0005	1	0.0005	0.0005
2	0.005	1	0.005	0.0055
3	0.1	0.4	0.04	0.0455
4	0.1	0.8	0.08	0.1255
5	1	0.15	0.15	0.2755
6	1	0.3	0.3	0.5755
7	1	0.6	0.6	1.1755
8	1	1	1	2.1755
9	1	2	2	4.1755
10	1	4	4	8.1755
11	1	8	8	16.1755
12	100	0.15	15	31.1755
13	100	0.3	30	61.1755
14	100	0.6	60	121.1755
15	100	1	100	221
16	100	2	200	421
17	100	4	400	821
18	100	8	800	1621

3) Intravenous vancomycin desensitization protocol[7]

a) Preparation: See table 6

- Vials of vancomycin are reconstituted to concentration of 50 mg/mL (5gm/100mL SW)
- Prepare 3 stock solutions.
  - Solution #1 is 50 mg/mL
    - Use vancomycin from vial
  - Solution #2 is 1 mg/mL
    - Draw 2 mL (100 mg) from vial
    - Place the 2 mL in 100 mL D5W
  - Solution #3 is 0.01 mg/mL
    - Draw 0.2 mL (10 mg) from vial
    - Place the 0.2 mL (10 mg) into 1 L D5W

b) Ensure adequate **flush** following each dose due to small volume administered.

Table 6. IV Vancomycin Desensitization Protocol

Infusion no.	Stock solution	Volume of stock solution (mL)	Vancomycin Dose (mg)	D5W Volume (mL)	Concentration (mg/mL)	Rate (mL/hr)
1	#3	0.5	0.005	50	0.0001	200
2	#3	1	0.01	50	0.0002	200
3	#3	2	0.02	50	0.0004	200
4	#3	4	0.04	50	0.0008	200
5	#3	8	0.08	50	0.0016	200
6	#3	16	0.16	50	0.0032	200
7	#2	0.32	0.32	50	0.0064	200
8	#2	0.64	0.64	50	0.0128	200
9	#2	1.25	1.25	50	0.025	200
10	#2	2.5	2.5	50	0.05	200
11	#2	5	5	50	0.1	200
12	#2	10	10	50	0.2	200
13	#1	0.4	20	50	0.4	200
14	#1	0.8	40	50	0.8	200
15	#1	1.6	80	50	1.6	200
16	#1	3.2	160	50	3.2	200
17	#1	6.4	320	100	3.2	200
18	#1	12.8	640	250	2.56	250
19	Premade	Premade	1000	250	4	250

4) Intravenous sulfamethoxazole/trimethoprim (SMX/TMP) desensitization protocol[8]

a) Preparation: See table 7

- Dilute 30 mL of SMX/TMP (80 mg/16 mg per mL) injection in 570 mL of diluent for a total volume of 600 mL to obtain a concentration of 4 mg/0.8 mg per mL.
- Administer each dose over **15 minutes,** wait 5 minutes, and administer the next dose (interval between doses is total of 20 minutes)
- If patient tolerates final dose (number 7), therapeutic doses of SMX/TMP may be scheduled at normal intervals

b) Ensure adequate **flush** following each dose due to small volume administered.

Table 7. IV Sulfamethoxazole/trimethoprim (SMX/TMP) Desensitization Protocol

Dose Number	Time (minutes)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	0	0.2*	0.8/0.16	0.8/0.16
2	20	2	8/1.6	8.8/1.76
3	40	10	40/8	48.8/9.76
4	60	20	80/16	128.9/92
5	80	100	400/80	528.9/172
6	100	170	680/136	1208.9/308
7	120	300	1200/240	2408/548

*Further dilute the first dose to 10 mL for ease of administration, if needed.

5) Intravenous ceftriaxone or cefazolin desensitization protocol[9]

a) Preparation: See table 8
   - Dilute 1 gram of ceftriaxone or cefazolin in 9.6 mL of 0.9% sodium chloride (normal saline or NS) to achieve the 100 mg/mL concentration. Repeat for a total of 2 vials.
   - Withdraw 2.5 mL from 100 mg/mL solution and add to 22.5 mL NS (10 mg/mL).
   - Stock solutions:
     - Solution for doses 1-3: Take 0.1 mL of 10 mg/mL solution and add to 99.9 mL NS (0.01 mg/mL)
     - Solution for doses 4-9: Take 0.8 mL of 10 mg/mL solution and add to 79.2 mL NS (0.1 mg/mL)
     - Solution for doses 10-14: Withdraw 24 mL of 10 mg/mL solution. Use appropriate volume to make doses (see table 8)
     - Solution for doses 15-16: Withdraw 7.5 mL of 100 mg/mL solution. Use appropriate volume to make doses (see table 8)
     - Solution for dose 17: Take 10 mL of 100 mg/mL solution to make dose

b) Administer each dose over **15 minutes** followed immediately by the next scheduled dose

c) Following final dose, observe patient for 15-30 minutes
   - If patient tolerates the final dose, administer full therapeutic dose

d) Ensure adequate **flush** following each dose due to small volume administered.

Table 8. IV Ceftriaxone or Cefazolin Desensitization Protocol

Dose Number	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	0.01	1.5	0.015	0.015
2	0.01	3	0.03	0.045
3	0.01	6	0.06	0.105
4	0.1	1.25	0.125	0.23
5	0.1	2.5	0.25	0.48
6	0.1	5	0.5	1
7	0.1	10	1	2
8	0.1	20	2	4
9	0.1	40	4	8
10	10	0.75	7.5	15
11	10	1.5	15	30
12	10	3	30	60
13	10	6.25	62.5	123
14	10	12.5	125	250
15	100	2.5	250	500
16	100	5	500	1000
17	100	10	1000	2000

6) Intravenous to oral metronidazole desensitization protocol[11]

a) Preparation: See Table 9
   - Solution for doses 1-2: Utilizing a metronidazole 500mg/100mL premixed solution, transfer 1 mL into a 1000 mL bag of normal saline (concentration 0.005mg/mL)
   - Solution for doses 3-4: Utilizing a metronidazole 500mg/100mL premixed solution, transfer 1 mL into a 100 mL bag of normal saline (concentration 0.05mg/mL)
   - Solution for doses 5-6: Utilizing a metronidazole 500mg/100mL premixed solution, transfer 10 mL into a 90 mL bag of normal saline (concentration 0.5mg/mL)
   - Solution for doses 7-11: Utilizing a metronidazole 500mg/100mL premixed solution, withdrawal required volume in table directly into a syringe

b) Administer intravenous doses in 15-20 minute intervals, administer oral doses 1 hour apart.

c) Following final dose, observe patient for 15-30 minutes.
   - If patient tolerates the final dose, administer full therapeutic dose.

d) Ensure adequate **flush** following each dose due to small volume administered.

Table 9. Intravenous to Oral Metronidazole Desensitization Protocol

Dose Number	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	0.005	1	0.005	0.005
2	0.005	3	0.015	0.02
3	0.05	1	0.05	0.07
4	0.05	3	0.15	0.22
5	0.5	1	0.5	0.72
6	0.5	3	1.5	2.22
7	5	1	5	7.22
8	5	3	15	22.22
9	5	6	30	52.22
10	5	12	60	112.22
11	5	25	125	237.22
12	250 mg orally	Tablet	250	487.22
13	500 mg orally	Tablets	500	987.22
14	2000 mg orally	Tablets	2000	2987.22

ORAL DESENSITIZATION PROTOCOLS

a) Oral penicillin (Penicillin VK) Desensitization[10]

b) Preparation: See table 10

1. Dilute penicillin VK as directed to make stock solution (250 mg/5mL or 80,000 units per mL). Take 2.5 mL of penicillin VK solution and add to 28.75 mL sterile water for irrigation and label this solution 4 mg/mL (6,400 units/mL)

- **Doses 1 to 2**: Take 1 mL of 4 mg/mL solution and add to 63 mL sterile water for irrigation to obtain a 0.0625 mg/mL (100 units/mL). Withdraw appropriate volumes to make doses.
- **Doses 3 to 6**: Take 2 mL of 4 mg/mL solution and add to 30 mL sterile water for irrigation to obtain a 0.25 mg/mL (400 units/mL). Withdraw appropriate volumes to make doses.
- **Doses 7 to 9**: Withdraw appropriate volumes from 4 mg/mL solution to make doses 7 to 9.
- **Doses 10 to 14**: Withdraw appropriate volumes from stock solution (50 mg/mL or 80,000 units/mL) to make doses 10 to 14.

c) Dilute drug volumes in 30 mL water prior to ingestion

d) Administer doses every 15 minutes

1. If patient tolerates the final dose, administer full therapeutic dose

Table 10. Oral Penicillin Desensitization Protocol

Dose Number	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	0.0625	1	0.0625	0.0625
2	0.0625	2	0.125	0.188
3	0.25	1	0.25	0.44
4	0.25	2	0.5	0.94
5	0.25	4	1	1.94
6	0.25	8	2	4
7	4	1	4	8
8	4	2	8	16
9	4	4	16	32
10	50	0.6	30	62
11	50	1	50	112
12	50	2	100	212
13	50	4	200	412
14	50	8	400	812

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