Antimicrobial Desensitization

NB Provincial Health Authorities Anti-Infective Stewardship Committee, May 2019

****See Appendices 1 – 5 for SAMPLE desensitization protocols. ****

Introduction

Beta-lactam antibiotics are the most commonly prescribed class of antimicrobials and include penicillins, cephalosporins, carbapenems and monobactams.[1] Allergies to beta-lactams are over diagnosed and over reported; up to 10% of the population will report an allergy to penicillin.[2-4] Studies have shown that up to 95% or more of these patients reporting a penicillin allergy do not in fact have a true allergy.[1-5]

Unfortunately, there remain patients with confirmed allergy, or in whom it is impossible to rule out the possibility of a true allergy with history alone. In most clinical scenarios, an alternative antibiotic that is not expected to induce an allergic reaction is available to treat these patients; however, there are certain scenarios where the best option for treatment is the antimicrobial which they are allergic to (e.g. penicillin for the treatment of syphilis). In addition, in the age of increasing antimicrobial resistance, situations may arise where there are no available alternatives.

Rapid drug desensitization is a process in which progressively increasing doses of a sensitizing drug are administered over the course of several hours to produce a temporary state of tolerance that allows safe treatment with the medication they are allergic to.[6,7] Desensitization should only be used in patients with a history of a type-1 immediate (IgE-mediated) hypersensitivity reaction (e.g. anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, and pruritis). Desensitization should not be attempted for patients with severe delayed (non-IgE mediated) reactions (e.g. interstitial nephritis, immune hepatitis, hemolytic anemia, serum sickness, severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), etc…).

The effect of desensitization is only TEMPORARY. Once the drug is discontinued, the effect will be lost after approximately 4 half-lives of the medication.[6-8] In the event that the same medication is needed again in the future after it has been discontinued; another desensitization procedure will be required. Therefore, it is essential that allergy labels in the patient's chart are NOT removed after desensitization, and that it is clearly communicated to the patient and to all relevant providers (e.g. primary care provider, community pharmacy, etc.) that desensitization does NOT induce permanent tolerance.

Please also note that a graduated challenge is not the same as rapid desensitization.[6,9] Graduated challenges are used when there is a low likelihood of drug allergy and differs in that they do not alter the patient's underlying immune response to the medication in question.[6,9] Their purpose is to allow the cautious administration in patients unlikely to be allergic, when there is no intention to alter the patient's immune response, in order to minimize the risk of a severe reaction.[6,9] A patient can be considered non-allergic if they show tolerance (i.e. no immediate or delayed reaction) to a graduated challenge.[8]

Indications/Contraindications/Precautions[6,7,10]

Indications	Contraindications

• The drug of concern is deemed irreplaceable
  ○ e.g. penicillin for the treatment of syphilis
• The drug of concern is more effective than available alternatives
• The drug of concern is much safer than available alternatives
  ○ e.g. ampicillin + cefTRIAXone for *Enterococcus faecalis* endocarditis
	• Uncontrolled asthma or uncontrolled cardiac disease
	• Hemodynamic instability
	• Gravely ill patients in which effective alternatives are readily available
	• History of severe non-IgE mediated hypersensitivity reaction (e.g. interstitial nephritis, immune hepatitis, hemolytic anemia, serum sickness, severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), etc…)

Precautions	
• There is a potential that desensitization could induce an acute hypersensitivity reaction; carefully evaluate risks and benefits in patients with a history of severe anaphylaxis and/or anaphylactic shock. • Beta-blockers may interfere with the treatment of anaphylaxis; if possible, hold beta-blockers prior to desensitization. • Antihistamines and corticosteroids may mask early signs of a hypersensitivity reaction; if possible, hold prior to desensitization. DO NOT pre-treat with these agents to prevent reactions.	

Desensitization setting

Because desensitization exposes patients to drugs that have the potential to induce an acute hypersensitivity reaction, it should only be performed in a setting where anaphylaxis can be managed, preferably with staff comfortable and/or experienced with the management of anaphylaxis.[6-8,10] It is essential that the patient be observed continually, with one-to-one nursing care, for signs of a hypersensitivity reaction. Patient factors, such as severity of past reactions and comorbidities, may assist in determining the best location for the desensitization procedure. Desensitization has been shown to be safe, and does not always require to be performed in an intensive care unit. Many centres safely perform desensitization in a general ward or on an outpatient basis.[6,10]

Checklist - Preparation for desensitization[6,7,10,11]

- ☑ Informed consent is mandatory prior to starting the procedure, since we are knowingly administering a medication that could provoke a hypersensitivity reaction.
- ☑ Benefits of the procedure should outweigh the risks.
- ☑ The physician should be available for immediate consultation, if required, throughout the procedure.
- ☑ All patients should have IV access BEFORE starting the procedure and any equipment or medications required to manage anaphylaxis should be readily available.
- ☑ Have all of the following medications readily available throughout the entire procedure:
  - ☑ EPINEPHrine 1 mg/mL ampule x 2
  - ☑ Salbutamol 100 mcg/inhalation MDI with aerochamber x1
  - ☑ DiphenhydrAMINE 50 mg IV x1
  - ☑ MethylPREDNISolone 125 mg IV x 1
  - ☑ Ranitidine 150 mg PO x1
  - ☑ Cetirizine 10 mg PO x 2

Desensitization procedure

Many desensitization protocols are available for both oral and intravenous formulations of beta-lactams. There is more evidence for penicillin desensitization; however, there are reports of successful desensitization to many other drug classes, such as: cephalosporins, carbapenems, aminoglycosides, sulfonamides, vancomycin, quinolones, and macrolides.[6] The oral route may be easier, more cost-effective, and potentially safer than the intravenous route.[6,7,10] Medications are typically started at diluted doses, usually 1/10,000th of the target dose, and, if no reaction, doses are doubled every 15-20 minutes until the target dose is achieved.[6,7,10,12,13] If a more conservative approach is desired for patients with a history of severe anaphylactic reactions, a starting dose of 1/1,000,000th of the target dose could be considered.[7] During the desensitization procedure, vital signs should be monitored closely and patients should be instructed to report symptoms of any potential hypersensitivity reaction.

While there have been no fatal reactions reported during desensitization, mild hypersensitivity reactions can occur in up to one-third of patients.[6,7,10,12,13] The vast majority of patients who suffer mild reactions during desensitization can go on to complete the procedure.[10] In cases of mild reactions, the desensitization procedure should be temporarily interrupted, and the reactions should be treated.[6,7,10] Simply interrupting the desensitization, with no treatment, can resolve up to 90% of mild reactions.[7] If reactions subside, or do not progress, the desensitization procedure can be restarted, going back one or two steps preceding the dose that caused the reaction, with or without adding intermediate dosing increments.[7] In the very unlikely event of a severe systemic reaction, the desensitization procedure should be immediately discontinued, and the reactions should be treated immediately.

It is important to note that in patients with syphilis, treatment with penicillin can induce a Jarisch-Herxheimer reaction (fever, chills, myalgia, flushing and skin rash). This reaction, which is often falsely diagnosed as a drug allergy, is thought to result from the rapid release of endotoxins and lipoproteins during the death of spirochetes. Jarisch-Herxheimer reactions begin approximately 4 hours after initiating penicillin, will peak at approximately 8 hours, and tend to subside within 16 hours.[10]

Appendix 1 – Sample general desensitization orders and patient monitoring[11,21]

Contraindications

- Uncontrolled asthma or uncontrolled cardiac disease
- Hemodynamic instability
- Gravely ill patients in which effective alternatives are readily available
- History of severe non-IgE mediated hypersensitivity reaction (e.g. interstitial nephritis, immune hepatitis, hemolytic anemia, serum sickness, severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), etc…)

Precautions

- There is potential that the desensitization could induce an acute hypersensitivity reaction; carefully evaluate risks and benefits in patients with a history of severe anaphylaxis and/or anaphylactic shock.
- Beta-blockers may interfere with the treatment of anaphylaxis; if possible, hold beta-blockers prior to desensitization.
- Antihistamines and corticosteroids may mask early signs of a hypersensitivity reaction; if possible, hold prior to desensitization. DO NOT pre-treat with these agents to prevent reactions.
- Desensitization only temporarily induces drug tolerance; DO NOT remove the allergy label from the patient's medical record. If the medication is not continued, tolerance will dissipate in as little as 24 hours, or approximately 4 half-lives of the medication.

Consent **mandatory**

☐ Written informed consent obtained – see local treatment consent form

Monitoring

- One-to-one nursing is MANDATORY during desensitization; may consider cardiac monitoring.
- Monitor for signs of an immediate hypersensitivity reaction (e.g. anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis)
- At baseline, and then at every dosing increment, monitor and record the following vital signs: temperature (T°), heart rate (HR), respiratory rate (RR), blood pressure (BP), and oxygen saturation (O_2 sat).
- Upon completion of the procedure, monitor the vital signs listed above q30min x4, then q6h x 4.

Medications

● Establish IV access PRIOR to initiating desensitization procedure

Have the following medications readily available at throughout the desensitization:

● EPINEPHrine 1 mg/mL ampule x 2
● Salbutamol 100 mcg/inhalation MDI (with aerochamber) x 1
● DiphenhydrAMINE 50 mg IV x 1
● MethylPREDNISolone 125 mg IV x 1
● Ranitidine 150 mg PO x 1
● Cetirizine 10 mg PO x 2
● Other: _____

If mild **SKIN** reaction (i.e. erythema, rash, pruritis, urticaria) **WITHOUT** systemic reaction:

- Administer: - Cetirizine 20 mg PO x1 dose
  - Ranitidine 150 mg PO x 1 dose
- ● HOLD desensitization and contact the prescriber

If **SYSTEMIC** reaction (i.e. hypotension, wheezing, bronchospasm, angioedema):

- Administer: - EPINEPHrine 0.3 mg IM x 1 dose STAT
  - DiphenhydrAMINE 50 mg IV direct x 1 dose
  - MethylPREDNISolone 125 mg IV x 1 dose
  - Salbutamol 4-8 puffs with aerochamber (if respiratory involvement)
- ● Immediately STOP desensitization and contact the prescriber STAT

** Adapted with permission from The Scarborough Hospital (03-2015)**

Appendix 2 – Sample Penicillin G IV desensitization[11]

Pharmacy to prepare the following:

Solution	Preparation	Concentration
Solution A	Penicillin G 50,000 units in 250 mL of NaCl 0.9%	**200 units/mL**
Solution B	Penicillin G 500,000 units in 250 mL of NaCl 0.9%	**2,000 units/mL**
Solution C	Penicillin G 5,000,000 units in 250 mL of NaCl 0.9%	**20,000 units/mL**

- **Refer to General desensitization orders and patient monitoring**
- **Administer the incremental doses in the table below in succession without interruption using the infusion solution, rate and duration indicated below. IV tubing should be pre-flushed with the appropriate solution (A, B, or C) and attached to the IV hub, prior to starting infusion with each bag. Do not wait between bags.**

					Nursing documentation						
Dose	**Solution**	**Infusion Rate**	**Infusion Duration**	**Dosage**	Time dose given	T°	HR	RR	BP	O_2 Sat	Initial
1	**A (200 units/mL)**	**2 mL/h**	**15 min**	100 units							
2		**5 mL/h**	**15 min**	250 units							
3		**10 mL/h**	**15 min**	500 units							
4		**20 mL/h**	**15 min**	1,000 units							
5	**B (2,000 units/mL)**	**5 mL/h**	**15 min**	2,500 units							
6		**10 mL/h**	**15 min**	5,000 units							
7		**20 mL/h**	**15 min**	10,000 units							
8		**40 mL/h**	**15 min**	20,000 units							
9	**C (20,000 units/mL)**	**10 mL/h**	**15 min**	50,000 units							
10		**12 mL/h**	***25 min***	100,000 units							
11		**24 ml/h**	**25 min**	200,000 units							
12		**45 mL/h**	**25 min**	375,000 units							
13		**50 mL/h**	***30 min***	500,000 units							
14		**100 mL/h**	**30 min**	1,000,000 units							
15		**150 mL/h**	***40 min***	2,000,000 units							
Totals:		240 mL infused	5 h 10 min	4,264,350 units							

<u>If desensitization procedure well tolerated:</u>

Penicillin G _____ units IV every _____ hours; for _____ days*

*To be started 4 hours after the last dose of the desensitization.

** Adapted with permission from The Scarborough Hospital (03-2015)**

Appendix 3 – Sample Oral Amoxicillin Desensitization[11]

Pharmacy to prepare the following:

Solution	Preparation	Concentration
Solution A	Take 0.5 mL of amoxicillin 50 mg/mL stock suspension (25 mg) and dilute to a total of 50 mL with distilled water	**0.5 mg/mL**
Solution B	Take 5 mL of amoxicillin 50 mg/mL stock suspension (250 mg) and dilute to a total of 50 mL with distilled water	**5 mg/mL**
Solution C	Amoxicillin stock suspension (50 mg/mL)	**50 mg/mL**

- **Refer to General desensitization orders and patient monitoring**
- **Administer the doses in the table below in succession every 15 minutes if the prior dose is well tolerated:**

				Nursing documentation						
Dose	**Solution**	**Dosage**	**Volume**	Time Dose Given	T°	HR	RR	BP	O_2 Sat	Initial
1	**Solution A (0.5 mg/mL)**	**0.05 mg**	**0.1 mL**							
2		**0.1 mg**	**0.2 mL**							
3		**0.2 mg**	**0.4 mL**							
4		**0.4 mg**	**0.8 mL**							
5		**0.8 mg**	**1.6 mL**							
6		**1.6 mg**	**3.2 mL**							
7		**3.2 mg**	**6.4 mL**							
8	**Solution B (5 mg/mL)**	**6 mg**	**1.2 mL**							
9		**12 mg**	**2.4 mL**							
10		**25 mg**	**5 mL**							
11	**Solution C (50 mg/mL)**	**50 mg**	**1 mL**							
12		**100 mg**	**2 mL**							
13		**200 mg**	**4 mL**							
14		**400 mg**	**8 mL**							
Total:		**799.35 mg**	**36.3 mL**							

<u>If desensitization procedure well tolerated:</u>

Amoxicillin_____ PO every _____ hours; for _____ days*

*To be started 8 hours after the last dose of the desensitization.

** Adapted with permission from The Scarborough Hospital (03-2015)**

Appendix 4 – Sample Beta-Lactam 2 gm IV Desensitization[11]

Pharmacy to prepare the following:

**** This protocol is intended for use for beta-lactams dosed at 2 gm per dose:**

Please specify the beta-lactam:_____

Solution	Preparation	Concentration
Solution A	10 mg in 250 mL of NaCl 0.9%	**0.04 mg/mL**
Solution B	100 mg in 250 mL of NaCl 0.9%	**0.4 mg/mL**
Solution C	1,000 mg in 250 mL NaCl 0.9%	**4 mg/mL**
Solution D	2,000 mg in 250 mL of NaCl 0.9%	**8 mg/mL**

- **Refer to General desensitization orders and patient monitoring**
- **Administer the incremental doses in the table below in succession without interruption using the infusion solution, rate and duration indicated below. IV tubing should be pre-flushed with the appropriate solution (A, B, C, or D) and attached to the IV hub, prior to starting infusion with each bag. Do not wait between bags.**

					Nursing documentation						
Dose	**Solution**	**Infusion Rate**	**Infusion Duration**	**Dosage**	Time dose given	T°	HR	RR	BP	O_2 Sat	Initial
1	**A (0.04 mg/mL)**	**2 mL/h**	**15 min**	**0.02 mg**							
2		**5 mL/h**	**15 min**	**0.05 mg**							
3		**10 mL/h**	**15 min**	**0.1 mg**							
4		**20 mL/h**	**15 min**	**0.2 mg**							
5	**B (0.4 mg/mL)**	**5 mL/h**	**15 min**	**0.5 mg**							
6		**10 mL/h**	**15 min**	**1 mg**							
7		**20 mL/h**	**15 min**	**2 mg**							
8		**40 mL/h**	**15 min**	**4 mg**							
9	**C (4 mg/mL)**	**10 mL/h**	**15 min**	**10 mg**							
10		**20 mL/h**	**15 min**	**20 mg**							
11		**40 mL/h**	**15 min**	**40 mg**							
12		**75 mL/h**	**15 min**	**75 mg**							
13		**100 mL/h**	**15 min**	**100 mg**							
14		**125 mL/h**	***30 min***	**250 mg**							
15	**D (8 mg/mL)**	**62.5 mL/h**	***60 min***	**500 mg**							
16		**125 mL/h**	***60 min***	**1,000 mg**							
Totals:		340 mL	5 h 45 min	2002.87 mg							

If desensitization procedure well tolerated:

- _____**every** _____ **hours; for** _____ **days***

(*To be started _____ hours after the last dose of the desensitization)

** Adapted with permission from The Scarborough Hospital (03-2015)**

Appendix 5 – Sample Beta-Lactam 1 gm IV Desensitization[11]

Pharmacy to prepare the following:

<u> This protocol is intended for use for beta-lactams dosed at 1 gm per dose:</u>**

Please specify the beta-lactam:_____

Solution	Preparation	Concentration
Solution A	10 mg in 250 mL of NaCl 0.9%	**0.04 mg/mL**
Solution B	100 mg in 250 mL of NaCl 0.9%	**0.4 mg/mL**
Solution C	1,000 mg in 250 mL NaCl 0.9%	**4 mg/mL**
Solution D	500 mg in 100 mL of NaCl 0.9%	**5 mg/mL**

- **Refer to General desensitization orders and patient monitoring**
- **Administer the incremental doses in the table below in succession without interruption using the infusion solution, rate and duration indicated below. IV tubing should be pre-flushed with the appropriate solution (A, B, C, or D) and attached to the IV hub, prior to starting infusion with each bag. Do not wait between bags.**

					Nursing documentation						
Dose	**Solution**	**Infusion Rate**	**Infusion Duration**	**Dosage**	Time dose given	T°	HR	RR	BP	O_2 Sat	Initial
1	**A (0.04 mg/mL)**	**2 mL/h**	**15 min**	**0.02 mg**							
2		**5 mL/h**	**15 min**	**0.05 mg**							
3		**10 mL/h**	**15 min**	**0.1 mg**							
4		**20 mL/h**	**15 min**	**0.2 mg**							
5	**B (0.4 mg/mL)**	**5 mL/h**	**15 min**	**0.5 mg**							
6		**10 mL/h**	**15 min**	**1 mg**							
7		**20 mL/h**	**15 min**	**2 mg**							
8		**40 mL/h**	**15 min**	**4 mg**							
9	**C (4 mg/mL)**	**10 mL/h**	**15 min**	**10 mg**							
10		**20 mL/h**	**15 min**	**20 mg**							
11		**40 mL/h**	**15 min**	**40 mg**							
12		**75 mL/h**	**15 min**	**75 mg**							
13		**100 mL/h**	**15 min**	**100 mg**							
14		**125 mL/h**	***30 min***	**250 mg**							
15	**D (5 mg/mL)**	**100 mL/h**	***60 min***	**500 mg**							
Totals:		250 mL	4 h 45 min	1002.87 mg							

<u>If desensitization procedure well tolerated:</u>

- _____**every** _____ **hours; for** _____ **days***

(*To be started _____ hours after the last dose of the desensitization)

** Adapted with permission from The Scarborough Hospital (03-2015)**

References:

1. Lagace-Wiens P, Rubinstein E. Adverse reactions to beta-lactam antimicrobials. *Expert opinion on drug safety.* 2012;11(3):381-399.
2. Solensky R. Allergy to beta-lactam antibiotics. *J Allergy Clin Immunol.* 2012;130(6):1442-1442 e1445.
3. Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *The Permanente journal.* 2009;13(2):12-18.
4. Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic & clinical pharmacology & toxicology.* 2006;98(4):357-362.
5. Macy E, Ngor E. Recommendations for the management of beta-lactam intolerance. *Clin Rev Allergy Immunol.* 2014;47(1):46-55.
6. Solensky R. Drug desensitization. *Immunology and allergy clinics of North America.* 2004;24(3):425-443, vi.
7. Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. *Allergy.* 2010;65(11):1357-1366.
8. Legendre DP, Muzny CA, Marshall GD, Swiatlo E. Antibiotic hypersensitivity reactions and approaches to desensitization. *Clin Infect Dis.* 2014;58(8):1140-1148.
9. Drug allergy: an updated practice parameter. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2010;105(4):259-273.
10. Pham MN, Ho HE, Desai M. Penicillin desensitization: Treatment of syphilis in pregnancy in penicillin-allergic patients. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology.* 2017;118(5):537-541.
11. The Scarborough Hospital. Desensitization Protocols; 2015. *Adapted with permission.*
12. Castells M. Rapid desensitization for hypersensitivity reactions to medications. *Immunology and allergy clinics of North America.* 2009;29(3):585-606.
13. Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy.* 2015;45(2):300-327.
14. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. Am J Med. 2008;121(7):572-576.
15. Liu A, Fanning L, Chong H, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. Clin Exp Allergy. 2011;41(12):1679-1689.
16. Wendel GD, Jr., Stark BJ, Jamison RB, Molina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. The New England journal of medicine. 1985;312(19):1229-1232.
17. Saskatoon Health Region. IV Antibiotic Desensitization for Type 1 Reaction Protocol: Cloxacillin.
18. Capital Health (NS). Antimicrobial Handbook - Beta-Lactam Desensitization Protocol. 2007.
19. Drug allergy: an updated practice parameter. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2010;105(4):259-273.
20. Blond-Hill E, Fryters S. Bugs and Drugs: An Antimicrobial/Infectious Disease. 2012:87-90.
21. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321(2):188-199.