Management of Antibiotic Allergy

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Management of Patients with Drug Allergy

History

Testing

Induction of Drug Tolerance (desensitization)

History in Evaluation of Drug Allergy

- **A thorough history is the best tool for management of drug allergy**
- Previous records if available may be very helpful
- The history is essential to determine
  - Classification of adverse drug reaction
  - Choice of diagnostic tests
  - Safety of reintroduction of medications
  - Need for induction of drug tolerance procedures (e.g. desensitization)

Stepwise Approach to Drug Allergy History

1	Confirm history is a drug allergic reaction
2	Classify drug allergic reaction
3	Determine likelihood of drug(s) in question to cause reaction
4	Determine elements that may influence drug allergy history
5	Evaluate if subsequent exposure to drug
6	What is likely future need of drug?

Khan DA. Manual of Allergy & Immunology 5th Ed. (in press)

Diagnostic Tools In Antibiotic Allergy

Skin Testing

In vitro Testing

Drug Challenge

(Old but not Ancient)

Penicillin Skin Testing

- Penicillin skin testing is the most reliable method for evaluating IgE-mediated penicillin allergy
- If available, penicillin skin testing should be performed with both major and minor determinants
- The negative predictive value of penicillin skin testing for severe immediate reactions approaches 100%.

PRE-PEN and PCN G Skin Testing

- Penicillin challenges of individuals skin test-negative to penicilloyl-polylysine and penicillin G have similar reaction rates compared to individuals skin test negative to the full set of major and minor penicillin determinants
- Therefore, based on the available literature, skin testing with penicilloyl-polylysine and penicillin G appears to have adequate negative predictive value in the evaluation of penicillin allergy

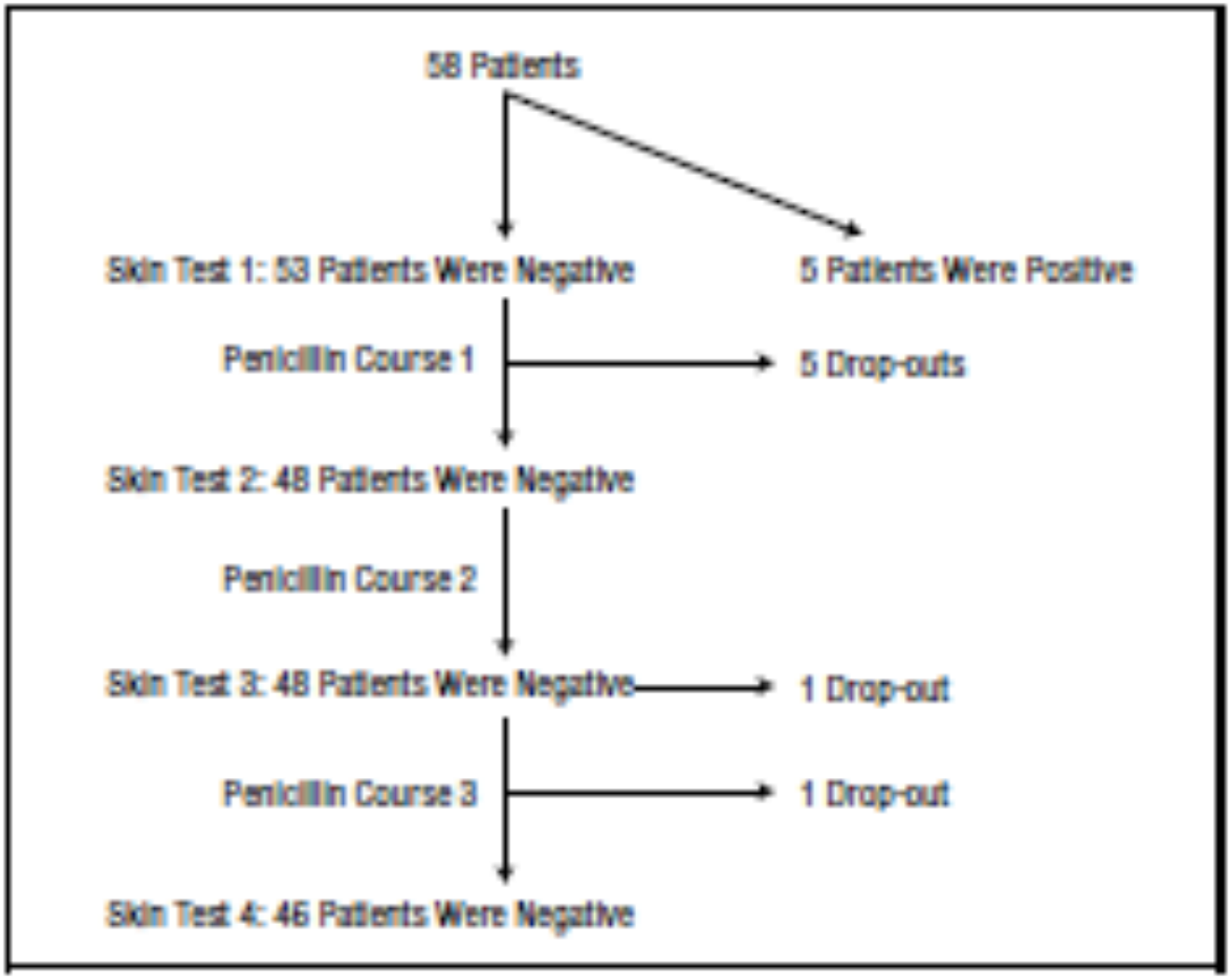
Green GR, et al. J Allergy Clin Immunol1977;60:339-45.
Brown BC, et al. JAMA1964;189:599-604.

Penicillin Resensitization

- Resensitization after treatment with oral penicillin is rare
- Penicillin skin testing does not routinely need to be repeated in patients with a history of penicillin allergy who have tolerated one or more courses of oral penicillin

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78.

Lack of Resensitization with Oral Penicillins



None of 46 pts who completed protocol converted to a positive PCN skin test

Solensky R, et al. Arch Intern Med 2002;162:822-6.

Skin testing for Other Antibiotics

- There are no validated diagnostic tests for evaluation of IgE-mediated allergy to non-penicillin antibiotics
- Skin testing with non-irritating concentrations of non-penicillin antibiotics established for 15 commonly used antibiotics
- **A negative skin test result does not rule out the possibility of an immediate-type allergy**
- Positive skin test results to a drug concentration known to be nonirritating suggests the presence of drug-specific IgE

Empedrad R et al. J Allergy Clin Immunology 2003;112:629.

Antimicrobial drug	Nonirritating concentration	Full-strength concentration	Dilution from full strength
azithromycin	10 μg/ml	100 mg/ml	1:10,000
cefotaxime	10 mg/ml	100 mg/ml	1:10
cefuroxime	10 mg/ml	100 mg/ml	1:10
cefazolin	33 mg/ml	330 mg/ml	1:10
ceftazidime	10 mg/ml	100 mg/ml	1:10
ceftriaxone	10 mg/ml	100 mg/ml	1:10
clindamycin	15 mg/ml	150 mg/ml	1:10
cotrimoxazole	800 μg/ml	80 mg/ml	1:100
erythromycin	50 μg/ml	50 mg/ml	1:1000
gentamicin	4 mg/ml	40 mg/ml	1:10
levofloxacin	25 μg/ml	25 mg/ml	1:1000
imipenem/cilastin	0.5 mg/ml	500 mg/100 ml	1:10
meropenem	1 mg/ml	50 mg/ml	1: 50
nafcillin	25 μg/ml	250 mg/ml	1:10,000
ticarcillin	20 mg/ml	200 mg/ml	1:10
tobramycin	4 mg/ml	80 mg/2 ml	1:10
vancomycin	5 μg/ml	50 mg/ml	1:10,000

Khan DA. Manual of Allergy & Immunology 5th Ed. (in press)

Skin Testing for Delayed Drug Reactions

Delayed Intradermal Tests

Patch Tests

Skin Testing for Delayed Reactions

- Skin testing using both intradermal and patch tests has been utilized for certain delayed immunologic drug reactions
- The negative predictive values for these techniques have not been well established and therefore a negative test does not preclude a drug allergy

Drug Allergy Skin Testing in Delayed Cutaneous Reactions

Eruption	Patch Test	Prick/ Intracutaneous Test
Maculopapular rash	may be useful	may be useful
Eczema	may be useful	may be useful
SDRIFE	may be useful	?
AGEP	may be useful	?
Fixed Drug	may be useful (on residual area)	?

Drug Reactions where skin tests have little or no value include:
DRESS, Vasculitis, TEN

Barbaud A. Immunol Allergy Clin N Am 2009;29:517-35.

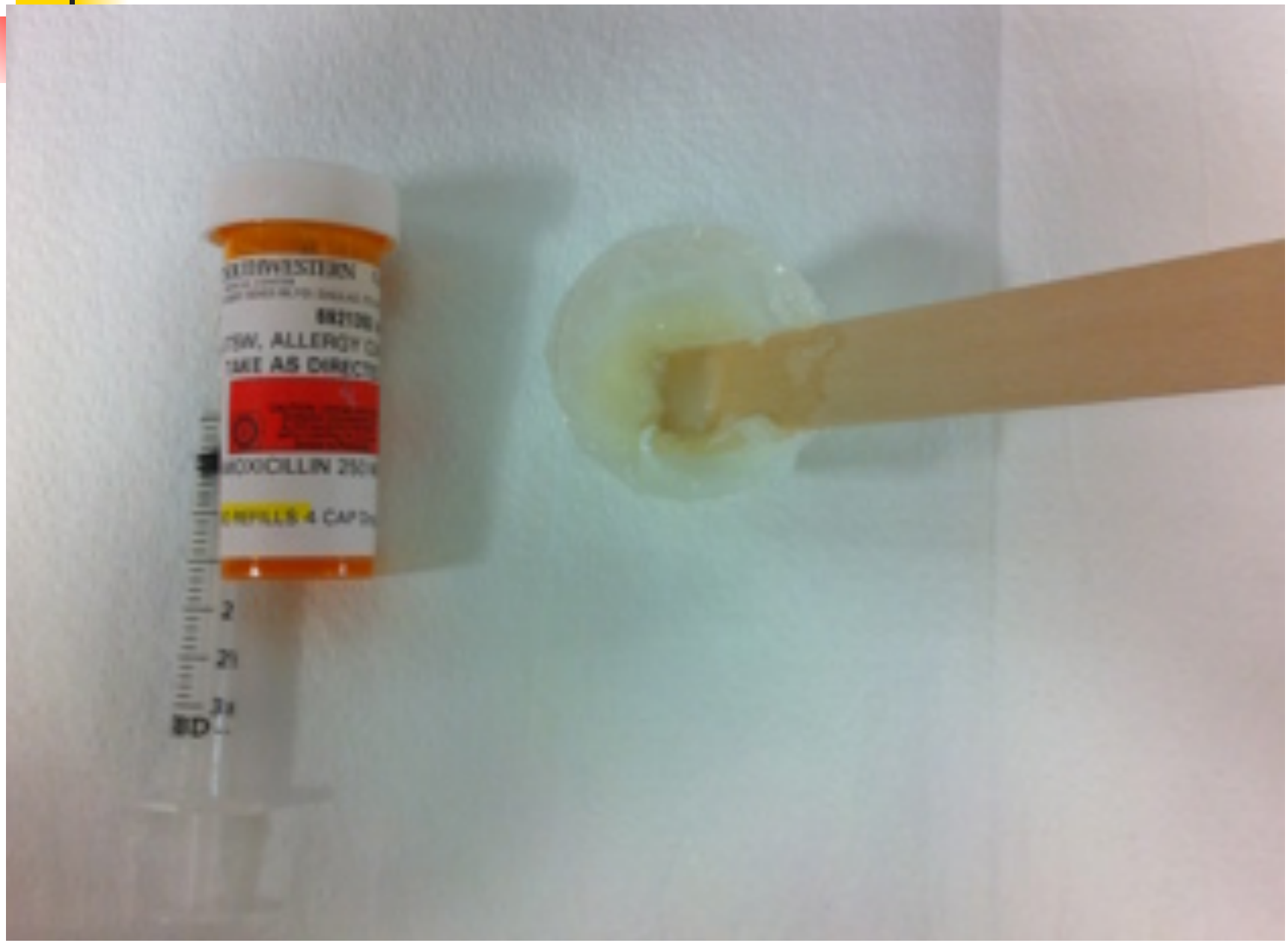
Delayed Intradermal Drug Tests

- Technique for performing delayed intradermal skin tests is similar to intradermal testing for immediate reactions
  - intradermal injection of 0.03-0.05 ml to raise a 3-5 mm wheal
  - tests are read after 24 hours or later and considered positive when there is an infiltrated erythematous reaction

Drug Patch Testing

- Patch testing has also been utilized in delayed immunologic drug reactions in a similar fashion as intradermal tests
- Non-irritating concentrations have not been firmly established for drug patch tests
- Typically, drug patch testing is performed starting with 1% concentration in petrolatum, going up to a 10% concentration
- A 30% concentration may be used for a pulverized tablet

Barbaud A. Immunol Allergy Clin N Am 29 (2009) 517–535.



Drug Patch Testing

- Drug patch testing may be more useful than delayed intradermal testing in:
  - fixed drug eruptions (at the residual site)
  - Acute generalized exanthematous pustulosis (AGEP)

In Vitro Tests for Drug Allergy

Specific IgE

Lymphocyte transformation

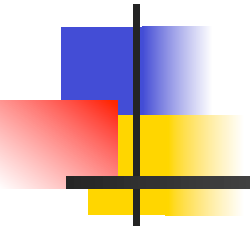
Basophil activation

Others

Basophil Activation Tests in Drug Allergy

- Basophil activation test is a method of evaluating expression of CD63 or CD203c on basophils after stimulation with an allergen
- Few studies with small numbers of patients have used this method to evaluate patients with possible allergies to antibiotics, muscle relaxants, NSAIDs
- Further confirmatory studies, especially with commercially available tests, are needed before its general acceptance as a diagnostic tool

Bernstein IL, et al. Ann Allergy Asthma Immunol 2008;100:S1-148.



Graded Challenges

Terminology

- Drug Challenge
  - Drug provocation test
  - Graded dose challenge
  - Incremental challenge
  - Test dosing

Graded Challenge Vs. Desensitization

- Clinical Question: **Will this patient tolerate this drug?**
  - Graded challenge will answer this question

- Clinical Question: **How do I treat this patient who is allergic to this drug?**
  - Drug desensitization is a procedure to address this question

Definition of Graded Challenge

- *Graded challenge* or test dosing describes administration of progressively increasing doses of a medication until a full dose is reached.
- The intention of a graded challenge is to verify that a patient will not experience an immediate adverse reaction to a given drug.
- The medication is introduced in a controlled manner to a patient who has a low likelihood of reacting to it.

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78.

Drug Challenge Doses and Intervals

	Dose	**Interval**
Immediate Reaction History	$1/1000^{th}$ to $1/10^{th}$ therapeutic dose	Every 30-60 minutes
Delayed Reaction History	$1/100^{th}$ to $1/10^{th}$ therapeutic dose	Every 2-7 days

Protocols for Antibiotic Desensitizations

Beta-lactam Drug Desensitization

- Typical starting dose is 1/10,000th of target therapeutic dose
- Can also use calculated dose from skin test as starting point
- Further dosage increases are typically twice the previous dose
- Administered at 15-20 minute intervals until therapeutic dosage achieved

Rapid Drug Desensitization

- Rapid drug desensitizations should be performed in an appropriate setting, supervised by physicians familiar with the procedure, with continual monitoring of the patient and readiness to treat reactions including anaphylaxis
- Do not need to be performed in intensive care setting
  - Advantage of intensive care setting is typically closer nursing supervision
- Many experienced centers may perform desensitizations in outpatient setting

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78.

Oral Penicillin Desensitization

Step	PCN V (units/ml)	Dose (ml)	Dose (units)	Cumulative Dose
1	**1000**	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300
7	1000	6.4	6400	12,700
8	**10,000**	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	**80,000**	1.0	80,000	176,000
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700
Administer PCN V orally every 15 minutes per step Total time: 3 hours 45 minutes; Total dose 1.3 million units; Total volume 36.1 ml				

Wendel GD et al. New Engl J Med 1985;312:1229-32.

Preparing Penicillin Solutions

Preparation of PCN-V Solutions		
Use penicillin V elixir 250 mg/ml=80,000 units/ml (1 mg = 1600 units)		
Add 2 ml of 80,000 unit/ml PCN to 14 ml normal saline to make 10,000 unit/ml PCN V		
Add 2 ml of 10,000 unit/ml PCN V to 18 ml normal saline to make 1,000 unit/ml PCN V		
Quantity of PCN-V Solutions		
# syringes	**Syringe volume**	**PCN-V Solution**
1	1 cc	1000 U/ml
2	10 cc	1000 U/ml
1	10 cc	10,000 U/ml
1	20 cc	80,000 U/ml

Buchmiller BL, Khan DA. Curr Allergy Asthma Rep 2007, 7:402–409.

Outcomes and Safety of Penicillin Desensitizations

- Most all patients can be desensitized
- ~1/3 patients have mild cutaneous reactions during desensitization
- Severe reactions extremely rare
- Delayed reactions (cutaneous, serum sickness, nephritis) <10%
- Long-acting benzathine penicillin may be administered after desensitization safely at intervals of 1-3 weeks*

*Wendel GD et al. New Engl J Med 1985;312:1229-32.

Cephalosporin Desensitization Protocol

Table 1 Rapid intravenous desensitization to 1 g of ceftazidime in a cystic fibrosis patient

Full dose	1000.0 mg				Total to be injected in each bottle (mg)
Solution 1	250 ml of 0.040 mg/ml				10.000
Solution 2	250 ml of 0.400 mg/ml				100.000
Solution 3	250 ml of 3.969 mg/ml				992.130
Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.0200	0.0200
2	1	5	15	0.0500	0.0700
3	1	10	15	0.1000	0.1700
4	1	20	15	0.2000	0.3700
5	2	5	15	0.5000	0.8700
6	2	10	15	1.0000	1.8700
7	2	20	15	2.0000	3.8700
8	2	40	15	4.0000	7.8700
9	3	10	15	9.9213	17.7913
10	3	20	15	19.8426	37.6339
11	3	40	15	39.6852	77.3191
12	3	75	186	922.6809	1000.0000
			Total time = 351 min		

Castells MC. Curr Opin Allergy Clin Immunol 2006;6:476–481.

Non-Beta-Lactam Desensitizations

Antibiotic Class	Example	Desensitization Described
aminoglycoside	tobramycin	Yes (Earl 1987)
glycopeptides	vancomycin	Yes (Lerner 1984; Wong 1994, etc)
lincosamides	clindamycin	Yes (Martin 1992)
lipopeptide	daptomycin	Yes (Metz 2008)
macrolide	erythromycin,clarithromycin	Yes (Swamy 2010)
nitrofurans	nitrofurantoin	?
quinolones	Ciprofloxacin, levofloxacin	Yes (Lantner 1995, etc)
sulfonamides	sulfamethoxazole	Yes (Gompels 1999, Demoly 1998, etc)
tetracyclines	doxycycline	?
Anti-mycobacterial	Isoniazid,ethambutol, rifampin	Berte 1964, Holland 1990, etc.

Non-Beta-Lactam Desensitizations

Other Antibiotics	**Desensitization Described**
chloramphenicol	?
linezolid	Yes (Cawley 2006)
metronidazole	Yes (Kurohara 1991)
tigecycline	?

Oral Clarithromycin Desensitization Protocol

Table 2. Clarithromycin Oral Desensitization Protocol[a]

Dose no.	Concentration, mg/mL	Dose	
		mL	mg
1	0.025	1.25	0.03
2	0.025	2.5	0.06
3	0.025	5	0.125
4	0.25	1	0.25
5	0.25	2	0.5
6	0.25	4	1
7	2.5	0.8	2
8	2.5	1.6	4
9	2.5	3.2	8
10	2.5	6.4	16
11	25	1.3	32
12	25	2.5	64
13	25	5	125
14	25	10	250
Cumulative dose			**503**

[a] Serial 10-fold dilutions of a clarithromycin suspension of 125 mg/5 mL (25 mg/mL) were performed to make clarithromycin solutions at 2.5, 0.25, and 0.025 mg/mL. Each dose was administered in 15-minute intervals.

Swamy N et al. Ann Allergy Asthma Immunol 2010;105:489-90.

Rapid Trimethoprim-Sulfamethoxazole Induction of Drug Tolerance

Table 9. Six-Hour Trimethoprim-Sulfamethoxazole Induction of Drug tolerance Procedure[82a]

Step	Drug dosage	Concentration of TMP-SMX	Volume of TMP-SMX solution, mL	Time, min
1	0.2/1 μg	8/40 μg/mL	0.025	0
2	0.6/3 μg	8/40 μg/mL	0.075	30
3	1.8/9 μg	8/40 μg/mL	0.225	60
4	6/30 μg	8/40 μg/mL	0.75	90
5	18/90 μg	8/40 μg/mL	2.25	120
6	60/300 μg	8/40 μg/mL	7.5	150
7	0.2/1 mg	80/400 μg/mL	2.5	180
8	0.6/3 mg	80/400 μg/mL	7.5	210
9	1.8/9 mg	0.8/4 mg/mL	2.25	240
10	6/30 mg	8/40 mg/mL	0.75	270
11	18/90 mg	8/40 mg/mL	2.25	300
12	60/300 mg	8/40 mg/mL	7.5	330

[a] Concentrations can be made by making 3 sequential 10-fold dilutions from the pediatric trimethoprim-sulfamethoxazole (TMP-SMX) solution available as 40/200/5 mL (8/40 mg/mL).

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78.
Adapted from Demoly P et al. J Allergy Cl;in Immunol 1998;102:1033-6.

Gradual Trimethorpim-Sulfamethoxazole Induction of Tolerance Procedure

10 day TMP-SMX Induction of Drug Tolerance Procedure

Day	Dosage TMP/SMX	Concentration/Tablet	Amount
1	0.4/2 mg	0.4/2 mg/ml	1 ml
2	0.8/4 mg	0.4/2 mg/ml	2 ml
3	1.6/8 mg	0.4/2 mg/ml	4 ml
4	3.2/16 mg	0.4/2 mg/ml	8 ml
5	8/40 mg	8/40 mg/ml	1 ml
6	16/80 mg	8/40 mg/ml	2 ml
7	32/160 mg	8/40 mg/ml	4 ml
8	64/320 mg	8/40 mg/ml	8 ml
9	80/400 mg	80/400 mg tablet	1 tablet
10	160/800 mg	160/800 mg tablet	1 tablet

Gompels MM, et al. J Infect 1999 Mar;38(2):111-5.

Rapid Vancomycin Induction of Drug Tolerance

Table 8. Vancomycin Induction of Drug Tolerance Procedure[344a]

Time, min	Concentration of vancomycin, mg/mL	Infusion rate, mL/min	Vancomycin infusion rate, mg/min	Cumulative dose, mg
0	0.0001[b]	1.0	0.00010	0
10	0.001	0.33	0.00033	0.0010
20	0.001[c]	1.0	0.001	0.0043
30	0.01	0.33	0.0033	0.0143
40	0.01	1.0	0.01	0.047
50	0.1	0.33	0.033	0.147
60	0.1	1.0	0.1	0.48
70	1	0.33	0.33	1.48
80	1	1	1	4.78
90	10	0.22	2.2	14.8
100	10	0.44	4.4	37

[a] Rest of infusion maintained at 4.4 mg/min of vancomycin until final dosage reached. Antihistamine pretreatment and concurrent treatment used during protocol.

[b] Typical starting concentration in patients with severe vancomycin reactions.

[c] Typical starting concentration in patients with moderate vancomycin reactions.

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78. Adapted from Wong J et al. J Allergy Clin Immunol 1994;94:189-4.

Rapid Induction of Drug Tolerance to Anti-Mycobacterial Drugs

Table 2 Rapid oral tolerance induction protocols

Time (minutes)	Dose (mg)	Cumulative dose (mg)
ISONIAZID		
0	0.05	0.05
20	0.10	0.15
40	0.25	0.40
60	0.50	0.90
80	1.00	1.90
100	2.00	3.90
120	4.10	8.00
140	8.20	16.20
160	16.30	32.50
180	30.60	63.10
200	50.30	113.40
340	100.00	213.40
480 (8 h)	150.00	363.40 (total daily dose)
RIFAMPICIN		
0	0.10	0.10
20	0.50	0.60
40	1.00	1.60
60	2.00	3.60
80	4.00	7.60
100	8.00	15.60
120	16.00	31.60 (suspended)
ETHAMBUTOL		
0	0.10	0.10
45	0.50	0.60
90	1.00	1.60
135	2.00	3.60
180	4.00	7.60
225	8.00	15.60
270	16.00	31.60
315	32.00	63.60
360	50.00	113.60
405	100.00	213.60
450	200.00	413.60
495	400.00	813.60
660 (11 h)	400.00	1213.60 (total daily dose)

Carvalho R et al. Allergol Immunopathol (Madr). 2009 Nov-Dec;37(6):336-8.

Reactions During Desensitization

- No consensus approach
- Options
  1) Treat through reaction and continue
  2) Treat symptoms, reduce by 1-2 doses and continue protocol
  3) Treat symptoms, modify protocol (adding steps) and resuming

Cernades JR et al. Allergy 2010;65:1357-66.

Conclusions

- Penicillin skin testing has excellent negative predictive value
- Skin testing for other antibiotics can be performed using non-irritating concentrations but the negative predictive value is not clearly defined
- More data with basophil activation tests are required before considering for clinical use
- Drug challenges are the standard for determining drug tolerance
- Several induction of drug tolerance procedures exist for numerous types of antibiotics