Non-Beta-lactam Antibiotic: Testing and Desensitization

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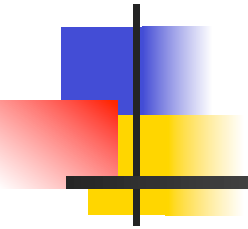
Case of Macrolide Allergy

- A 68-year-old woman developed urticaria and shortness of breath six days into a course of clarithromycin for *Mycobacterium avium intracellulare* infection
- Her pulmonologist advised her to take a "test" dose of azithromycin 250 mg. Within an hour she developed urticaria, shortness of breath, and throat tightness resulting in an emergency department visit.

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

Testing in Non-Beta-lactam Antibiotic Allergy



Diagnostic Tools In Drug Allergy

Skin Testing

In vitro Testing

Drug Challenge

Immediate and Delayed Skin Testing

Skin testing for Non-beta-lactam Antibiotics

- There are no validated diagnostic tests for evaluation of IgE-mediated allergy to non-beta-lactam 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.

Non-Irritating Skin Test Concentrations for Non-Beta-lactam antibiotics

Antimicrobial drug	Nonirritating concentration	Full-strength concentration	Dilution from full strength
azithromycin	10 μg/ml	100 mg/ml	1:10,000
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
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 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.

In Vitro Tests for Drug Allergy

Specific IgE

Lymphocyte transformation

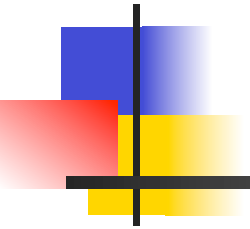
Basophil activation

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.

Diagnostic Testing in Macrolide and Quinolone Allergy

Macrolide Allergy Testing

- 107 patients with histories of reactions to macrolides evaluated with oral challenge to causative macrolide
  - Macrolides challenged: erythromycin, spiramycin, josamycin, clarithromycin, roxithromycin, azithromycin, dithromycin
  - Historical reactions: 26 maculopapular, 41 urticaria, 16 angioedema, 5 anaphylaxis
- 8/107 (7.5%) had positive challenges

Benahmed S et al. Allergy 2004;59:1130-33.

Skin Testing in Macrolide Allergy

- Skin tests performed in 33/107 subjects
- Skin testing performed to injectable erythromycin and spiramycin up to 10 mg/ml
- Control subjects not tested to determine non-irritating concentration

	Positive Challenge	**Negative Challenge**
Positive Skin Test	4	7
Negative Skin Test	4	18

Specificity: 72%; Sensitivity: 50%
Positive predictive value: 36%; Negative predictive value: 82%

Benahmed S et al. Allergy 2004;59:1130-33.

Clarithromycin Allergy Testing

- 64 children with histories of cutaneous reactions to clarithromycin evaluatd
  - 19% maculopapular, 62% urticaria, 18% angioedema
  - 44 (69%) had reactions > 1 hr from last dose
  - 20 (31%) had reactions within an hour
- Evaluation included skin tests and oral challenge

Mori F et al. Ann Allergy Asthma Immunol 2010;104:417-19.

Clarithromycin Skin Testing

- A **lyophilized form of clarithromycin available as an injectable formulation was used** (not available in U.S.)
  - Non-irritating dose determined to be 0.5 mg/ml in 18 clarithromycin tolerant children
- 10 children had positive skin tests
  - 9/10 to the 0.5 mg/ml ID test
  - 1/10 to the 0.05 mg/ml ID test
- 4/64 had positive challenges
  - 2 immediate and 2 delayed

Mori F et al. Ann Allergy Asthma Immunol 2010;104:417-19.

Clarithromycin Skin Testing

- ¾ children with positive skin tests had positive challenges
- Sensitivity 75%
- Specificity 90%
- Negative predictive value 98%
- Positive predictive value 33%

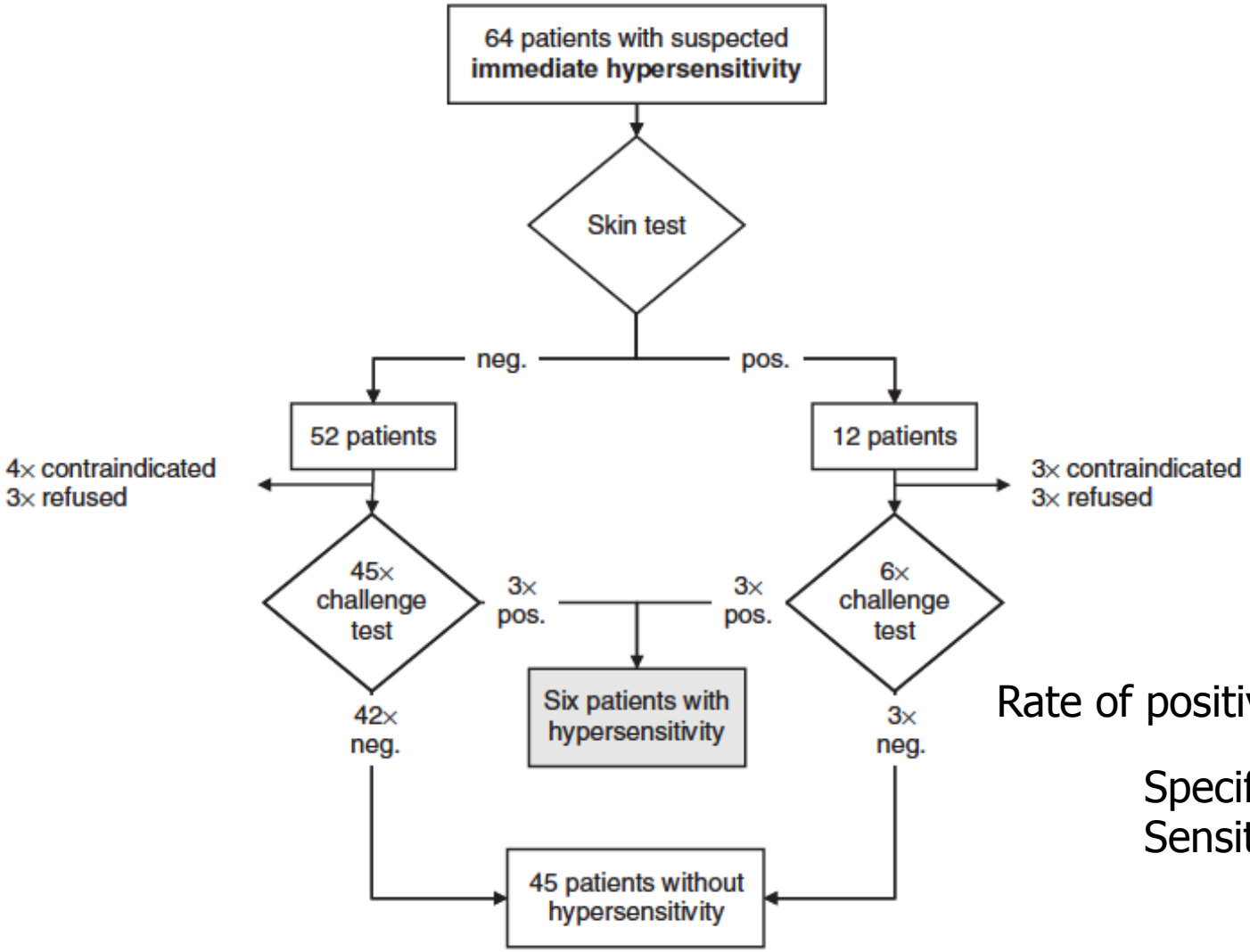
Mori F et al. Ann Allergy Asthma Immunol 2010;104:417-19.

Quinolone Testing

- 101 patients with histories of quinolone reactions evaluated with oral challenges
  - 64 had histories of immediate reactions
    - Prick testing performed at therapeutic concentration
      - Authors unable to identify reliable non-irritating concentration for intradermal tests
  - 37 had histories of delayed reactions
    - Patch testing performed

Seitz CS et al. Clin Exp Allergy 2009;39:1738-45.

Prick Testing and Quinolone Challenge Results in Suspected Immediate Reactors

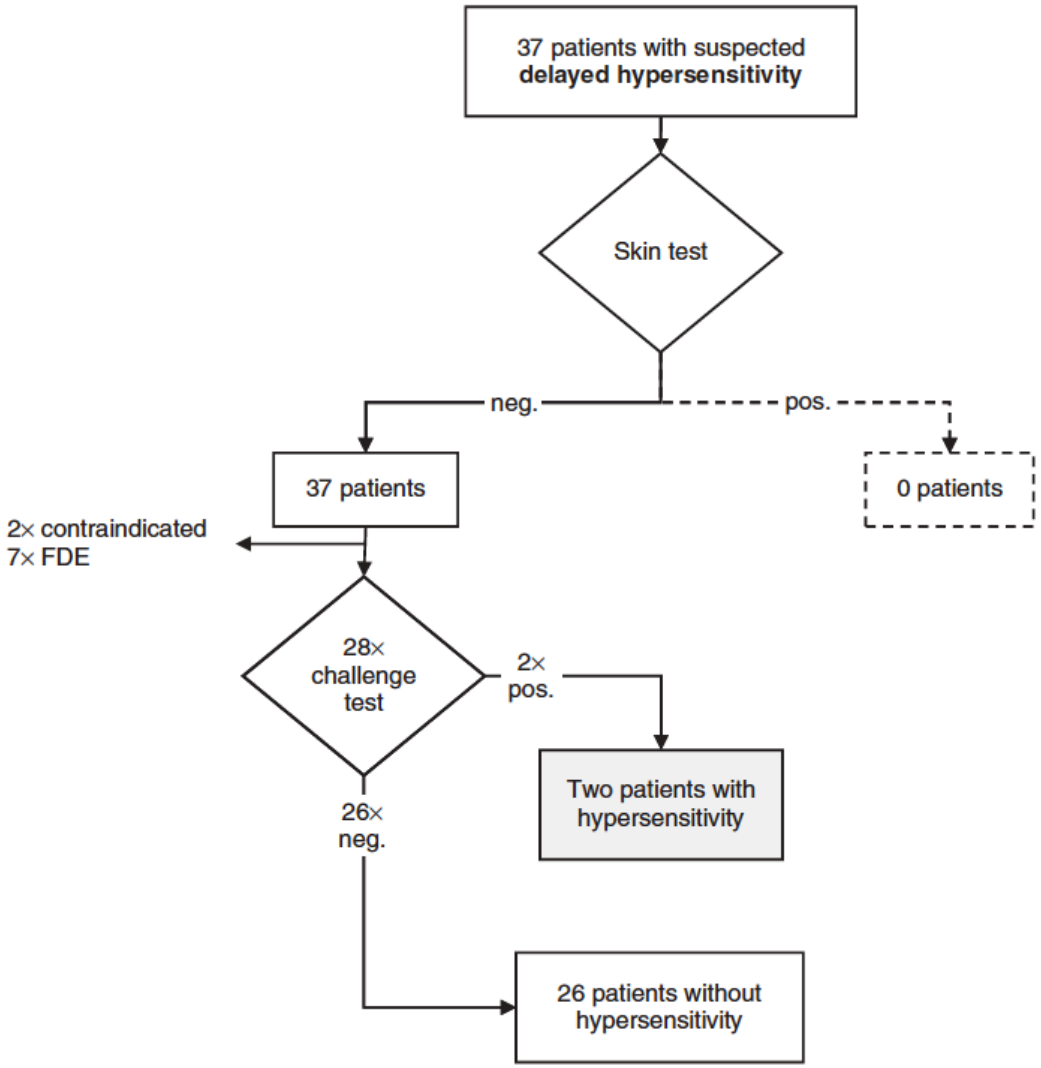


Rate of positive challenges: 12%

Specificity: 93%
Sensitivity: 50%

Seitz CS et al. Clin Exp Allergy 2009;39:1738-45.

Patch Testing and Quinolone Challenge Results in Suspected Delayed Reactors



All patch tests negative

Rate of positive challenges: 7%

Seitz CS et al. Clin Exp Allergy 2009;39:1738-45.

Quinolone Allerg Testing

- Retrospective study from Spain of 71 patients with quinolone reactions
  - Immediate: < 1hr of 1st dose (27 patients)
  - Accelerated: 1-24 hrs after 1st dose (8 patients)
  - Delayed: > 24 hrs (24 patients)
  - Atypical symptoms: isolated gastrointestinal or pruritus (12 patients)
- All patients had prick testing, some had intradermal testing
- 44/71 had drug challenges

Diaz M et al. J Investig Allergol Clin Immunol 2007;17:393-8.

Quinolone Skin Test Concentrations

Table 1. Quinolone Skin Test Concentrations

Drug	Concentrations	
	Prick	Intradermal
Ciprofloxacin	0.02 mg/mL	0.02 mg/mL
Norfloxacin	Tablet, 400 mg suspended in saline solution	NP
Ofloxacin	Tablet, 400 mg suspended in saline solution	NP
Moxifloxacin	Tablet, 400 mg suspended in saline solution	NP
Levofloxacin	5 mg/mL	0.05 mg/mL
Pipemidic acid	Tablet, 400 mg suspended in saline solution	NP
Trovafloxacin	Tablet, 200 mg suspended in saline solution	NP

*NP indicates not performed. (Intradermal tests were not performed when the drug was unavailable as an injectable solution.)

Diaz M et al. J Investig Allergol Clin Immunol 2007;17:393-8.

Quinolone Skin Test and Challenge Results

Table 2. Results of Challenge Tests According to the Type of Allergic Reaction or Timing and According to Skin Test Positivity or Negativity

Adverse Reaction Type	Skin Test Result	Challenge Test Result			
		Positive	Negative	Not Performed	Total
Immediate (group 1)	Positive	5	1	11	17
	Negative	1	4	5	10
	Total	6	5	16	27
Accelerated (group 2)	Positive		1	2	3
	Negative		5		5
	Total		6	2	8
After 24 hours (group 3)	Positive		1	6	7
	Negative	1	15	1	17
	Total	1	16	7	24
Atypical symptoms (group 4)	Positive		2	2	4
	Negative		8		8
	Total		10	2	12

Overall 7/44 (16%) had positive challenges

Specificity: 86%; Sensitivity: 71%

Positive predictive value: 50%; Negative predictive value: 94%

Diaz M et al. J Investig Allergol Clin Immunol 2007;17:393-8.

Basophil Activation Test in Quinolone Allergy

- Evaluated 38 patients with recent immediate reactions to quinolones
- Allergy confirmed by drug provocation for histories of urticaria and assumed for those with anaphylaxis
- BAT positive in:
  - 60% ciprofloxacin
  - 32% moxifloxacin
  - 21% levofloxacin

Aranda A et al. Allergy 2011;66:247-54.

Drug Desensitization in Non-Beta-lactam Antibiotic Allergy

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	?

Induction of Drug Tolerance Procedures

Type of tolerance	Time/ Duration	Initial Dose	Possible outcomes	Example
Immunologic IgE (drug desensitization)	Hours	mcg	antigen-specific mediator depletion, down-regulation of receptors	penicillin
Immunologic non-IgE	Hours to Days	mcg-mg	Unknown	TMP/SMX
Pharmacologic	Hours to Days	mg	metabolic shift, internalization of receptors	aspirin
Nonimmunologic mast cell activation	Hours	mcg	Unknown	paclitaxel
Undefined	Days to Weeks	mcg-mg	Unknown	allopurinol

Khan DA, Solensky R. J Allergy Clin Immunol 2010;125(2 Suppl 2):S126-37.

Protocols for Non-Beta-lactam Antibiotic Desensitization

Macrolide Allergy Case: Confirmed with Skin Tests

Table 1. Macrolide Skin Test Results[a]

Drug	Baseline	
Clarithromycin[b]	Prick: negative	
	Intradermal	
	0 min	4 × 6 mm
	15 min	7 × 8 mm[c]
Azithromycin[d]	Prick: 4 × 4 mm	
	Intradermal	
	0 min	4 × 4 mm
	15 min	7 × 7 mm[c]

[b] Clarithromycin concentrations used were 25 mg/mL for prick testing and 1 mg/mL for intradermal testing.
[c] A positive skin test result.
[d] Azithromycin concentrations used were 100 mg/mL for prick testing and 0.01 mg/mL for intradermal testing.

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

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.

Conclusions

- Skin testing for non-beta-lactam antibiotics can be performed using non-irritating concentrations
- Data for macrolide and quinolone skin tests suggest reasonable negative predictive value but are limited by overall low prevalence of true allergy
- More data with basophil activation tests are required before considering for clinical use
- Drug challenges are the standard for determining drug tolerance and are negative in the majority of patients with histories of macrolide and quinolone reactions
- Several induction of drug tolerance procedures exist for non-beta lactam antibiotics