Drug Desensitization

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Faculty Disclosure for Anne Liu, MD

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I will not be discussing products that are investigational or not labeled for use under discussion.

Overview

- Desensitization basics
- Patient selection
- Rapid desensitization
  - Protocol
  - Premedication
  - Treating reactions
  - Antibiotics
  - Chemotherapy
  - Monoclonal antibodies
  - Mechanism
- Slow desensitization
  - Protocols

1928

1947

SUCCESSFUL DESENSITIZATION IN PENICILLIN SENSITIVITY

SAMUEL M. PECK, M.D.
and
SHEPPARD SIEGAL, M.D.
With the assistance of
ROSE BERGAMINI, B.A.
New York

Penicillin is finding increasingly wide use in present day medical practice. The clinical indications for its use were at

third days. On the fourth day only three injections totaling 90,000 units could be given, because the patient developed an acute erythematovesicular eruption on the hands, feet and groin. The eruption rapidly spread to involve the entire body. The skin on the body showed a scarlatiniform type of eruption with edema of the face. There were some vesicles on the forearms. The eruption gradually subsided, but desquamation of the hands and feet was still evident one month later. There

arises when resumption of penicillin therapy becomes necessary or a person who previously exhibited such an allergic reaction.

Drug Desensitization Basics

- Incremental dose administration of a drug over hours or days
- Abrogates immediate and delayed HSR
- History of HSR:
  - IgE mediated
  - Non-IgE mediated with immediate features
  - Delayed type HSR

Drug Desensitization Basics

- Desensitization is a temporary state
- Lasts as long as drug is in circulation (2-3 half lives)
- Subsequent administrations must be by desensitization
- Redesensitization is required if doses are missed

Desensitization protocols

- Antibiotics
- Biologics / Monoclonals
- Chemotherapy
- Antiretrovirals, antimycobacterials
- ASA
- Iron
- Progesterone
- Allopurinol
- Insulin
- Vaccines

Desensitization protocols

- **Antibiotics**
- **Biologics / Monoclonals**
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Candidate selection

- Reaction characteristics
  - Immediate vs delayed
  - Severity
- Patient characteristics
  - Comorbidities
  - Ability to report/monitor symptoms
  - Ability to follow up
- Skin testing
- Indication for medication

Rapid desensitization: process

- Inpatient (first time in ICU)
- Allergy consultation
- Monitored setting where intubation and resuscitation can be performed easily
- 1:1 nursing ratio
- Rescue medications immediately available
- Reactions are not always predicted by prior desensitization

Rapid desensitization protocols

- Many protocols published.
- BWH experience with a 3-4 concentration protocol, with doubling doses/rates every 15-30 minutes.
- For chemotherapy, antibiotics, monoclonals, iron.

Castells 2008
Brennan 2009
Legere 2009

Sample protocol

TABLE I. Desensitization protocol for intravenous infliximab (600 mg)

Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.012	0.012
2	1	5.0	15	1.25	0.030	0.042
3	1	10.0	15	2.50	0.060	0.102
4	1	20.0	15	5.00	0.120	0.222
5	2	5.0	15	1.25	0.300	0.522
6	2	10.0	15	2.50	0.600	1.122
7	2	20.0	15	5.00	1.200	2.322
8	2	40.0	15	10.00	2.400	4.722
9	3	10.0	15	2.50	5.953	10.675
10	3	20.0	15	5.00	11.906	22.580
11	3	40.0	15	10.00	23.811	46.392
12	3	80.0	174.38	232.50	553.609	600.000
Total time = 340 min (5.66 h)						

Solution 1, 0.024 mg/mL; *solution 2*, 0.24 mg/mL; *solution 3*, 2.38 mg/mL.

Brennan 2009

Premedication

- H1 antagonist?
- H2 antagonist
- +/- ASA
- +/- Montelukast
- Avoid steroids
- Hold beta blockers if possible

Breslow 2009

Rescue medications

- H1 antagonists
- H2 antagonists
- Epinephrine (+/- glucagon)
- Albuterol, ipratropium
- Role of steroids
- ASA
- Leukotriene antagonists
- Anxiolytics
- Role of methylene blue?

Treating reactions

- Take careful note of details of reaction (VS, symptoms, duration, medications required for resolutions, protocol step)
- Pause protocol, treat to resolution, resume.
  - Usually can resume rate at which infusion was paused.

Adjunctive medications

- Post medications
- Anticipatory modifications for patient's subsequent desensitization:
  - Prolonging step prior to anticipated
  - Add intermediate rate step
  - Premed at specific step

Antibiotic desensitization

- Extensive experience of repeated desensitizations in cystic fibrosis patients
- Target concentration should be the standard concentration for that antibiotic, since completion of course will occur at that concentration.

Legere 2009

Antibiotic desensitization

- If there are alternatives, why still pursue desensitization?
  - Inferior efficacy
  - Higher cost
  - Development of resistance
  - Greater toxicities

Chemotherapy: skin testing

- Carboplatin skin test: false negative rate ~8% (false positive rate unknown)
  - 30% carboplatin-allergic patients are cross-sensitized to cisplatin.
- Cyclophosphamide, MTX
- Taxane skin testing: not predictive
- Do not ST using known vesiccants (e.g., doxorubicin).

Markman 2003
Lee 2005
Weiss 1990

Chemotherapy desensitization

- 413 chemotherapy desensitizations.
  - 94% mild/no reaction.
  - 6% severe reactions
  - All successfully received tx.
  - Reactions were more mild than the original reaction.
- Reactions tend to occur after interval without chemotherapy.

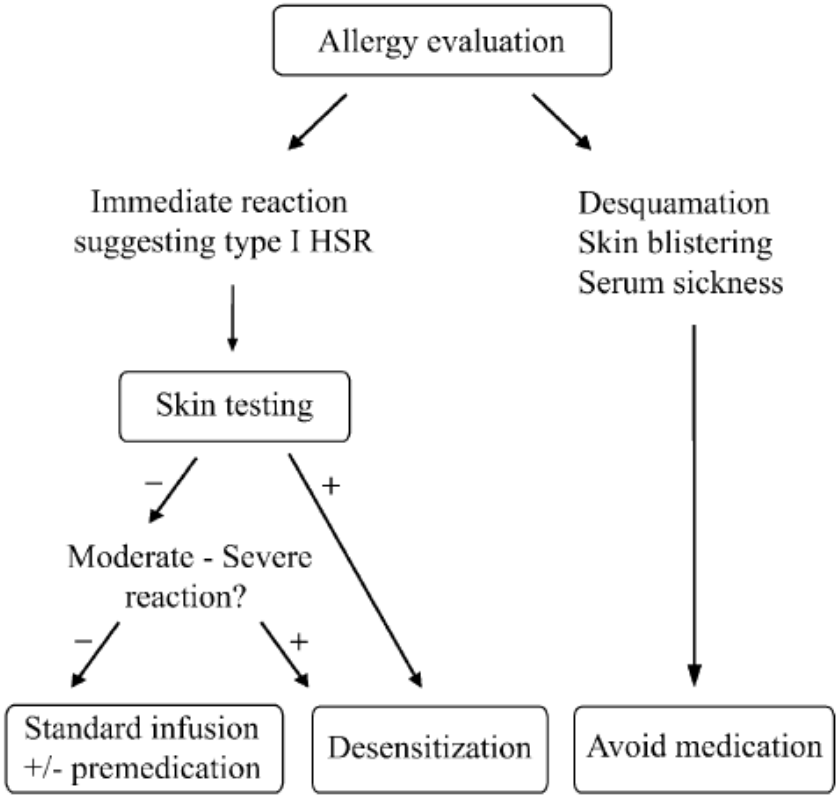
Castells 2008

Monoclonal antibody reactions

- Large MW, act as complete Ag
- Targeted by both T and B cells
- On-target effects, usu. surface receptors
- Long half-lives, dosing intervals
- Humanized versions may be an alternative.
- Fevers, rigors, myalgias
- Majority of reactions occur on first administration

Desensitization to mAb

- Patient selection challenges
- ST can be helpful

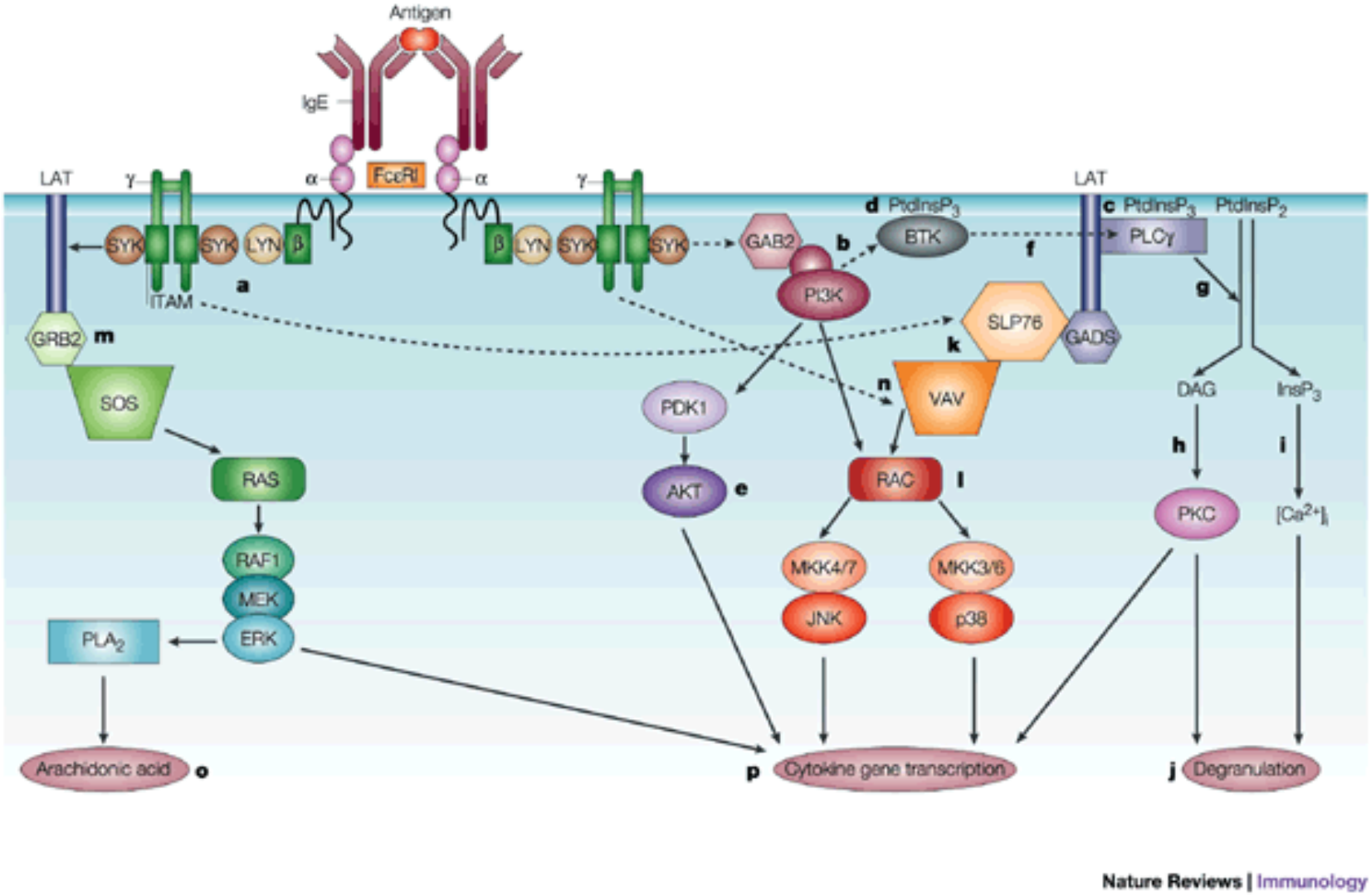


Brennan 2009

Proposed mechanisms for rapid desensitization

- Gradual cross-linking of drug-specific IgE on mast cells, < threshold
- Rapid internalization cross-linked FcεRI receptors
- Excess monomeric Ag incapable of cross-linking surface FcεRI receptors
- IgE induced loss of Syk kinase
- STAT6 involvement?
- Not well understood

Solensky 2004
Chisholm-Burns 2007
Macglashan 2004
Morales 2005



Kawakami 2002

Slow desensitization

- Benign delayed type hypersensitivities
- Careful patient selection
- Compounding pharmacies
- Established protocols:
  - Trimethoprim/sulfamethoxazole
  - Allopurinol
  - Some anti-mycobacterials, anti-retrovirals

Slow desensitization

- Many protocols described in literature
- Vary by starting dose, number of steps, number of days.
- Little data comparing different protocols
- Fluconazole, rifampin, isoniazid, acyclovir
- Unknown mechanism
- Role of skin and patch testing unknown

Challenges of desensitization

- Labor and resource intensive
- Requires close and continuous monitoring
- Variability in administration
- Idiosyncratic reactions can mimic immediate type HSR
- Slow oral desensitizations have variable success rates

Future questions

- Role of omalizumab in drug desensitization
- Predictors of successful and continued desensitization
- Special populations:
  - Organ transplant
  - Neutropenic, chemotherapy
  - ICU patients : low sensitivity of skin testing
- Other types of hypersensitivity reactions?

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