Cluster and rush allergen and venom immunotherapy (AIT/VIT)

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Disclosures

- No relevant disclosures

Objectives

- Understand the different risks and benefits with accelerated immunotherapy protocols
- Be able to prescribe and supervise medications utilized in accelerated IT protocols
- Correctly document and code patient encounters where accelerated IT protocols are utilized

Immunotherapy (IT) approach

- Detailed clinical history
- Skin and/or sIgE testing
- IT options
  - Sublingual immunotherapy (SLIT)
  - Intralymphatic immunotherapy (ILIT)
  - Subcutaneous immunotherapy (SCIT)
    - "Conventional" (standard)
    - Cluster
    - Rush
    - Ultrarush
  - Oral
  - Intranasal
  - Epicutaneous

Cox L et at. J Allergy Clin Immunol 2011; 127(1): S1-S55.

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Accelerated immunotherapy protocols

- Any patient who is considered for SCIT should be considered for an accelerated protocol
- Allows patients to reach the desired "maintenance dose" faster
- Reduced injections and visits compared to "conventional" buildup schedules
- Some unique occupations or situations may necessitate patients to undergo a faster buildup (e.g., military, underlying mastocytosis, venom allergy)

Accelerated immunotherapy protocols

- Increased risk for systemic reactions compared to conventional buildup schedules*
- Premedication is recommended
- Acceptance varies among providers/staff
  - Education
  - Scheduling
  - Risk aversion
  - Support staff reluctance/unease/untrained

* VIT can be safer when administer faster

Allergen immunotherapy: A practice parameter third update (2011)

- **Summary statement 30:** Antihistamines have been demonstrated to be beneficial in decreasing local reactions during cluster and rush protocols, where leukotriene antagonists were shown to be helpful in a rush protocol.
- **Summary statement 52:** With cluster immunotherapy, 2 or more injections are administered per visit to achieve a maintenance dose more rapidly than with conventional schedules.
- **Summary statement 53:** Studies with single allergens using a cluster schedule demonstrated a similar or increased frequency of systemic reactions compared with immunotherapy with conventional schedules.

Allergen immunotherapy: A practice parameter third update (2011)

- **Summary statement 54:** Rush schedules can achieve a maintenance dose more quickly than weekly schedules.
- **Summary statement 55:** Rush schedules with inhalant allergens are associated with an increased risk of systemic reactions. However, rush protocols for administering Hymenoptera venom have not been associated with a similar high incidence of systemic reaction.
- **Summary statement 57:** Premedication before cluster and rush immunotherapy with aeroallergens might reduce the rate of systemic reactions, Combination therapy is effective in reducing systemic and local reactions during accelerated immunotherapy buildup protocols.

Cluster buildup

- Different protocols
- Different pre-treatment regimens
- Varied number and dose of individual allergens

My cluster experience

- 90+% who want SCIT want cluster
- My AIT prescription*
  - 1-2 vials for T/G/W (0.2-0.4mL per allergen)
  - 1 vial for pet dander (1mL each)
  - 1 vial for HDM/molds (1mL for HDM)

	Conventional	Cluster
# visits	50	12
# injections**	100	34
Time required (hrs)**	58.3	19

* 5mL vial
** 20 min commute 1-way with 90 minute wait time per each cluster visit and 30 min for usual shot visit for a patient on 2 injections

Cluster outcomes - big picture

Vial #_____

Visit#	Date	Dose #	Dose Volume (ml)	Vial
1		1	0.1	SILVER
		2	0.4	SILVER
2		3	0.2	GREEN
		4	0.3	GREEN
3		5	0.2	BLUE
		6	0.3	BLUE
4		7	0.1	YELLOW
		8	0.2	YELLOW
5		9	0.2	YELLOW
		10	0.3	YELLOW
6		11	0.05	PINK
7		12	0.1	PINK
8		13	0.15	PINK
9		14	0.2	PINK
10		15	0.3	PINK
11		16	0.4	PINK
12		17	0.5	PINK

No systemic reaction

n = 3 (epi)

n = 1 (epi)

n = 1 (epi)

1:625-Dilution 4

1:125-Dilution 3

1:25-Dilution 2

1:5-Dilution1

1:1-Concentrate

Cluster protocol

- Visit 1 - OA in AM
- Visit 2 - same as visit 1
- Visit 3 – OA +pred 20mg + famotidine 20mg in AM
- Visit 4 - OA + pred 20mg + famotidine night prior and AM
- Visit 5 – same as visit 4

Visit#	Date	Dose #	Dose Volume (ml)	Vial
1		1	0.1	SILVER
		2	0.4	SILVER
2		3	0.2	GREEN
		4	0.3	GREEN
3		5	0.2	BLUE
		6	0.3	BLUE
4		7	0.1	YELLOW
		8	0.2	YELLOW
5		9	0.2	YELLOW
		10	0.3	YELLOW

1:625-Dilution 4	1:125-Dilution 3	1:25-Dilution 2	1:5-Dilution1	1:1-Concentrate

Cluster outcomes - Demographics

- Feb 2023 - July 2024
- 87 patients signed up
- 86 cluster starts
  - 1 did not return after ordering
  - 47 (54%) female
  - 39 ± 19 yrs (5-91)
  - 28 (32%) with asthma
    - FEV1 89 ± 10% (66-113)
  - 26 (30%) on AIT previously
    - 3/26 (12%) with hx/o systemic reaction

Cluster outcomes - Results

- 86 started cluster
- 3 still in cluster
- 5/83 (6%) experienced systemic reactions
  - 2 reported by patient occurring after leaving clinic (no epi)
  - 3/83 (3.6%) occurred in cluster visit 4 after 2nd dose
    - 1 Grade I systemic reaction
    - 2 Grade 2 systemic reactions
- 4.8 ± 0.8 visits (2-7)
- 34 ± 9.4 days (14-65) to complete

Cluster outcomes - Results

…and now for the rest of the story

- Visits 6-12
  - OA morning of

6		11	0.05	PINK
7		12	0.1	PINK
8		13	0.15	PINK
9		14	0.2	PINK
10		15	0.3	PINK
11		16	0.4	PINK
12		17	0.5	PINK

Cluster outcomes - Results

- 9 lost to follow up*
- 17 still building up in pink vial
- 46 patients reached the desired 0.5 mL maintenance dose
- 9.6 ± 3.1visits (6-19)
- 77 ± 43 days (33-210) to complete
- All 12 visits averaged 110 days to complete
- 2 systemic reactions
  - 1 at 0.15 mL dose; 1 at 0.5 mL dose
  - No reported systemic reactions after leaving
- All reactions: 7/86 (8.1%)

* defined as > 3 months since last injection appointment

Cluster refills

- When starting a "fresh" vial for SCIT, the dose is decreased 50-90% of the current dose and build back to maintenance based on the usual schedule
- Retrospective study with two 0.25mL "red" 1:1 v/v doses 30 min apart
- 6/115 (5.2%) patients experienced systemic reactions for 174 cluster refills[1]
- Cluster refills are safe and should be considered

Oberhelman, et al. J Allergy Clin Immunol 2021; 147(2): AB 129.

SCIT Cluster refills

- Prospective refill study
- 52/59 enrolled patients completed per protocol, ages 9-73yrs
- Patients had been on allergy shots; 38% had only had 1 prior refill
- 3 (6%) had a previous systemic reaction on SCIT; 29% had asthma
- 65% took an oral antihistamine in past 24hrs
- 0/52 reactions
- 92% definitely would do again, 88% completely satisfied

Waibel KH, Owens T, Crisp H, Gomez RA. J Allergy Clin Immunol Pract 2014; 2(6): 793-4.

SCIT Cluster refills

TABLE I. Characteristics of standard refill vs cluster refill*

	Last refill (n = 52)	Cluster refill (n = 52)	*P* value
SR	0	0	
No. visits to reach maintenance dose	4.6 ± 1.4	1.0 ± 0.0	<.001
No. days to reach maintenance dose	31.0 ± 9.5	1.0 ± 0.0	<.001
Total time invested (h)	6.5 ± 3.6	1.9 ± 0.7	<.001
No. total injections	7.7 ± 4.3	3.2 ± 1.3	<.001

*Values are mean ± SD, unless otherwise noted.

Waibel KH, Owens T, Crisp H, Gomez RA. J Allergy Clin Immunol Pract 2014; 2(6): 793-4.

SCIT
Cluster refills

TABLE E3. Protein determination of "old" vs "new" allergen extracts

Allergen contents (allergen)	Vial	Concentration (µg/mg)
Cat (2 mL), acetone-precipitated dog (2 mL), mites, *pteronysinnus* (2 mL)	Old	483
1:500 w/v; 2,000 BAU/ml; 2,000 AU/mL	New	487
% Difference		+0.8
Grass (3 mL)	Old	536
1:200 w/v; 11,000 BAU/mL	New	671
% Difference		+20.1
Grass (2 mL) and molds (2 mL)	Old	383
1:200 w/v; 11,000 BAU/mL	New	566
% Difference		+32.3
Molds (5 mL)	Old	404
1:200 w/v	New	476
% Difference		+15.1
Trees (4 mL), grasses (2 mL), weeds (2 mL)	Old	879
1:200 w/v; 11,000 BAU/mL	New	908
% Difference		+3.2

Waibel KH, Owens T, Crisp H, Gomez RA. J Allergy Clin Immunol Pract 2014; 2(6): 793-4.

KEEP
CALM
CLUSTER
ON

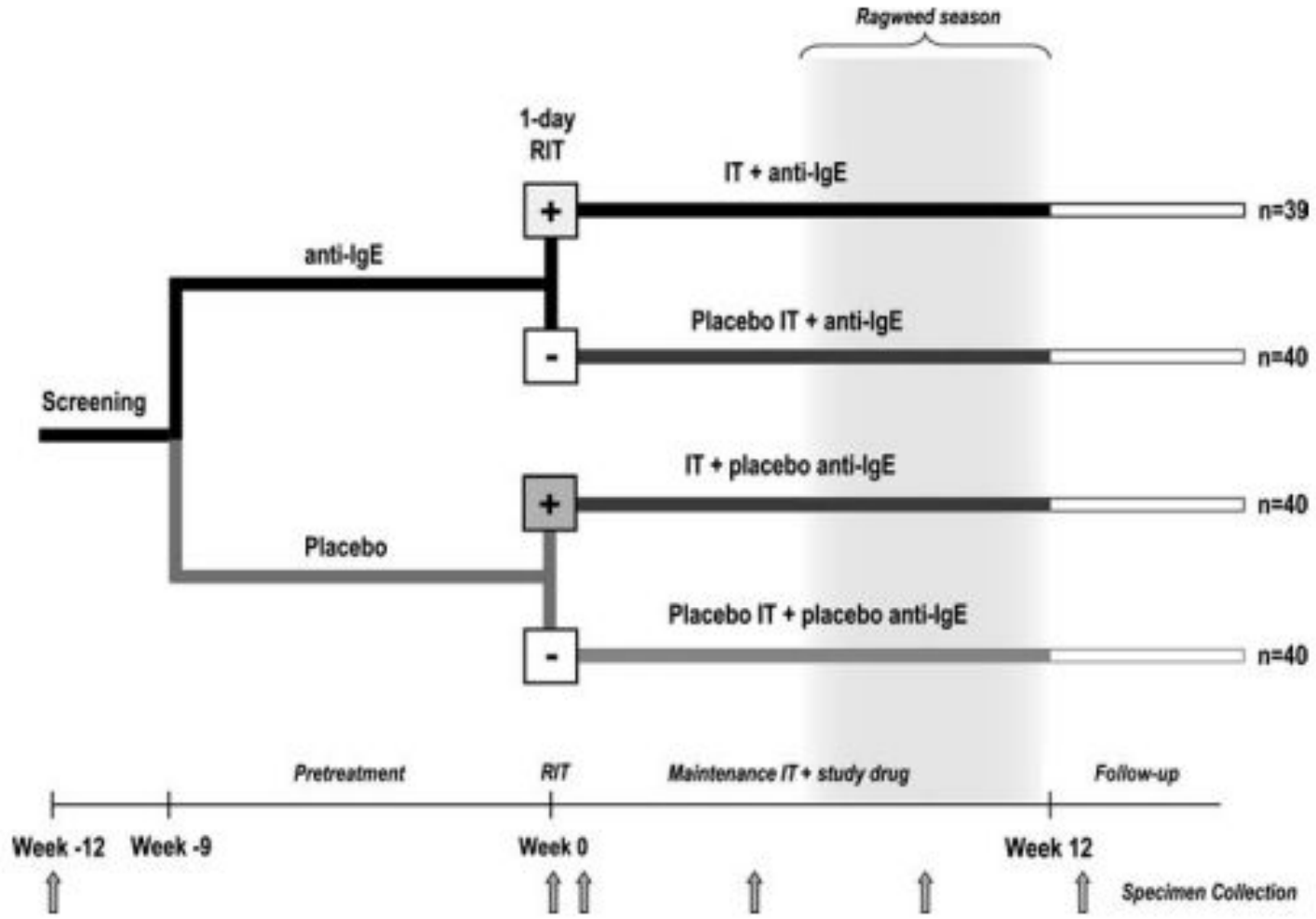
Rush immunotherapy

- Similar to cluster but reaching the target dose over day(s) instead of weeks
- Doses typically administered every 30-60 minutes for 5-8 hours but stops short of the desired dose

Allergen immunotherapy: A practice parameter third update (2011)

- **Summary statement 58:** Omalizumab pretreatment has been shown to improve the safety and tolerability of cluster and rush immunotherapy schedules in patients with moderate persistent asthma and allergic rhinitis, respectively.

Omalizumab and AIT



% anaphylaxis
2/36 (5.6%)
1/37 (2.7%)
10/39 (25.6%)
1/37 (2.7%)

Casale TB, Busse WW, Kline JN et al. J Allergy Clin Immunol 2006; 117(1):

Rush immunotherapy

- 1-day 6hr protocol in 22 children with asthma with 2-hr wait
- Premedication 2 days prior and day of
  - Astemizole 10mg
  - Ranitidine 150mg BID
  - Prednisone 30mg BID
- 5/22 (23%) had systemic reaction

Table 1. Schedule for Administration of 1-Day Rush Immunotherapy

Time	Volume, mL	Dilution w/v
09:00	0.30	1:100,000
09:30	0.10	1:10,000
10:00	0.30	1:10,000
10:30	0.05	1:1000
11:00	0.15	1:1000
12:00	0.30	1:1000
13:00	0.05	1:100
14:00	0.10	1:100
***Total**	**0.20**	**1:100**

* Total is the cumulative dose given over 6 hours

Sharkey P and Portnoy J. Ann Allergy Asthma Immunol 1996; 76(2): 175-180

Rush immunotherapy (Southwestern gro up)

- 1-day 4hr protocol in adults with multi-allergen extracts
- Pretreated day prior and day of with prednisone, zyrtec, ranitidine, and montelukast/zafairlukast
- 2hr wait after last dose
- 25/65 (38%) had a SR

Time	Conc v/v	mL
0	1:10,000	0.3
30	1:1,000	0.3
60	1:100	0.1
90	1:100	0.30
120	1:10	0.1
180	1:10	0.2
240	1:1	0.05

100%

72%

Harvey SM et al. Ann Allergy Asthma Immunol 2004; 92(4): 414-9.

Rush immunotherapy - my experience

- Retrospective chart review (6/21-2/23)
- n = 22 (1 fire ant for 13 yr old)
- 12/22 (55%) female
- Pretreatment regimen:
  - 2 days prior and the morning of:
  - BID 20mg prednisone
  - BID 150mg ranitidine/20mg famotidine
  - BID 10mg cetirizine

Step	Conc (v/v)	Dose (mL)
1	1:1,000	0.1
2	1:1,000	0.3
3	1:100	0.1
4	1:100	0.3
5	1:10	0.05
6	1:10	0.1
7	1:10	0.2
8	1:10	0.3
9	1:1	0.05

Rush immunotherapy - my experience

- 2/22 (9%) with systemic reaction, both after final dose
- 50 yr old male. 15-20 minutes developed pruritis, flushing, and coughing. Epi x 1 with resolution of symptoms
- 36 yr old female. 50 min developed flushing, diaphoresis and intense abdominal pain and diarrhea. Epi x 1 but symptoms persisted; 2nd epi 10-15 minutes after initial epi and symptoms gradually resolved.

Other rush protocols (1 visit protocol)

Dose	Volume	Concentration
1	0.3mL	Silver
2	0.2mL	Green
3	0.5mL	Green
4	0.3mL	Blue
5	0.5mL	Blue
6	0.15mL	Yellow
7	0.2mL	Yellow

Yellow	Pink/red
0.25	0.05
0.3	0.1
0.35	0.15
0.4	0.2
0.45	0.25
0.5	0.3
	0.35
	0.4
	0.45
	0.5

23 visits total

Head-to-head comparisons

- Retrospective 4-year review
- 2.54 million injections for 11,982 patients

Modality (%pts)	# visits	#shot rounds	Starting conc. (v/v)	%SR per patient
Conventional (77%)	30-40	30-40	1:10,000	2.8
Cluster (21.5%)	9	22	1:10,000	2.5
Rush (1.5%)	2	18	1:100,000	11.9

Winslow AW et al. Ann Allergy Asthma Immunol 2016; 117(5): 542-545.

Head-to-head comparisons

- Retrospective 5-year review
- Standard buildup (n=41), cluster (n=122), and rush (n=74)

Modality (%pts)	# visits	#shot rounds	Starting conc. (v/v)	%SR per patient
Conventional (17.3%)	22 (22 wks)	30-40	1:1,000	9.8
Cluster (51.4%)	22 (9wks)	22	1:1,000	9.8
Rush (31%)	20 (14wks)	20	1:10,000	14.9

Lee MC, Puglisi LB, and Kelso JM. J Allergy Clin Immunol Pract 2023; 11(9): 2884-2889.

Venom immunotherapy (VIT)

- "Patients with a history of anaphylaxis after a sting have a mean of almost 50% frequency of a systemic reaction to a sting."[1]
- VIT can reduce the risk of systemic reaction to <5%*
- Maintenance dose of 100ug for each venom (0.5 mL of a 1:100 w/v maintenance dose for fire ant)

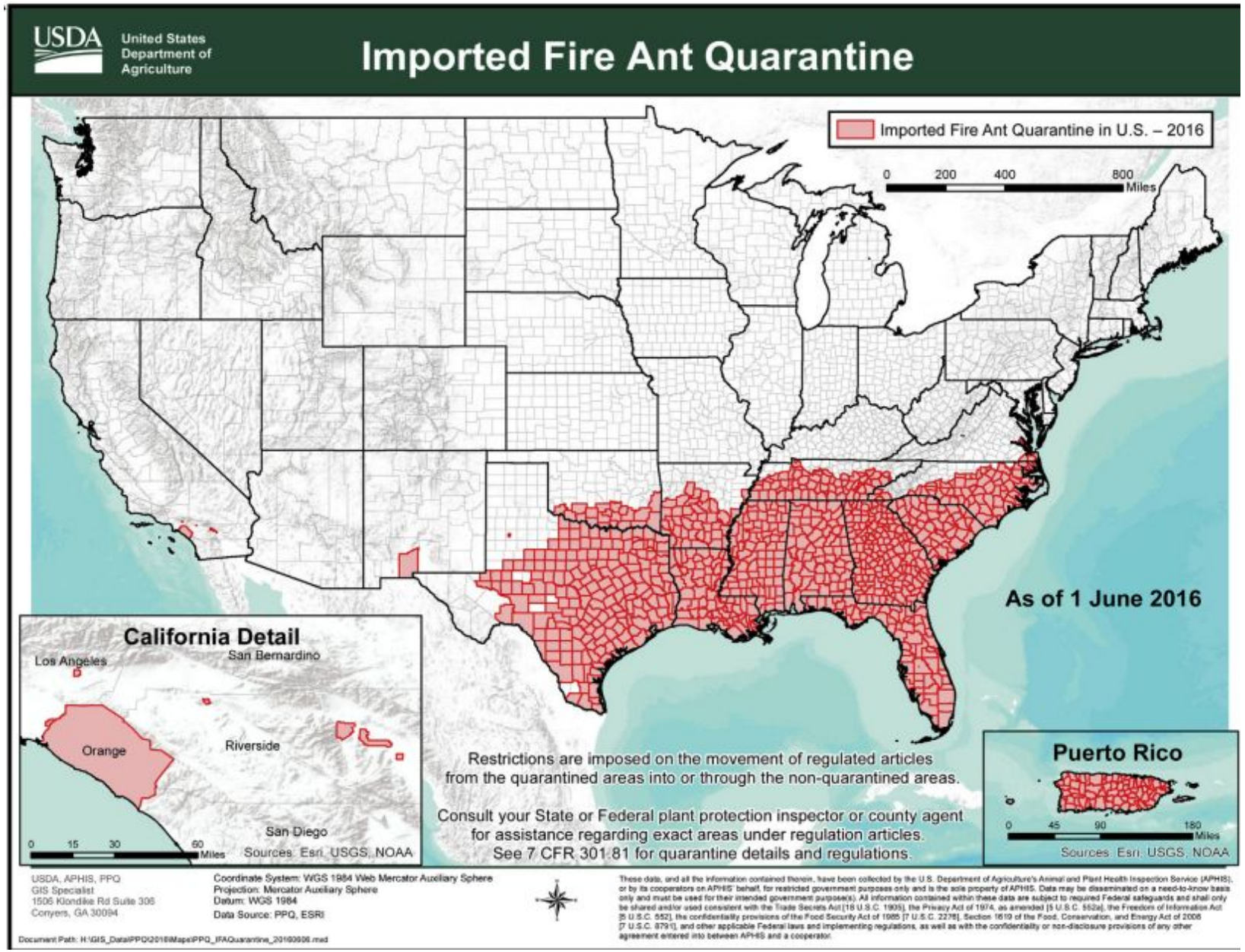
[1]Golden DBK et al. Stinging insect hypersensitivity. A Practice parameter update 2016. Ann Allergy Asthma Immunol 2017; 118: 28-54.

VIT Summary Statements (n=28)[1]

- **Summary statement 21.** Maintenance dose and protection can be achieved with equal safety using conventional (4 months) or modified rush (8 weeks) regimens. The risk of systemic reaction is similar using rush regimens (2-3 days) but may be slightly greater using ultrarush regimens (4-6 hours).
- 5-10% systemic reactions in rush and 0-28% in ultrarush

[1]Golden DBK et al. Stinging insect hypersensitivity. A Practice paramter update 2016. Ann Allergy Asthma Immunol 2017; 118: 28-54.

Fire ant allergy



[1]Golden DBK et al. Stinging insect hypersensitivity. A Practice paramter update 2016. Ann Allergy Asthma Immunol 2017; 118: 28-54.

Fire ant VIT standard protocol[1]

Dose	Concentration, wt/vol	Volume, mL
1	1:100,000	0.05
2	1:100,000	0.15
3	1:100,000	0.25
4	1:100,000	0.50
5	1:10,000	0.05
6	1:10,000	0.10
7	1:10,000	0.20
8	1:10,000	0.30
9	1:10,000	0.40
10	1:10,000	0.50
11	1:1000	0.05
12	1:1000	0.10
13	1:1000	0.20
14	1:1000	0.30
15	1:1000	0.40
16	1:1000	0.50
17	1:100	0.05
18	1:100	0.07
19	1:100	0.10
20	1:100	0.15
21	1:100	0.20
22	1:100	0.25
23	1:100	0.40
25	1:100	0.50

[1]Golden DBK et al. Stinging insect hypersensitivity. A Practice paramter update 2016. Ann Allergy Asthma Immunol 2017; 118: 28-54.

Fire ant rush immunotherapy

- 1-day rush protocol with and without premedication
- Pretreatment 2 days prior and day of (BID prednisone, ranitidine, loratadine)
- Day 1 - 10 injections every 30-60 minutes reaching a 0.3mL (1:100 w/v) dose
  - 4/42 (9.5%) systemic reaction

Arseneau AM et al. Ann Allergy Asthma Immunol 2013; 111(6): 562-6.

27 yr old Navy pilot with fire ant allergy.

- Military will not let you fly unless you reach the maintenance dose
- 1-day rush protocol
- Similar pretreatment regimen used
- Reached the 0.5 mL 1:100 w/v cumulative dose
- No reaction

Step	Conc (v/v)	Dose (mL)
1	1:1,000	0.3
2	1:100	0.1
3	1:10	0.05
4	1:10	0.15
5	1:10	0.3
6	1:1	0.05
7	1:1	0.1
8	1:1	0.2
9	1:1	0.3

Administrative and coding

- Ordering and compounding will be different than conventional protocols
- Certain insurance plans will not accept 95180 procedures codes (AETNA, Medicare)
- Nursing only vs provider visit
- 99213/99214 visit, brief PE
- Peak flow vs spirometry
- 95180 (rapid desensitization) - 1 unit per hour

Procedure	Office work RVUs
95115	0.31
95117	0.37
95180	4.15

Discussion

- Accelerated SCIT is highly desired
- Many ways to approach
- Minimal work for staff but significant wRVU reimbursement
- Symptom reduction much faster compared with conventional schedules
- Almost all reactions occur in yellow or red vials but still low risk (3-10%) with pretreatment