3HP and "Flu Syndrome" – What is the Underlying Mechanism?

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Objectives

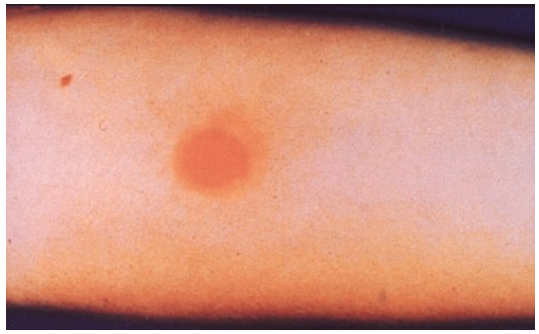
- Illustrate the side effect of 3HP flu-like syndrome after its initiation to raise awareness in providers of this adverse effect to ensure adequate therapy for patients with TB.

- Discuss the literature of patient factors associated with flu like syndrome and the possible biologic mechanisms underlying its development with 3HP to enhance the knowledge of its providers.

Case #1

- 25y/o white female with history of Crohns disease on certolizumab (Cimzia)
- PPD positive (10mm) in August 2013, Quantiferon Gold positive, chest Xray negative
- Denied fevers, chills, sweats, weight loss, cough or shortness of breath
- No known TB contacts

  or TB exposures



Case #1

- Past Medical History: Crohns disease, diagnosed in 2008
- Allergies: fentanyl, infliximab (antibodies to it)
- Family history: grandmother with UC, mother with thyroid disease, uncle with non hodgkins lymphoma
- Social history: lives in Brentwood, TN with family; works part-time in restaurant; denies tobacco or illicit drug use, +social ETOH

Case #1

- Started INH/rifapentine/B6 on 9/24/13
  - A few days of “dizziness” and this resolved
- 10/2/13: ER visit for diarrhea, fever, myalgias, chest pain, shortness of breath
  - Temperature 102.4, HR 112
  - CT scan notable for severe Crohns (colon and terminal ileum)
  - CRP peaked at 116.9 mg/L (not typical of her other Crohns flares)
  - Restarted certolizumab as inpatient and INH monotherapy on discharge
  - Fevers, cp, dyspnea resolved and she was discharged home on 10/7/13

Case #1

- 10/8/13 – fever to 102, dizziness, BP 85/59, HR 130's → referred to ER
  - Had taken one dose of INH at home
- Discharged after 48 hours in hospital, IVF.
- She finished a 4 month course of PO rifampin without difficulty.

Case #2

- 61y/o woman diagnosed with Crohns disease 30 years ago
  - Previously on adalimumab but developed psoriaform dermatitis. Receives weekly methotrexate.
  - History of positive PPD in 1976 (nurse) and received almost 9 months of INH at that time
  - 2013 – positive Quantiferon and negative T-Spot.
  - Negative CXR and no symptoms of active TB

Case #2

- PMHx: Crohns disease, migraines, anal fissure
- Allergies: infliximab (anaphylaxis), azathioprine (pancreatitis)
- Family history: colon cancer, breast cancer, lung cancer
- Social history: Hermitage, TN with husband. Nurse (now administrator); no tobacco, illicits, +social ETOH. Travels to Haiti a few times a year on mission trips, works in outpatient clinic.

Case #2

- 12/3: Began INH/rifapentine/B6
- 12/10: chills, severe pain in back and extremities, improved in 24 hours
- 12/17: chills, severe pain within 4 hours of dose
  - CRP 100.1 mg/L, CBC normal, AST 47
- Successfully completed 4 months of rifampin
  - Noted flushing/hot flashes with this but had also started a new TNF-alpha blocker concurrently.

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Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

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- Open-label, randomized noninferiority trial
  - 3 months of once weekly INH/rifapentine was noninferior to 9 months of daily INH for treatment of LTBI
  - Combination group more likely to discontinue due to adverse event (4.9% vs. 3.7%, p=0.009)
  - Serious adverse events were less common in combination group (1.6% vs. 2.9%, p<0.001)
  - 2.9% INH/RPT compared to 0.4% INH discontinued due to possible hypersensitivity

Tolerability of rifapentine

- In combination with INH, less hepatotoxic compared to 9 months INH
  - PREVENT TB trial: 0.4% (3HP) vs. 1.8% (9H)
- Phase 1 trial of twice daily RPT or RPT given with high fat meal (egg) increased RPT levels but led to increased discontinuation due to hypersensitivity

Bliven-Sizemore, et al. *IJTLD*; 2015
Dooley, et al. *Antimicrob Agents Chemo;* 2015

Flu-like syndrome has been reported with rifampin

- More common with intermittent, high doses
- Fever, chills, fatigue, malaise, headache, myalgia, arthralgia
  - After 3-6 months of treatment, 1-2hrs after dose, lasts 8 hours
- Dose-dependent and interval-dependent (seen most commonly after intermittent doses exceeded 900mg)
  - 1200-1800mg – 35-57% developed syndrome
  - 900mg – 22-31%
  - 600mg – 10%
  - More likely to occur in once weekly dosing compared to twice weekly dosing

Girling, et al. J Antimicrob Chemother, 1977

Flu-like syndrome has been reported with rifampin

- May be less common in patients who initially have lower daily dosing
- Patients who develop the syndrome may be able to subsequently tolerate lower daily dosing
- More common in women compared with men, increases with age

Isoniazid is rarely associated with a drug hypersensitivity reaction

- Fever, flu-like syndrome
- Skin eruptions, lymphadenopathy, hepatitis, eosinophilia
- Isoniazid can also react with foods rich in monoamines (i.e. tyramine)
  - First MAO inhibitors were developed after mood elevation was noted in patients taking INH for treatment of TB
  - Flushing, chills, headache, diarrhea, pruritus,

Rubira, et al. *Allergy*; 1999
Smith, et al. *Ann Int Med*; 1978

PREVENT TB sub-study

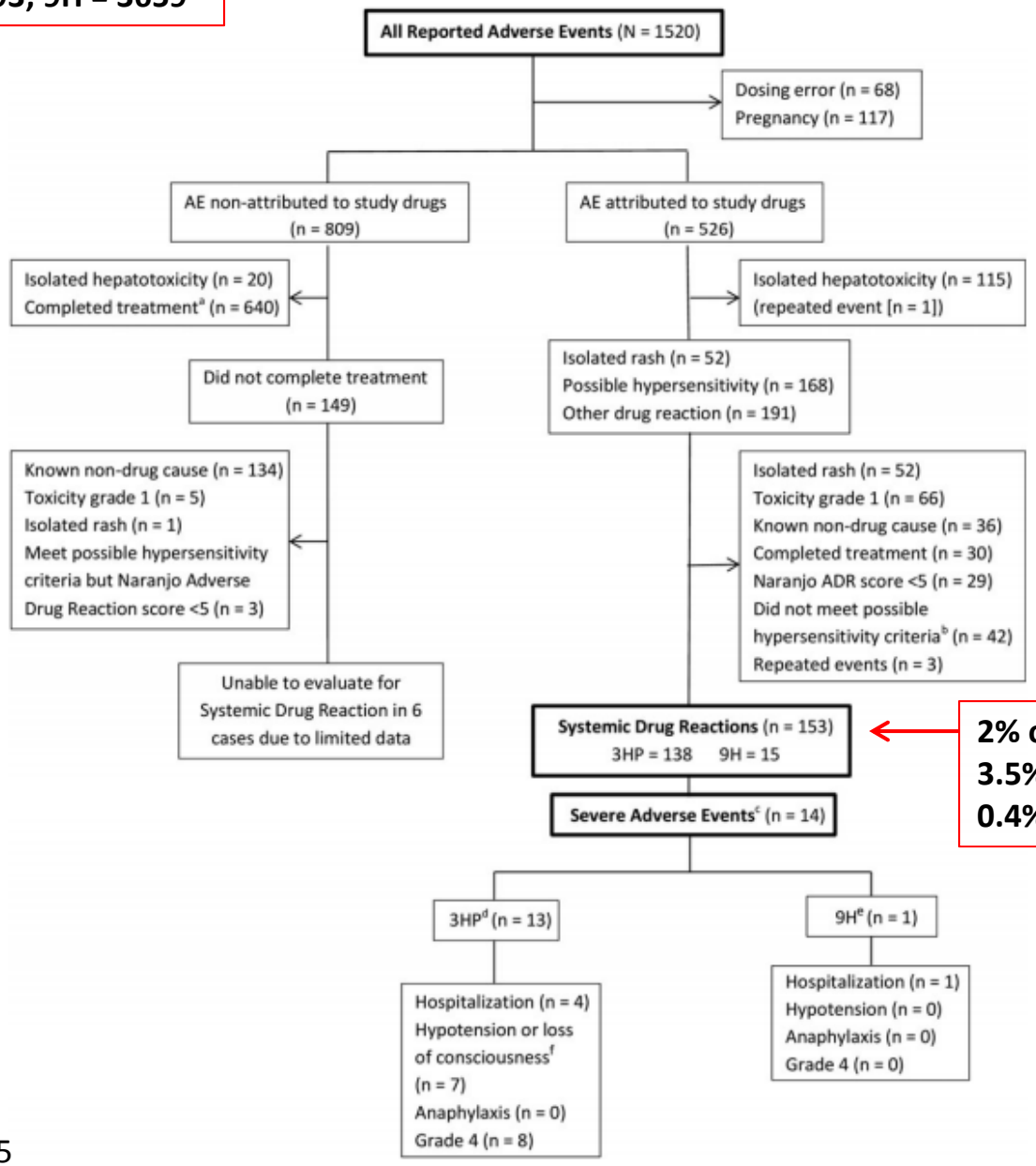
- Retrospective evaluation of adverse events (AE) in the PREVENT TB trial
- Hypersensitivity definition (Systemic drug reaction (SDR)

  (1) hypotension (SBP <90mmHg), urticaria (hives), angioedema, acute bronchospasm, or conjunctivitis **AND**

  (2) >4 of the following: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, chills
- Severe AE: result in hospitalization, hypotension, LOC, anaphylaxis, or grade 4 toxicity

Sterling, et al. *CID*; 2015

N=7552 (3HP = 3893; 9H = 3659



2% of all participants
3.5% 3HP
0.4% in 9H

Sterling, et al. *CID*; 2015

Table 2. Characterization of the 153 Systemic Drug Reactions According to Syndrome

	3HP (n = 138)	9H (n = 15)
Cutaneous[a]	23 (17%)	9 (60%)
Severe	3	1
Nonsevere	20	8
Flu-like[b]	87 (63%)	2 (13%)
Severe	6	0
Nonsevere	81	2
Gastrointestinal[c]	7 (5%)	1 (7%)
Severe	2	0
Nonsevere	5	1
Respiratory[d]	5 (4%)	0 (0%)
Severe	1	0
Nonsevere	4	0
Not defined[e]	16 (12%)	3 (20%)
Severe	1	0
Nonsevere	15	3

Table S5. Frequency of signs and symptoms in 153 cases of systemic drug reactions (SDR), stratified by arm

Signs and symptoms	3HP (n=138)		9H (n=15)	
	Number	%	Number	%
Fatigue	99	72	8	53
Headache	97	70	7	47
Nausea	94	68	5	33
Weakness	91	66	3	20
Chills	82	59	5	33
Myalgia (muscle pain)	79	57	3	20
Fever	77	56	4	27
Rash	36	26	10	67
Itching	28	20	9	60

Table 3: Time to Symptom Onset and Resolution

Event	3HP (n=138)	9H (N=15)	P-value
Median doses prior to event onset	3 (2.0-5.0) (n=138)	17 (9-57) (n=15)	NA
Median time from drug ingestion to event (hrs)	4 (1.0-8.0) (n=135)	1.5 (1.0-13.5) (n=8)	0.60
Median time to symptom resolution (hrs)	24 (12-48) (n=132)	24 (2-48) (n=11)	0.89
Median time to resolution – nonsevere (hrs)	24 (12-62) (n=119)	36 (12-48) (n=10)	
Median time to resolution – severe (hrs)	21 (6-24) (n=13)	2 (n=1)	

Table S4. Clinical and demographic characteristics of PREVENT TB participants with systemic drug reactions (SDR) compared to persons without adverse drug reactions.

Characteristic	Systemic drug reaction N=153	No systemic drug reaction N=7,399	P-value
Regimen (3HP)	138 (90)	3,755 (51)	<0.001
Age (median, IQR)	41 (31-51)	35 (25-46)	<0.001[a]
Female sex	97 (63)	3,349 (45)	<0.001
White non-Hispanic race/ethnicity	54 (35)	1,024 (14)	<0.001
Any concomitant non-study medication[b]	85 (56)	3,281 (44)	0.006
HIV-infected	1 (1)	151 (2)	0.38[c]
Smoking	41 (27)	1,987 (27)	0.99
Body Mass Index (median, IQR)	25 (23-31)	27 (23-31)	0.30[a]

Table 4. Univariate Logistic Regression Analysis of Risk Factors for Systemic Drug Reactions

	OR	95% CI	*P* Value
3HP (n = 3893) vs 9H (n = 3659)	8.9	5.2, 15.2	<.001
White-non-Hispanic race	3.4	2.4, 4.8	<.001
Female sex	2.1	1.5, 2.9	<.001
Age ≥35 y (median[a])	2.0	1.4, 2.8	<.001
Body mass index			.03
18.5–24.9 (normal)	reference		
<18.5 (underweight)	0.8	.3, 1.8	.55
25–29.9 (overweight)	0.5	.4, .8	.004
≥30 (obese)	0.9	.6, 1.3	.58
Any concomitant nonstudy drug	1.6	1.1, 2.2	.006
HIV infection	0.3	.04, 2.3	.25
Smoking	1.0	.7, 1.5	.99

Table 5. Multivariate Logistic Regression of Risk Factors for Systemic Drug Reactions

	Adjusted OR	95% CI	*P* Value
3HP vs 9H	9.4	5.5, 16.2	<.001
White-non-Hispanic race	3.3	2.3, 4.7	<.001
Female sex	2.0	1.4, 2.9	<.001
Age ≥35 y (median[a])	2.0	1.4, 2.9	<.001
Body mass index (BMI)			.009
18.5–24.9 (normal)	reference		
<18.5 (underweight)	0.9	.4, 2.2	.88
25–29.9 (overweight)	0.5	.3, .7	.001
≥30 (obese)	0.7	.4, 1.0	.05
Any concomitant non-study drug	1.2	.8, 1.7	.33

Table 6. Final Multivariate Logistic Regression Model of Risk Factors for Systemic Drug Reactions, Evaluating Regimen by Sex

	Adjusted OR	95% CI	*P* Value
Regimen – sex			<.001
9H male (reference)	. . .		
9H female	15.1	2.0, 115.5	.009
3HP male	53.4	7.4, 386.3	<.001
3HP female	94.4	13.1, 680.6	<.001
White-non-Hispanic	3.3	2.3, 4.7	<.001
Age ≥35 y (median[a])	2.0	1.4, 2.9	<.001
Body mass index			.01
18.5–24.9 (normal)	reference		
<18.5 (underweight)	0.9	.4, 2.3	.9
25–29.9 (overweight)	0.5	.3, .7	.001
≥30 (obese)	0.7	.5, 1.0	.05

Table S6. Probability of developing a systemic drug reaction or severe systemic drug reaction among persons with specific clinical and demographic characteristics

Systemic drug reaction	Number at risk	Number with event	Probability[a] (95% CI)
3HP + non-Hispanic white race	537	50	2.4% (0.8%, 7.8%)
3HP + non-Hispanic white race + female	250	31	8.9% (5.5%, 17.4%)
3HP + non-Hispanic white race + female + >35 years	149	21	12.3% (8.1%, 24.4%)
Severe systemic drug reaction			
3HP + non-Hispanic white race	537	7	0.7% (0.3%, 1.9%)
3HP + non-Hispanic white race + concomitant meds	324	6	1.8% (0.9%, 4%)

Flow chart for 3HP re-challenge protocol

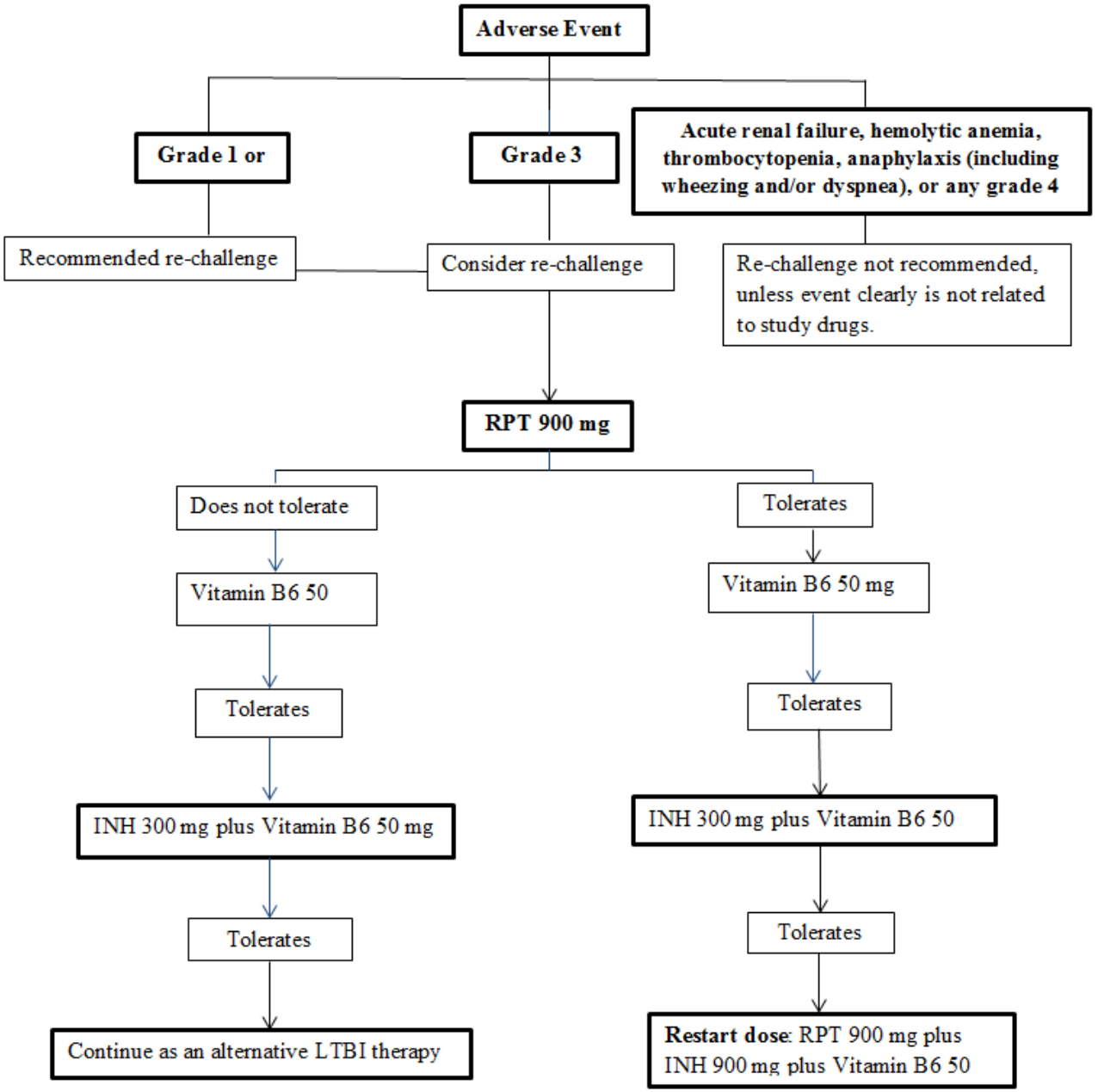


Table S3. Drug re-challenge in participants who received 3HP and developed a systemic drug reaction (SDR) in the PREVENT TB study

First Drug re-challenge			Second Drug re-challenge		
First drug	Number re-challenged	Tolerated	Second drug	Number re-challenged	Tolerated
INH	20	Yes (n=3) (15%)	---	0	--
		No (n=17) (85%)	RPT[c]	5	Yes (n=3) (60%)
					No (n=2) (40%)
RPT	51	Yes (n=36) (71%)	INH	12	Yes (n=2) (17%)
					No (n=10) (83%)
		No (n=15) (29%)	INH	7	Yes (n=3) (43%)
					No (n=4) (57%)
INH + RPT	2	Yes (n=0)			
		No (n=2) (100%)			
Total	73	Yes (n=39) (53%)		24	Yes (n=8) (33%)

Controversy – is the flu-like reaction immunologically mediated?

- Has been suggested that the "flu-like" reaction has an immunologic basis (rifampicin-antibody complexes)
- Circulating anti-rifampin antibodies (IgM) – not detectable during daily administration, only when receiving intermittent dosing at high doses (>900mg)
- Flu-like reaction coincided with peak concentration of rifampin (2-4 hours) and level of antibody fell during reaction ("used up")
- Daily administration of rifampin could produce immune tolerance
  - RCT of daily rifapentine followed by intermittent dosing – no reports of flu-like syndrome or hypersensitivity

Poole, et al. *BMJ;* 1971
O'Mahony, et al. *Clin Allergy*; 1973
Jindani, et al. *NEJM.* 2014

Controversy – is the flu-like reaction immunologically mediated?

- Inconsistency in reproducibility of symptoms upon rechallenge
- Associated with female sex and lower BMI
- Successful completion of treatment in many patients without morbidity despite previous SDR
- Differs than flu-like syndrome associated with immunologically-mediated reaction to meds such as abacavir
  - Significant intensification with continued dosing and severe disease upon rechallenge

Conclusion

- Systemic drug reaction more common in 3HP than 9H
- Flu-like syndrome, did not meet strict drug hypersensitivity criteria
  - Did not meet criteria of severe immunologically mediated drug reaction
- Most reactions are mild, resolve within 24hrs
- Highest risk: white race, female sex, increased age, lower BMI