HLA Updates into Vancomycin and Phenytoin: Moving beyond screening

Elizabeth J. Phillips, MD, FIDSA, FAAAAI

John A. Oates Chair in Clinical Research

Professor of Medicine, Dermatology, Pathology, Microbiology, Immunology and Pharmacology

VANDERBILT UNIVERSITY MEDICAL CENTER

CPIC Meeting - December 7, 2023

Disclosures (none relevant to content of this talk)

- Consultant: Janssen, Novavax, Verve, AstraZeneca, Regeneron, Biocryst
- Contributor and Drug Allergy Section Editor: UpToDate/Lexicomp
- Patent for HLA-A*32:01 tests for diagnosis of vancomycin DRESS

Disclaimers

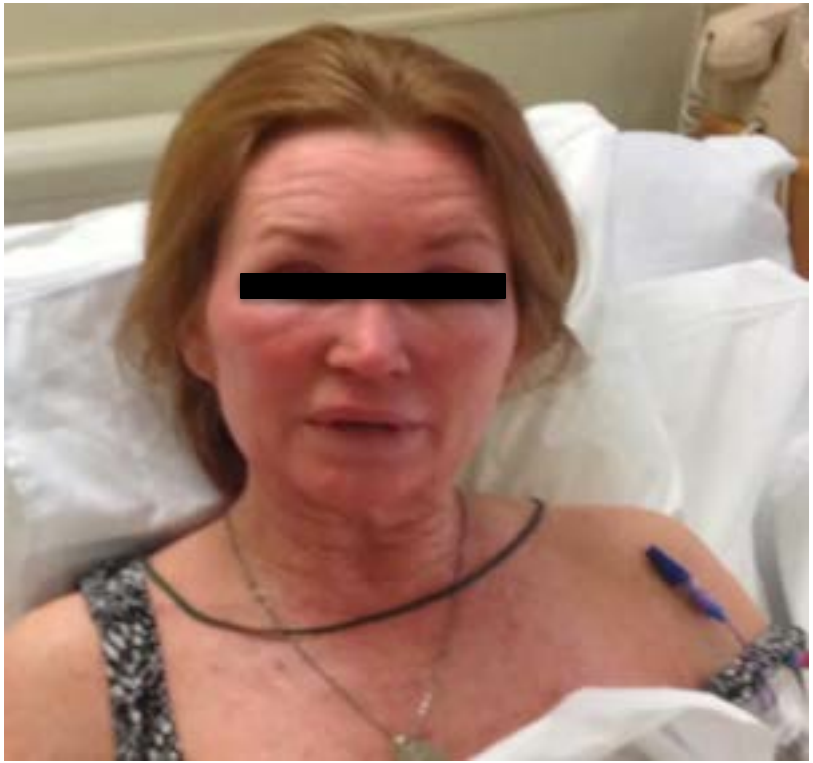
- all processes I will discuss are active not passive
- ChatGPT was not used in the development or content of this presentation
- I will discuss the pharmacogenomics and immunopathology relevant to small molecule severe cutaneous adverse drug reactions (SCAR)

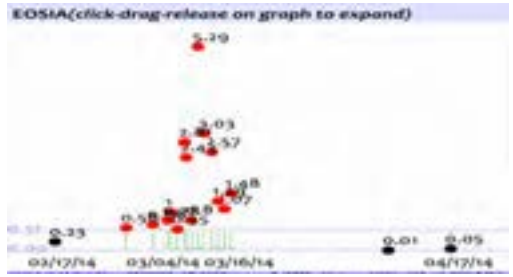
Part I: Vancomycin DRESS

- Understand primary HLA association
- Understand other risk factors for vancomycin DRESS
- Understand potential use of HLA beyond screening

Case

- 53 year old women started on vancomycin for infected breast implants
- Levofloxacin + fluconazole added
- 6 days later (and 3 weeks following initiation of vancomycin) she develops fever, skin rash with facial edema and lymphadenopathy followed by eosinophilia and increased ALT and acute kidney injury
- Hepatitis without rash relapse on weaning steroids – slower wean over 16 weeks
- Follow-up over 5 years negative for sequelae




EOSIA(click-drag-release on graph to expand)
03/12/14
03/04/14
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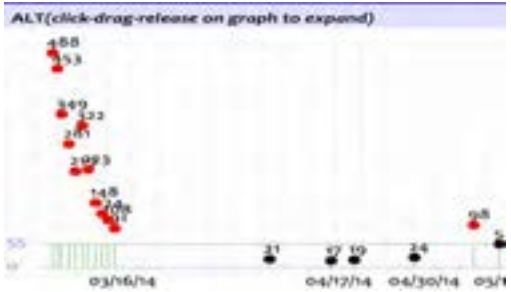
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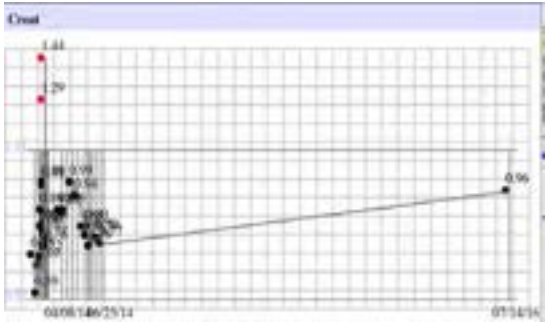
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Case Questions?

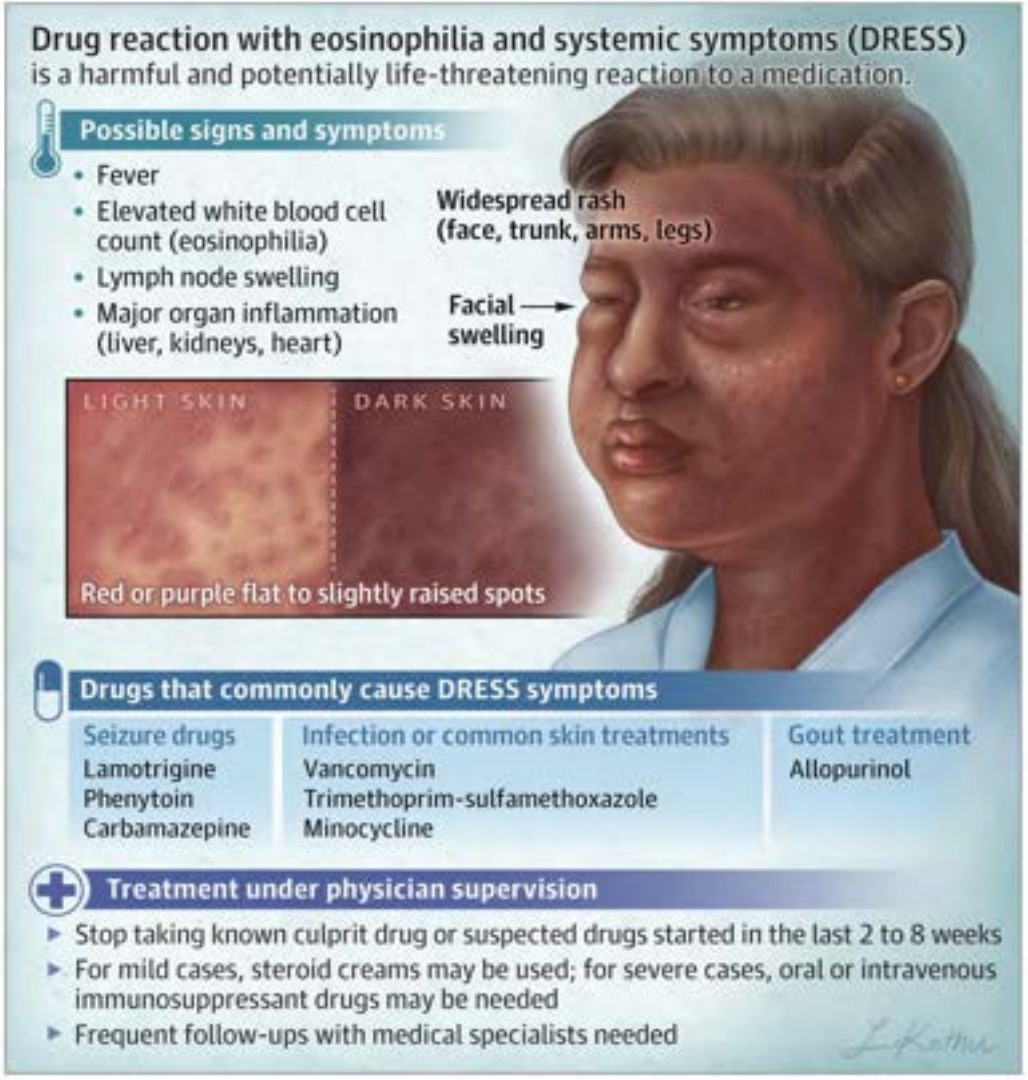
- What is the likely diagnosis?
- Is this drug related?
- Is there a most likely implicated drug (antibiotic) and how would you determine this?
- Can this be prevented or preempted?
- Can antibiotic choice and drug safety be preserved in the future?

CLINICAL DIAGNOSIS & RECOGNITION IS KEY: DRESS

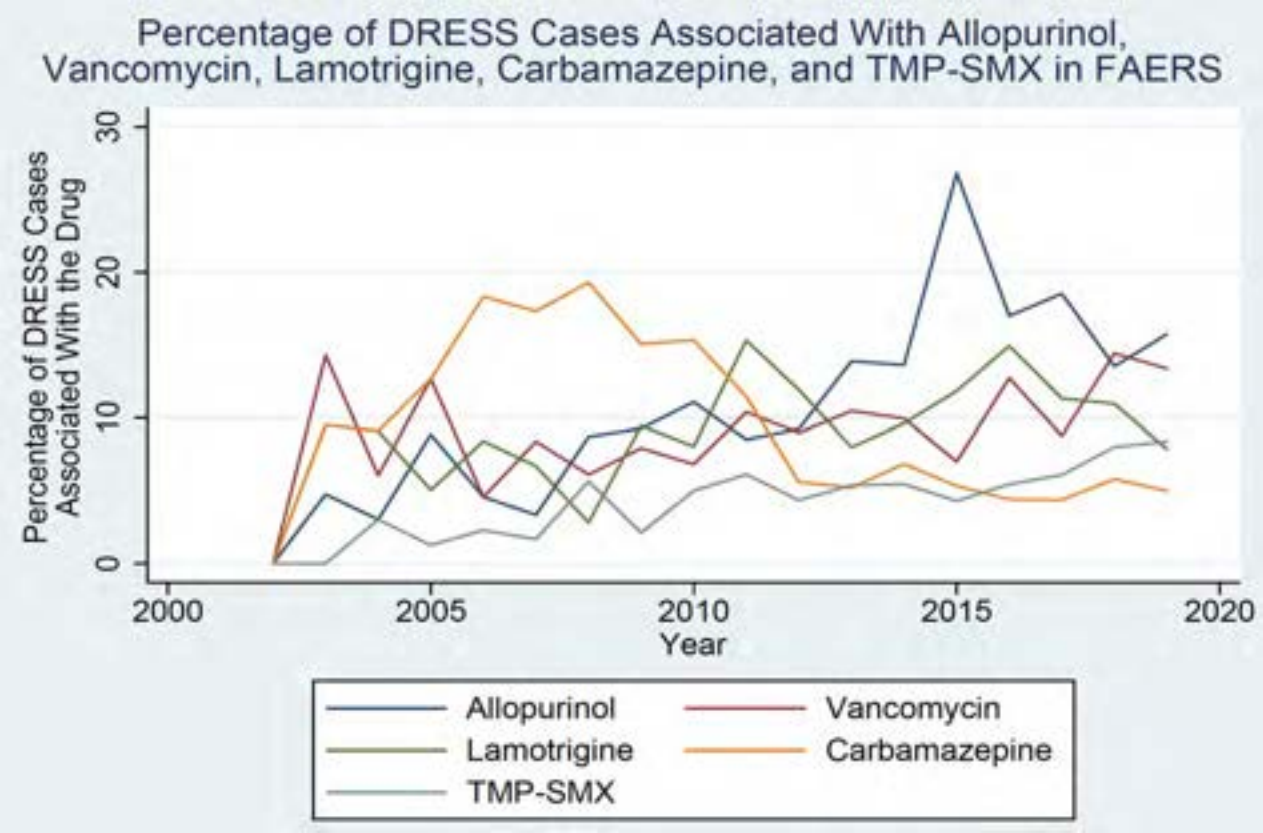
- Top drugs still sulfa antibiotics, allopurinol and anticonvulsants
- Can involve any organ
- Diverse skin morphologies and pathologies
- Relapse and/or late complications (autoimmune) occur 1/10
- RegiSCAR, J-SCAR and Bocquet are scoring systems that assign probability
- Early and late risk and severity scoring (CMV disease risk)

Krantz M, Phillips E JAMA Dermatology 2023 Jan 11

Mizikawa et al JAAD 2019; 80(3):670-678



Causes of DRESS in FAERS over time



Reporting of drug reaction with eosinophilia and systemic symptoms from 2002 to 2019 in the US Food and Drug Administration Adverse Event Reporting System

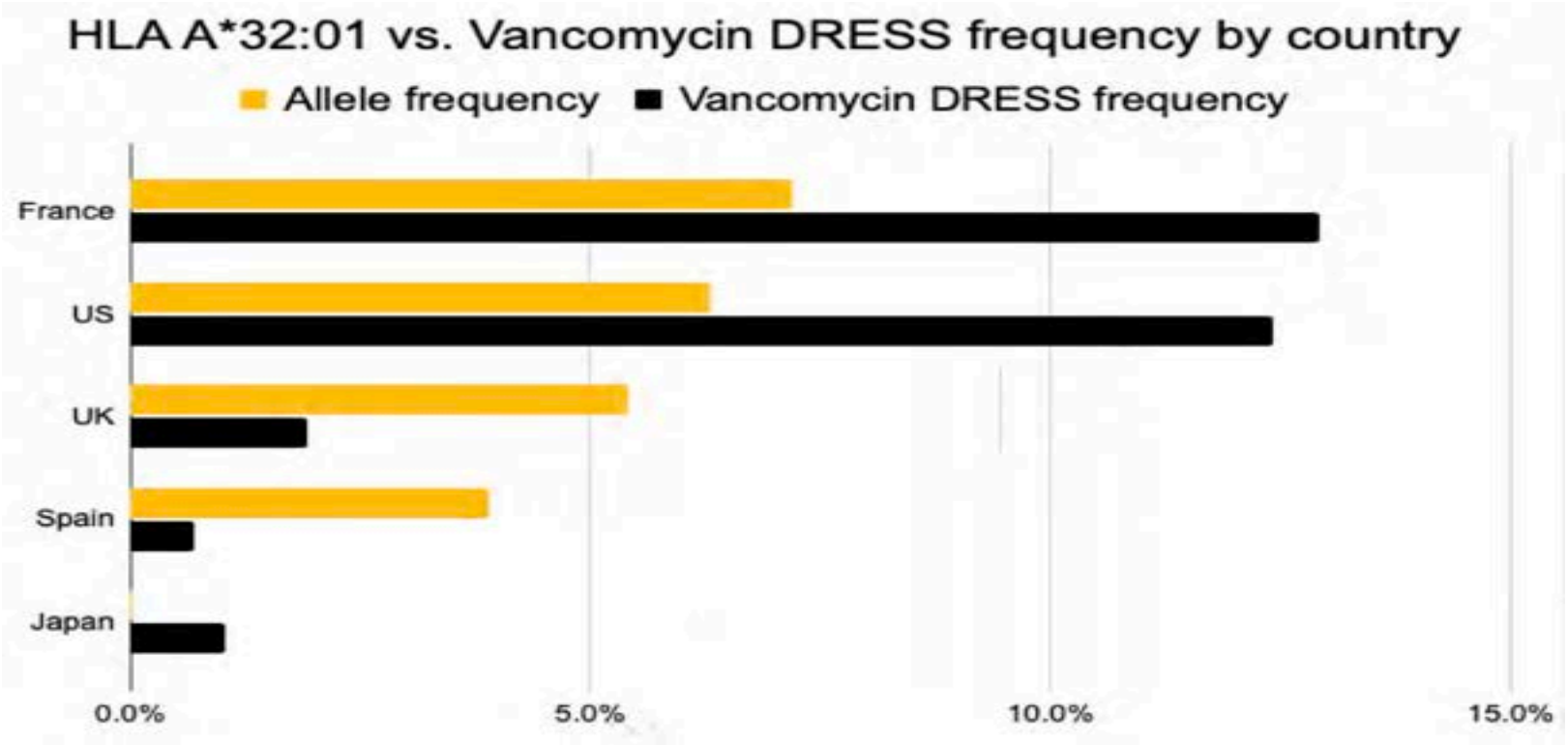
Sara Beth Bluestein, MD[a,*], Roger Yu, BA[b,c,*], Cosby Stone, Jr., MD, MPH[a], and Elizabeth J. Phillips, MD[a,b,d]

Clinical Implications

- Of drug reaction with eosinophilia and systemic symptoms cases identified in the Food and Drug Administration Adverse Event Reporting System, five drugs account for more than 50% of cases and three have actionable HLA risk factors identifying implementation strategies for prevention and earlier diagnosis.

J ALLERGY CLIN IMMUNOL PRACT p 3208-11
VOLUME 9, NUMBER 8

*FDA Adverse event reporting system



- Risk allele carriage frequency of HLA A*32:01 by each of the top 5 countries reporting DRESS compared to the rate of reported vancomycin-specific DRESS for each country

Bluestein et al J Allergy Clin Immunol Pract 2021 Aug;9(8):3208-3211

Classification & Phenotype

DRESS (RegiSCAR)

Items	Score			Comments
	-1	0	1	
Fever ≧ 38.5 °C	N/U	Y		
Enlarged lymph nodes		N/U	Y	>1 cm and ≧ 2 different areas
Eosinophilia ≧ 0.7 × 10^9/L or ≧ 10% if WBC < 4.0 × 10^9/L		N/U	Y	Score 2, when ≧ 1.5 × 10^9/L or ≧ 20% if WBC < 4.0 × 10^9/L
Atypical lymphocytosis		N/U	Y	
Skin rash				Rash suggesting DRESS: ≧ 2 symptoms: purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Extent > 50% of BSA		N/U	Y	
Rash suggesting DRESS	N	U	Y	
Skin biopsy suggesting DRESS	N	Y/U		
Organ involvement		N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution ≧ 15 days	N/U	Y		
Excluding other causes		N/U	Y	Score 1 if 3 tests of the following tests were performed and all were negative: HAV, HBV, HCV, Mycoplasma, Chlamydia, ANA, blood culture

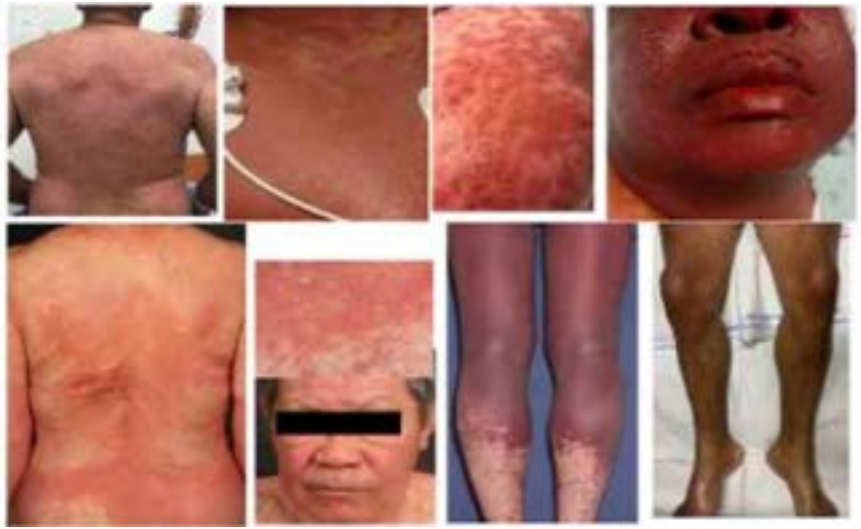
ANA: anti-nuclear antibody; BSA: body surface area; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; N: no; U: unknown; WBC: white blood cell; Y: yes.

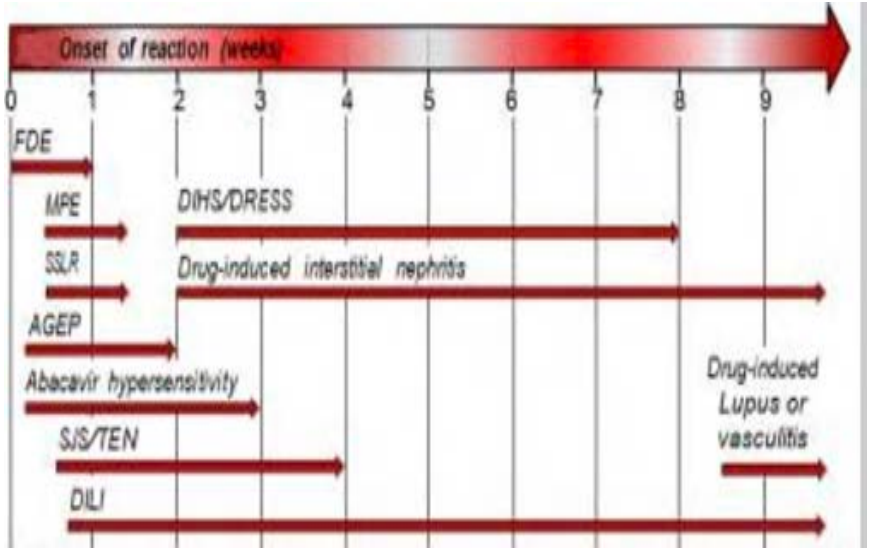
DiHS (Japanese Consensus Group)

- Maculopapular rash developing > 3 weeks after starting with a limited# drugs
- Prolonged clinical symptoms after discontinuation
- Fever (>38^o C)
- Liver abnormalities (ALT>100 U/L)*
- Leukocytosis (>11 x 10^9/L)
- Atypical lymphocytosis (>5%)
- Eosinophilia (> 1.5 x 10^9/L)
- Lymphadenopathy
- HHV-6 Reactivation

*other organ involvement also

*Bocquet description 1996 – Skin eruption + eosinophilia and addition systemic abnormalities

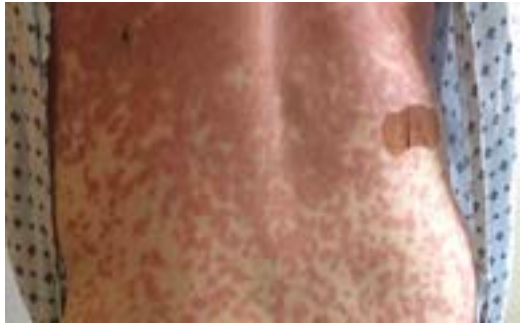




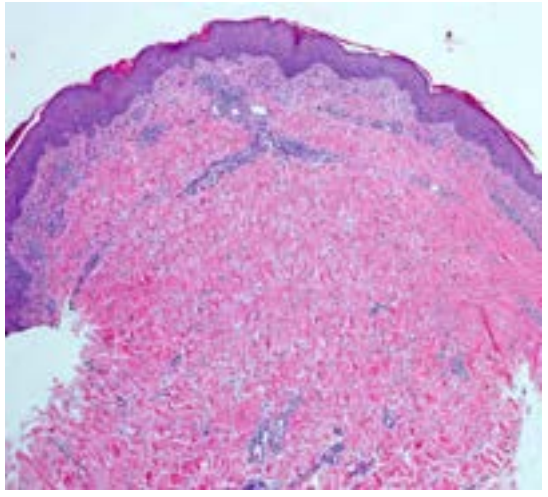
DRESS TIME COURSE AND MANIFESTATIONS

- *Hama et al J Allergy Clin Immunol Pract*
- *. 2022 May;10(5):1155-1167*

Diverse Clinical and Histopathological Characteristics



Variable	n	%
General rash morphology		
Extent ≥50% body surface area	67	44
Erythroderma	14	9
Rash unspecified	28	19
No rash	1	0.7
Mucosal involvement	24	16
Specific rash morphology		
Maculopapular	100	66
Patch/plaque	10	7
Infiltrative	6	4
Purpuric	16	11
Targets/targetoid	3	2
Exfoliative	27	18
Desquamation	24	16
Blistering	16	11
Pustules	8	5
Crusting	4	3



Pathology is not necessarily distinct for DRESS and requires clinical correlation

Variable	n	%
Skin biopsy findings		
Spongiosis	29	19
Interface dermatitis (including interface lichenoid reaction)	27	18
Dermal interstitial or perivascular infiltrate	47	31
Eosinophilic infiltrate	37	25
Unspecified but "consistent with DRESS"	12	8

Awad et al J Allergy Clin Immunol Pract 2023 Mar 7

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Research Letter

November 2, 2022

Risk Factors for Vancomycin Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome

Kimberly G. Blumenthal, MD, MSc[1,2,3]; Santiago Alvarez-Arango, MD[4,5]; Xiaoqing Fu, MS[1,3]; Daniela Kroshinsky, MD, MPH[2,6]; Hyon Choi, MD, DrPH[1,2,3]; Elizabeth Phillips, MD[7]; Li Zhou, MD, PhD[2,8]

Table. Characteristics of Patients With Vancomycin Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Syndrome and Vancomycin-Tolerant Control Patients (continued)

Characteristic	No. (%)			P value
	All (N = 1356)	Vancomycin DRESS syndrome (n = 54)[a]	Vancomycin tolerant (n = 1302)	
Infection and drug specific				
Previous vancomycin exposure in the past year	1338 (99)	49 (91)	1289 (99)	<.001
Vancomycin administration in previous year, median (IQR)	9 (6-15)	9 (4-15)	9 (6-15)	.24
Time on vancomycin, wk				
Median (IQR)	5.9 (4.3-6.1)	3.1 (2.1-3.9)	6.0 (4.4-6.3)	<.001
1 to <2	79 (8)	12 (24)	67 (8)	<.001
2 to <3	87 (9)	15 (29)	72 (8)	
3 to <4	145 (15)	17 (33)	128 (14)	
4 to <5	136 (15)	5 (10)	131 (15)	
5 to <6	491 (52)	2 (4)	489 (55)	
6 to <7	320 (24)	3 (6)	317 (24)	
7 to <8	98 (7)	0	98 (8)	
Elevated vancomycin trough	944 (70)	35 (65)	909 (70)	.43
Vancomycin trough, μg/mL, mean (SD)	21.2 (4.2)	23.9 (6.9)	21.1 (4.1)	.02
<20	824 (61)	29 (54)	795 (61)	<.001
20-24	391 (29)	13 (24)	379 (29)	
25-29	111 (8)	5 (9)	106 (8)	
≥30	29 (2)	7 (13)	22 (2)	
Highest vancomycin trough, μg/mL, mean (SD)	22.1 (8.8)	26.3 (16.2)	21.9 (8.4)	.08

Abbreviations: COPD, chronic obstructive pulmonary disease; CVID, common variable immune deficiency.

[a] Specialist diagnosed. Registry of severe cutaneous adverse reactions (RegiSCAR) score was less than 2 in 14 patients (26%), 2 to 3 in 16 patients (30%), 4 to 5 in 14 patients (26%), and greater than 5 in 10 patients (19%). Twenty-four patients were in the subgroup with a RegiSCAR score of 4 or greater; 29 patients were in the vancomycin-only subgroup, in which vancomycin was the only potential trigger (eMethods in the Supplement).

[b] In unadjusted analyses, Asian race was associated with an increased risk of vancomycin DRESS syndrome (unadjusted odds ratio, 3.77; 95% CI, 1.09-13.10, P = .04).

[c] The electronic health record did not provide a breakdown of the other race category.

[d] There were 239 patients (14 in the vancomycin DRESS syndrome group and 225 vancomycin tolerant) who did not have a body mass index value (calculated as weight in kilograms divided by height in meters squared) in the electronic health record.

- Vancomycin DRESS occurs a median of 21-22 days following dosing

JAMA Dermatol 2022 Dec 1;158(12):1449-1453

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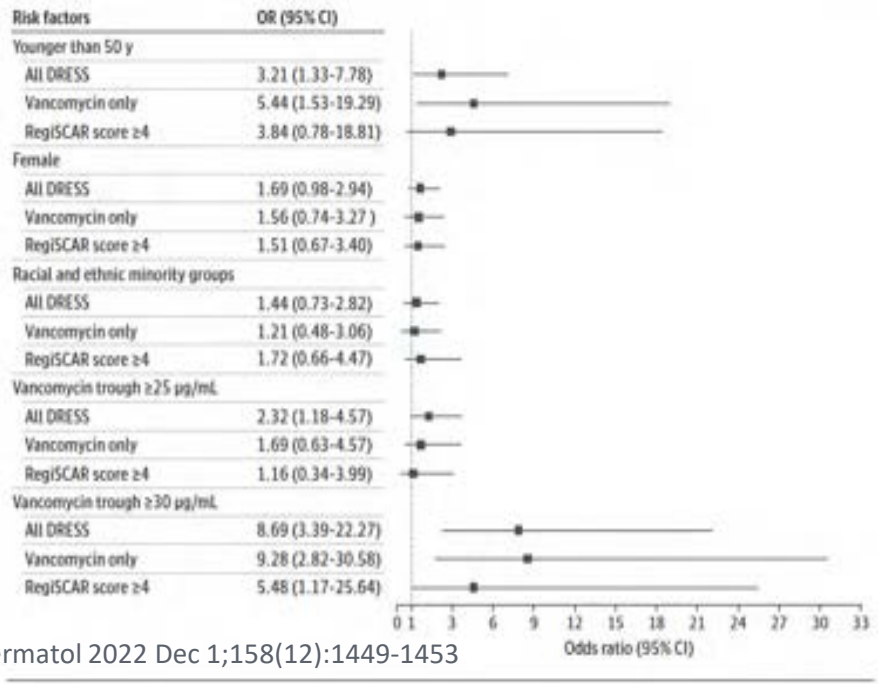
Figure. Risk Factors Associated With Vancomycin Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Syndrome



RegiSCAR indicates registry of severe cutaneous adverse reactions.

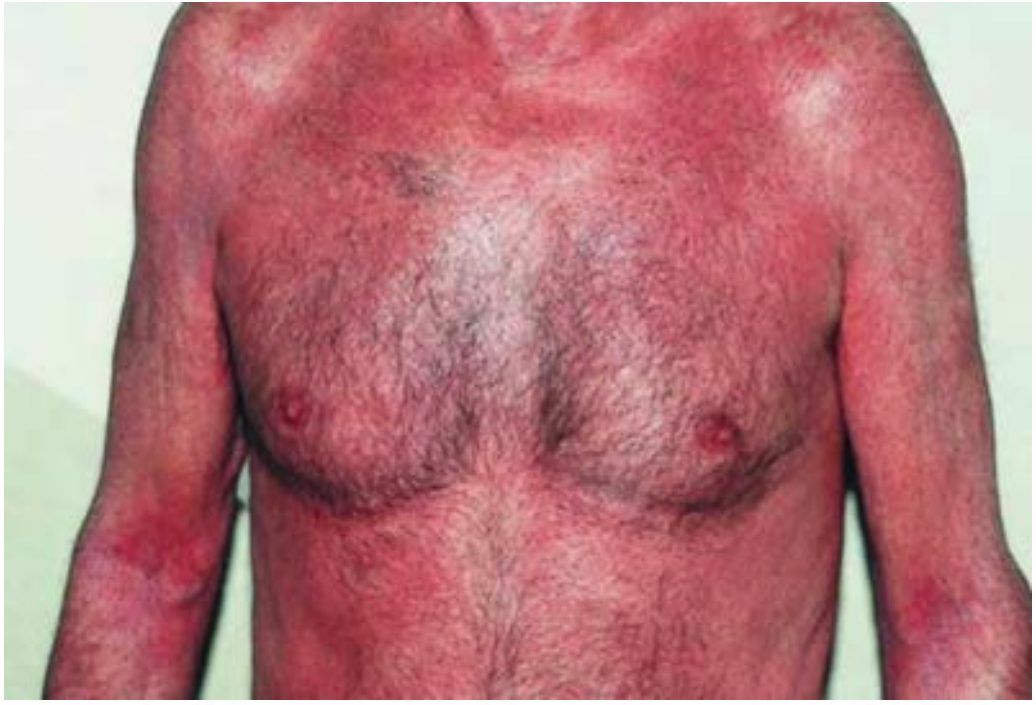
- Younger age a risk factor for vancomycin DRESS
- Higher vancomycin trough level a risk factor for vancomycin DRESS

JAMA Dermatol 2022 Dec 1;158(12):1449-1453

LETTER 12 MARCH 2015 | VOL 519 | NATURE | 237
doi:10.1038/nature14022

Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions

Benjamin D. McNeil[1], Priyanka Pundir[2], Sonya Meeker[3], Liang Han[1], Bradley J. Undem[3], Marianna Kulka[2,4] & Xinzhong Dong[1,5]



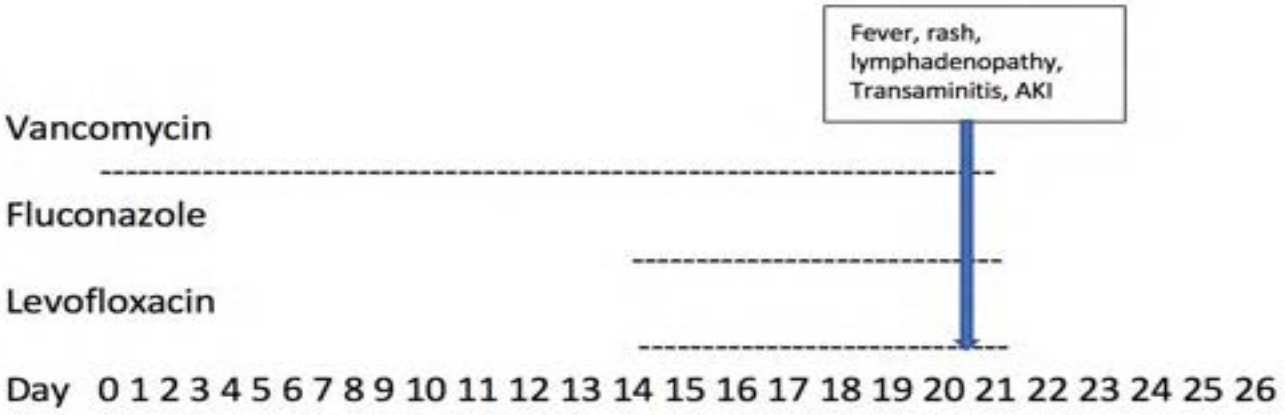
MRGPRX2 Agonists associated with non-IgE mediated reactions

- **Fluoroquinolones** (ciprofloxacin>moxifloxacin> levofloxacin)
- **Vancomycin**
- Neuromuscular blocking agents
- **Morphine/opioids** (not fentanyl)
- Radiocontrast dye
- Injectable peptidergic drugs (icatibant, leuprolide, octreotide, sermorelin, cetrorelix)

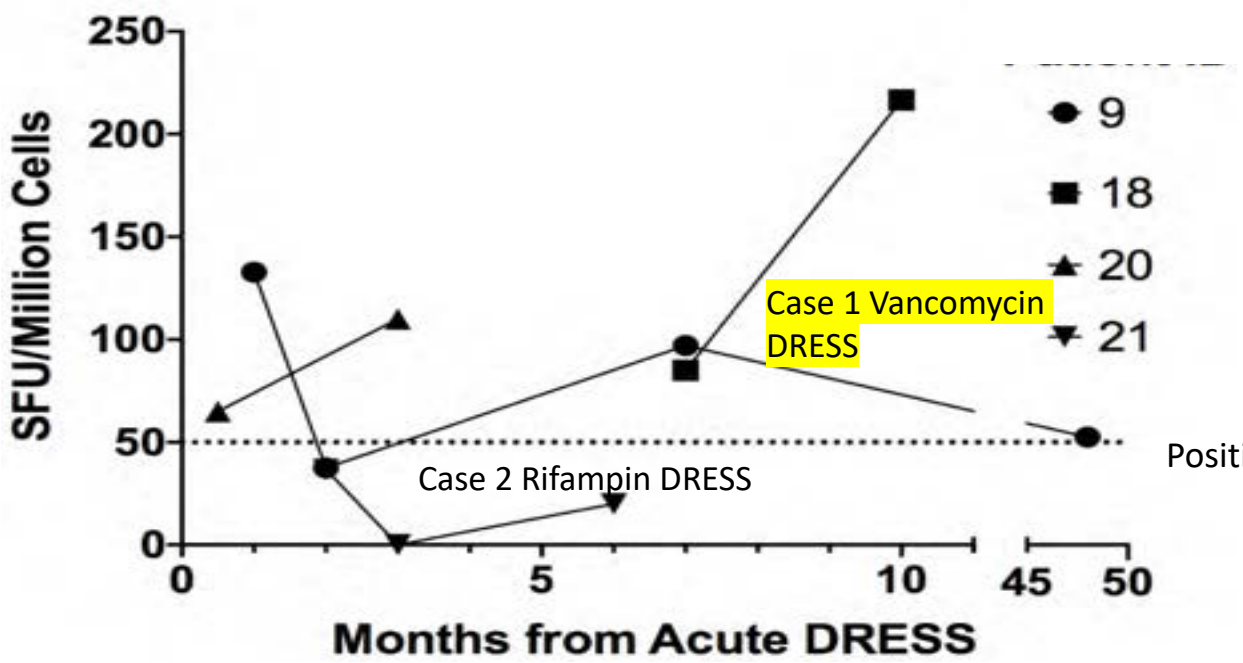
Case Questions?

- What is the likely diagnosis?
- Is this drug related?
- Is there a most likely implicated drug (antibiotic) and how would you determine this?
- Can this be prevented or preempted?
- Can antibiotic choice and drug safety be preserved in the future?

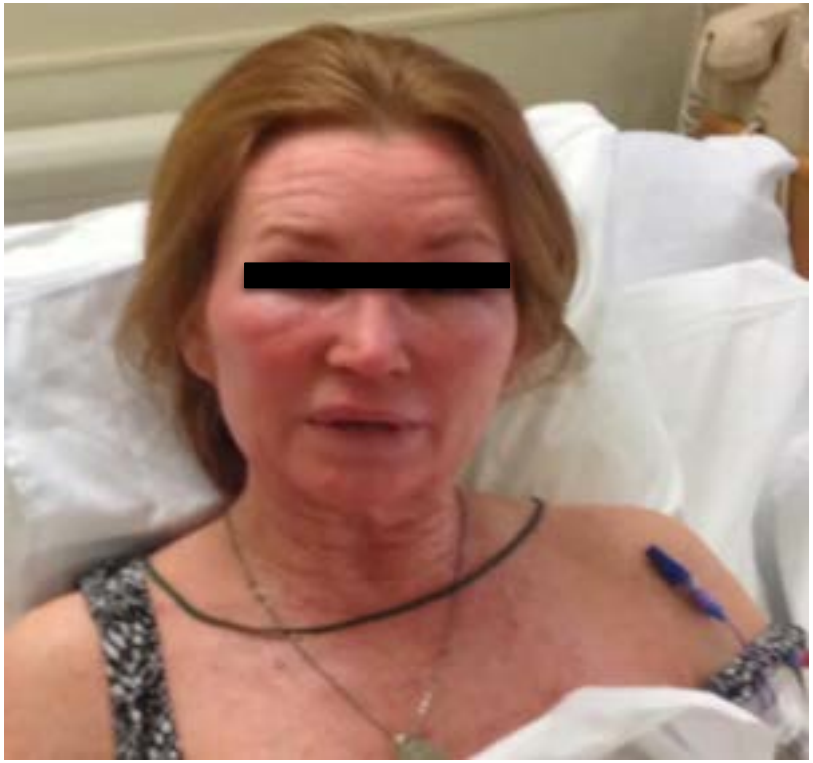
What is the most likely drug in our Case?

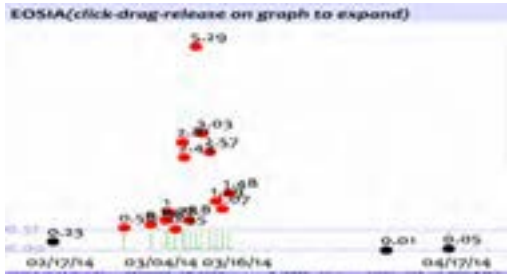


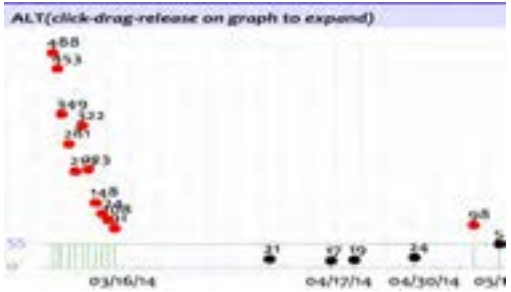
γ-interferon ELISpot Responses to Vancomycin over Time

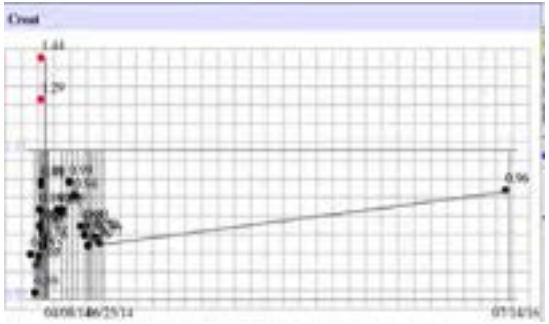


CASE









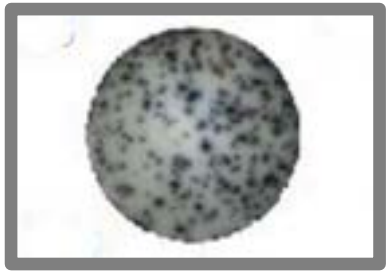
HLA-A*32:01+ Vancomycin DRESS

Research Role of Drug-Specific Adjunctive Blood Tests

- Clinical pre-test probability is important and a negative test does not alter that
- At >50 spots/well, 100% specific, 50% sensitive (validation needed)
- Use integrated with other testing (e.g. skin and HLA)
- Concentrations needed are often supra-pharmacological
- Rare cells in peripheral blood (Cells in SJS/TEN blister fluid may be more sensitive)

Patient PBMCs (fresh or frozen)

CMV pp65



Too numerous to count

Vancomycin 500 mcg/ml

465 spots per million

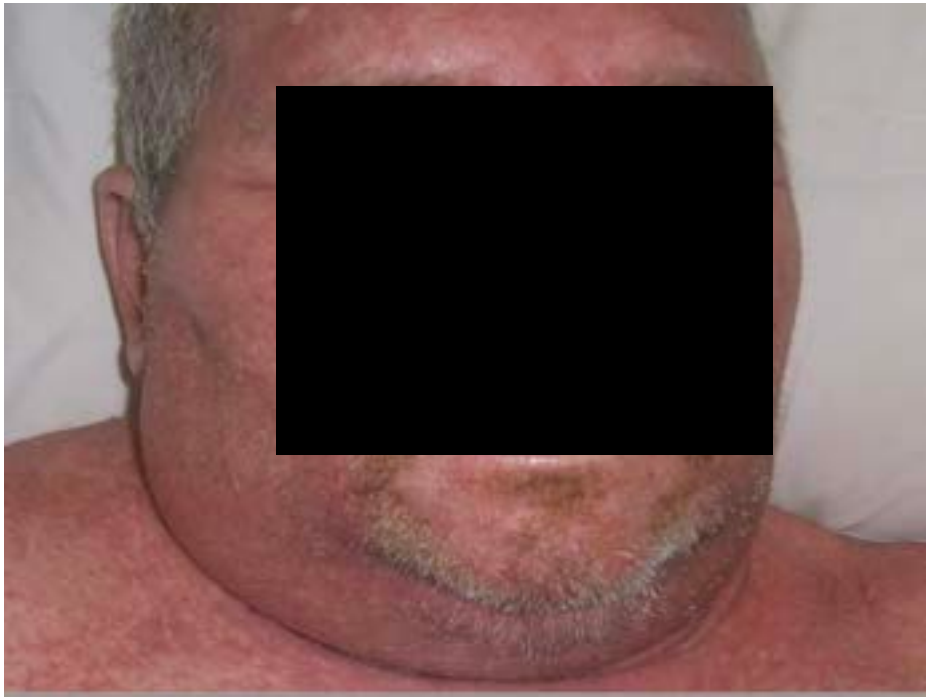
Antigen specific T-cells producing γ-INF

γ-INTERFERON ELISpot

Copaescu et al. Front Pharmacol 2021 Jan 12;11:573573
Trubiano et al. J Allerg Clin Immunol Pract 2018;6(4):1287-1296
Porter et al. J Invest Dermatol 2022;142(11):2920-2928
Awad et al. JACI Global 2022;1(1):16-21

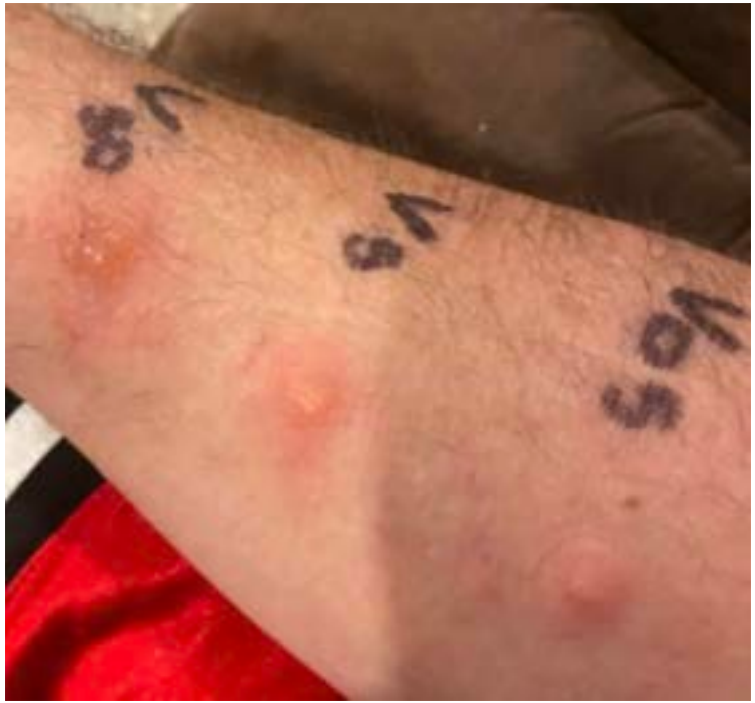
SCAR Responses are Durable Over Time: Avoid Drug Permanently

2013



Acute Vancomycin DRESS

2021

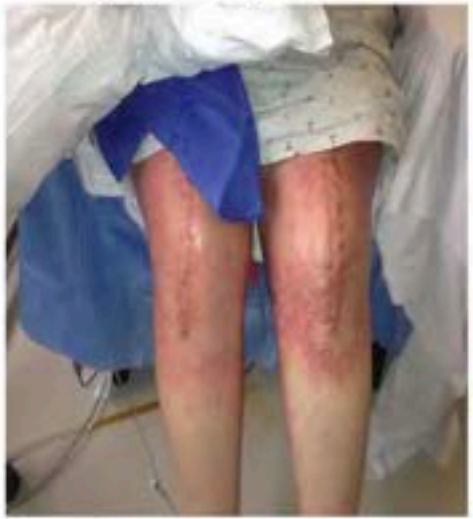


Vancomycin Skin Test Positive
HLA-A*32:01+

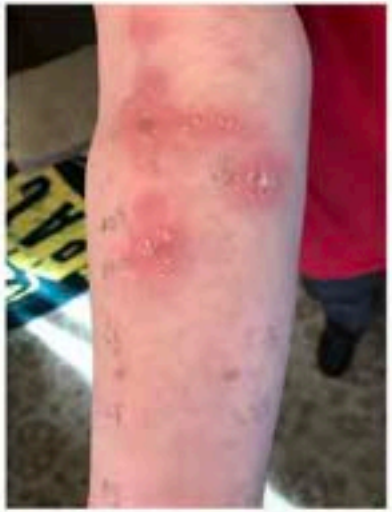
Blumenthal et al. JAMA Dermatol 2022 Dec 1;158(12):1449-1453 **(High vancomycin trough levels associated with DRESS)**
Awad et al JACI in practice.2023 (in press) – LongSCAR - skin test responses are durable

Diagnostic Clues for Clinical Phenotype

Vancomycin AGEP 2013
7 days post exposure

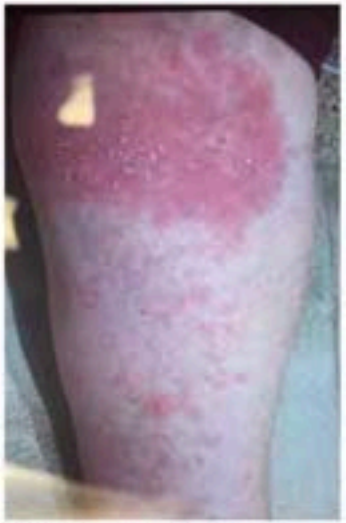


Intradermal Skin testing 2017



Intradermal at 48 hours

December 2020



3 weeks post acute
COVID-19 Infection

Intradermal testing
Feburary 2021

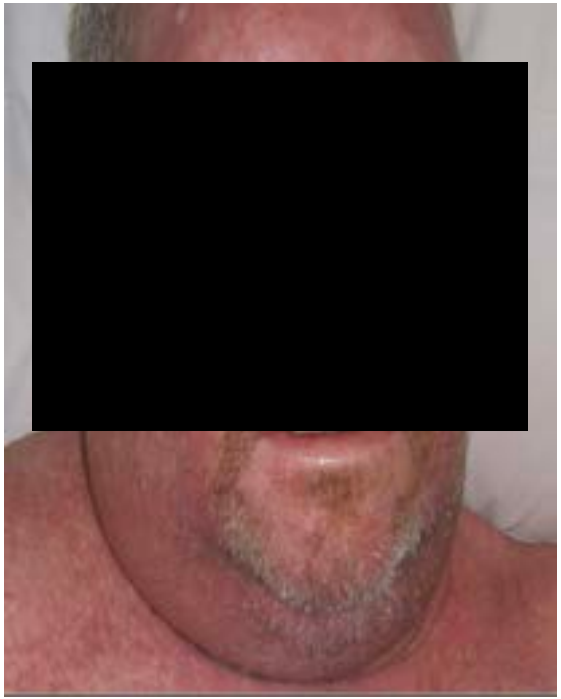
Intradermal at 48 hours

-Skin and Patch Testing with AGEP
Mimics the Acute Reaction
-HLA-A*32:01+ vancomycin AGEP

Retained Skin-test Positivity Remotely

Unusual Case of DRESS and AGEP in Same Patient

2013

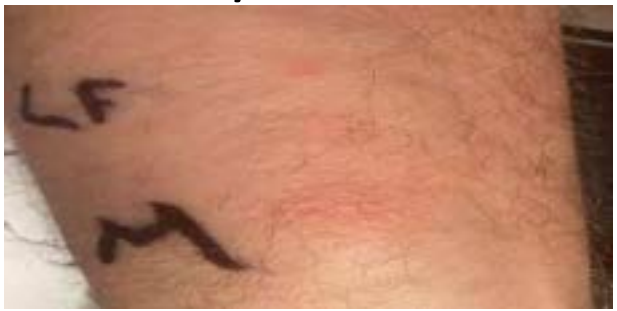


Acute DRESS on vancomycin
And ceftriaxone

07/2021

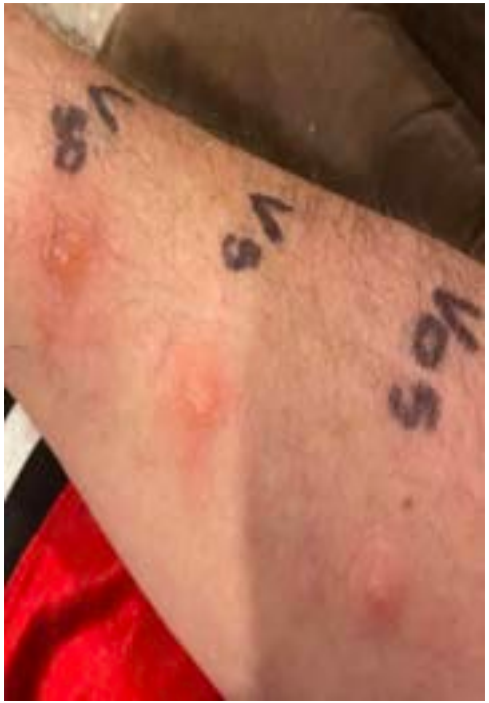
Acute AGEP 24 hours following
metronidazole and levofloxacin

09/2021



Positive skin test to metronidazole
(”AGEP” response

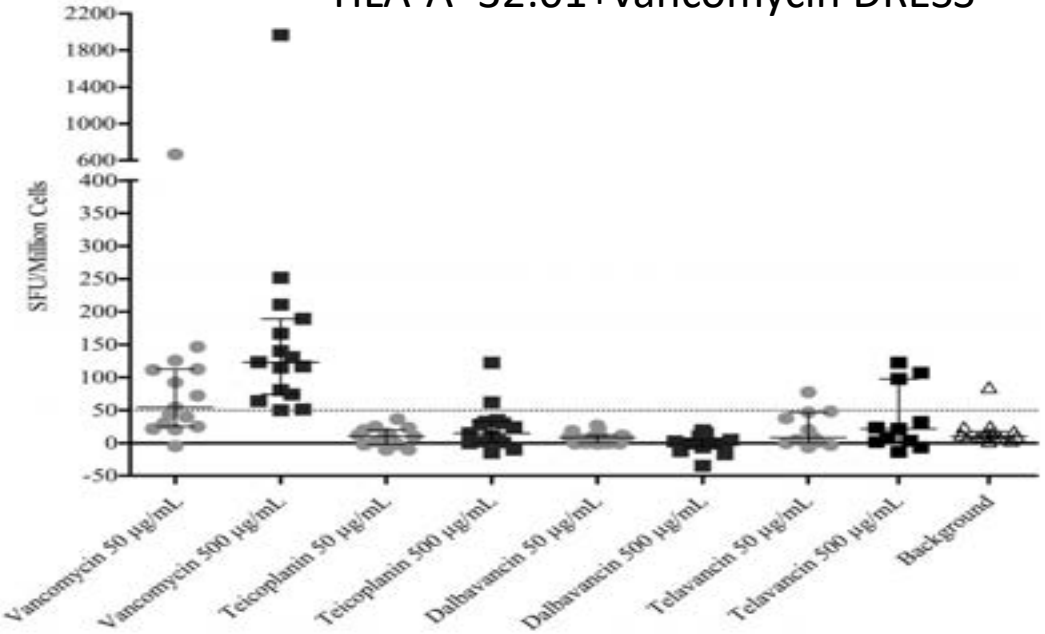
09/2021



Vancomycin Skin Test Positive
HLA-A*32:01 Positive

Ex Vivo Approaches to Predict Cross-reactivity

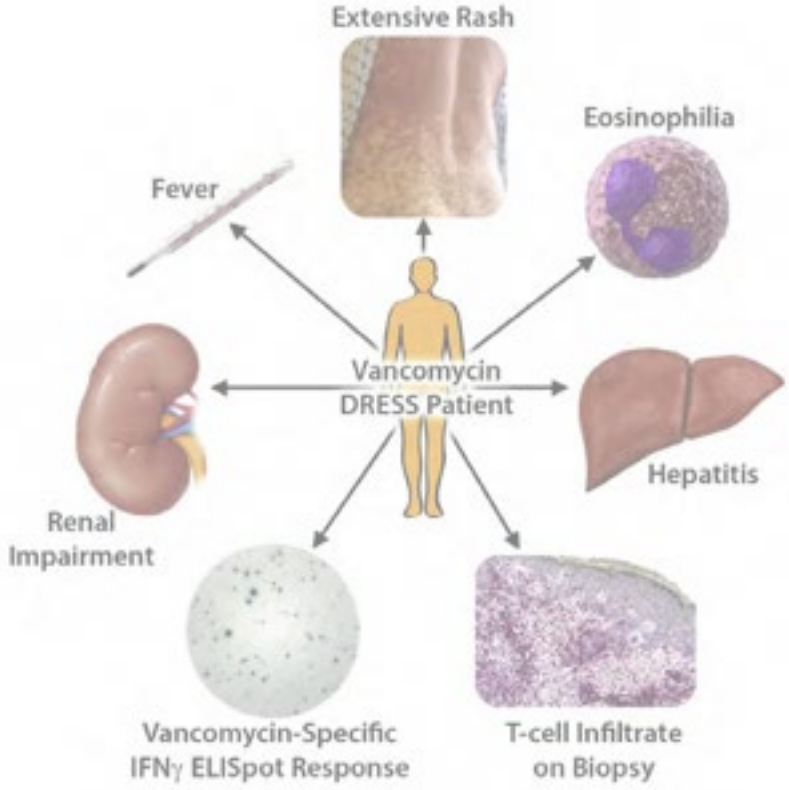
HLA-A*32:01+vancomycin DRESS

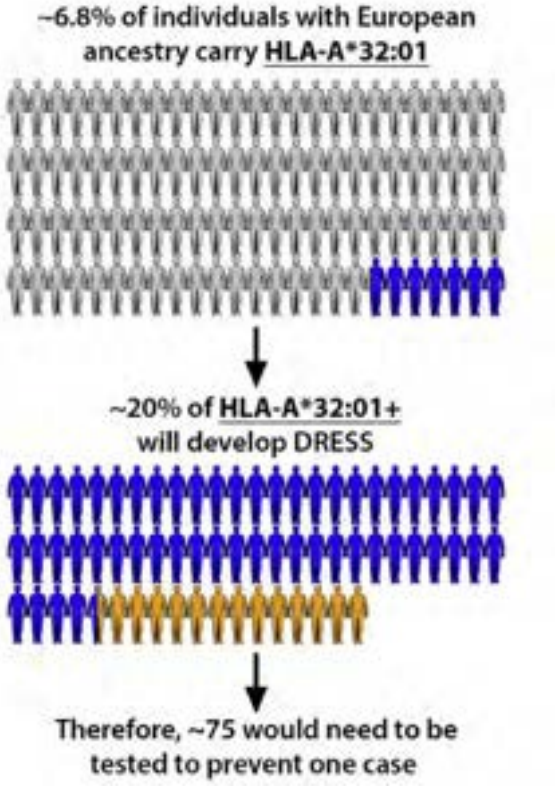


-low cross-reactivity between vancomycin, teicoplanin and telavancin
-cross-reactivity was predicted in 2/15 by a shared class II HLA haplotype

Nakkam et al J Allerg Clin Immun 2021 Jan;147(1):403-405.
doi: 10.1016/j.jaci.2020.04.056. Epub 2020 May 19.

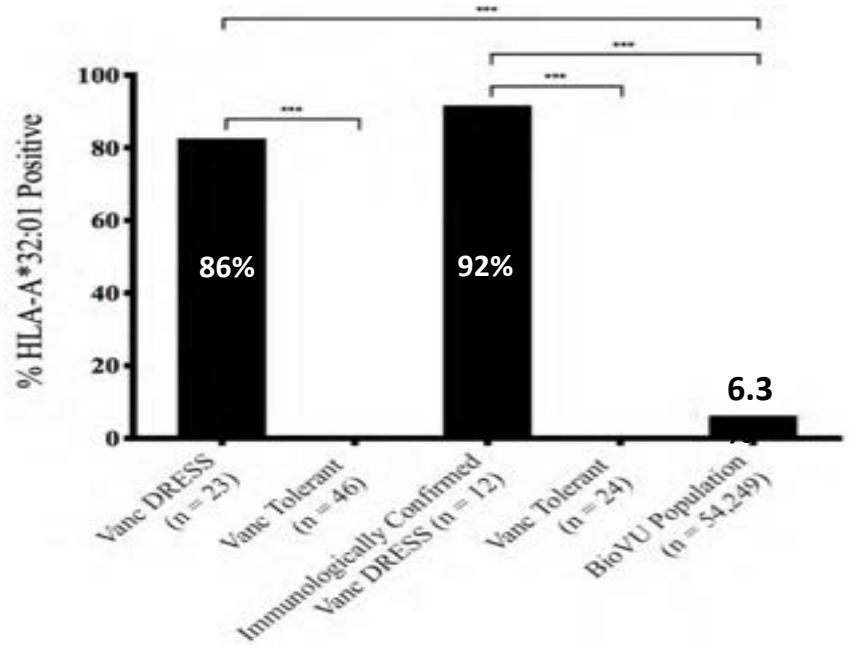
HLA-A*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms





Konvinse et al J Allergy Clin Immunol. 2019;144(1):183-192

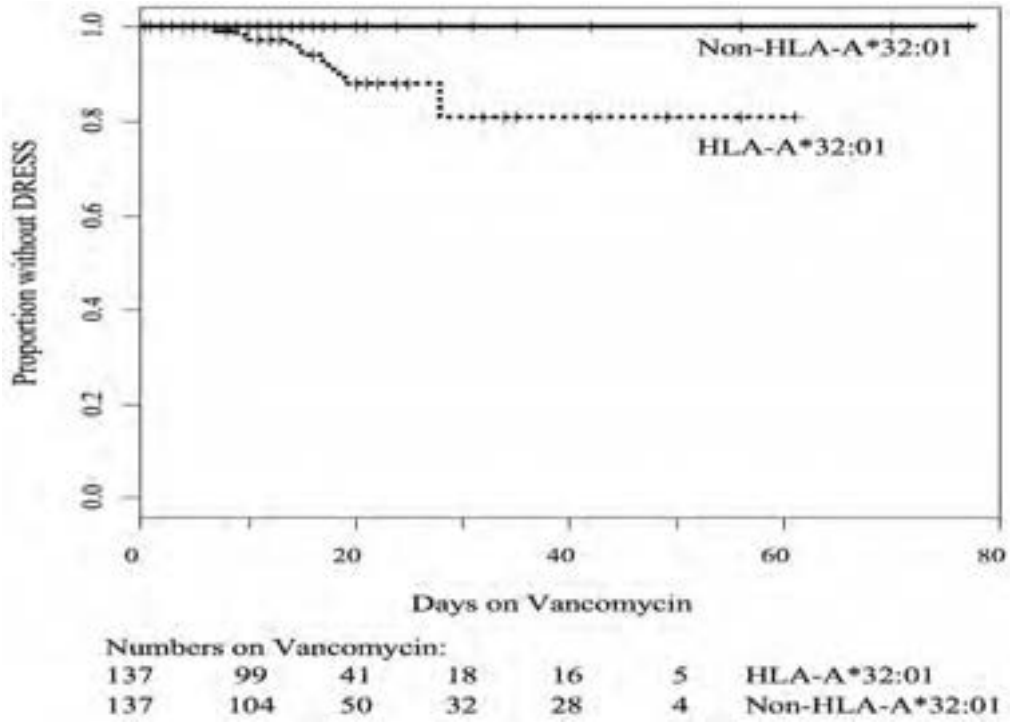
HLA-A*32:01 is Strongly Associated With Vancomycin DRESS



P= 1 x 10^{-8} conditional logistic analysis; Bonferroni control for multiple comparison

Konvinse et al J Allergy Clin Immunol. 2019;144(1):183-192

Time to Event Analysis



-end stage renal disease on hemodialysis protective against DRESS
-immunocompromised state protective against DRESS

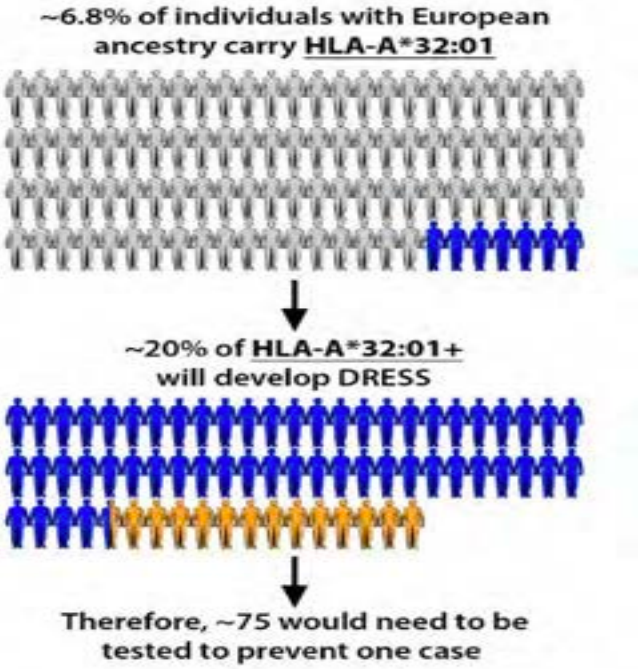
*approximately 20% of patients carrying HLA-A*32:01 developed DRESS by 4 weeks

Konvinse et al J Allergy Clin Immunol. 2019;144(1):183-192

Vancomycin DRESS and HLA-A*32:01

-SCREEN – for emergent use not practical but DRESS latency ≥2 weeks

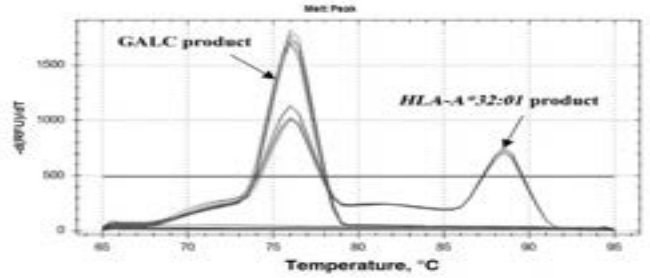
- ✓ **PREEMPT- intervene early if patient at risk**
- ✓ **DIAGNOSIS – adds to causality (with clinical and functional assessments)**

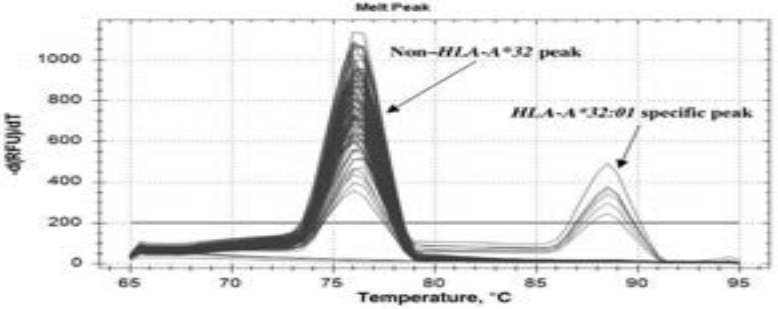


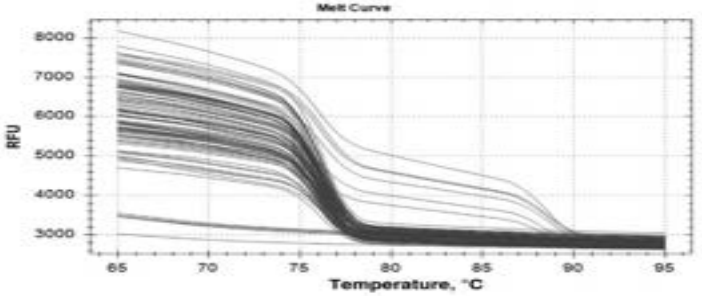
Konvinse et al. J Allergy Clin Immunol. 2019 Jul;144(1):183-192

A Rapid Allele-Specific Assay for *HLA-A*32:01* to Identify Patients at Risk for Vancomycin-Induced Drug Reaction with Eosinophilia and Systemic Symptoms

Francois X. Rwandamuriye,* Abha Chopra,*† Katherine C. Konvinse,‡ Linda Choo,* Jason A. Trubiano,‡¶ Christian M. Shaffer,‖ Mark Watson,* Simon A. Mallal,*†‖ and Elizabeth J. Phillips*,**††







Vancomycin DRESS: Global Distribution May not be Equal

http://www.allelefrequencies.net/

- Vancomycin use differs globally
- Duration of vancomycin use differs globally
  - *Median time to DRESS = 3 weeks*
- Prevalence of risk alleles (HLA-A*32:01 differs globally)
- HLA risk outside of HLA-A*32:01 in different populations

HLA-A*32:01 Homozygosity is Overrepresented in Vancomycin DRESS

	Vancomycin DRESS cases (n = 78)	Vancomycin tolerant controls (HLA-A*32:01 positive) (n = 113)	Vancomycin tolerant controls (all) (n = 2,702)	BioVU Population (n = 94,489)
HLA-A*32:01 Homozygous	5/78 (6.4%)	1/105 (0.96%)	1/2,702 (0.037%)	113/94,489 (0.12%)

Krantz et al

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P<0.0001

Original Article

Vancomycin-Induced Liver Injury, DRESS, and HLA-A*32:01

Bilal A. Asif, MD[a], Christopher Koh, MD, MHSc[a], Elizabeth J. Phillips, MD[b], Jiezhun Gu, PhD[c], Yi-Ju Li, PhD[c], Huiman Barnhart, PhD[c], Naga Chalasani, MD[d], Robert J. Fontana, MD[e], Paul H. Hayashi, MD, MPH[f], Victor J. Navarro, MD[g], and Jay H. Hoofnagle, MD[h]; for the Drug Induced Liver Injury Network (DILIN) *Bethesda and Silver Spring, Md; Nashville, Tenn; Durham, NC; Indianapolis, Ind; and Philadelphia, Pa*

TABLE IV. Vancomycin hepatotoxicity: 9 cases

Case	HLA-A (1)	HLA-A (2)	Rash	Fever	Eos	Renal	DRESS	DRESS score	Duration of therapy (d)	Time to onset (d)	*R* value	Pattern	Peak bilirubin	Severity score	Causality score
1	A*32:01	A*32:01	1	1	1	1	Yes	8	37	20	28.2	HC	3.0	4	3
2	A*25:01	A*32:01	1	1	1	1	Yes	5	22	22	3.7	Mix	0.9	1	2
3	A*02:01	A*03:01	1	1	1	1	Yes	4	15	10	9.9	HC	1.9	3	3
4	A*24:02	A*24:02	0	0	0	0	No	1	1	6*	0.6	Chol	14.3	2	3
5	A*26:01	A*32:01	1	1	Unk	1	Yes	3	26	27	3.4	Mix	19.4	4	3
6	A*01:01	A*32:01	1	1	1	1	Yes	5	31	20	0.8	Chol	0.7	1	2
7†	A*03:01	A*32:01	1	1	1	Unk	Yes	5	18	16	0.2	Chol	3.3	3	3
8†‡	A*32:01	A*33:03	1	1	1	1	Yes	6	30	16	2.1	Mix	38.6	5	3
9†	A*01:01	A*32:01	1	1	1	1	Yes	6	30	19	1.7	Chol	13.0	4	2

Alk, Alkaline phosphatase; *ALT*, alanine aminotransferase; *Chol*, cholestatic; *HC*, hepatocellular; *Mix*, mixed; *R* = (ALT/ULN ÷ Alk P/ULN); *ULN*, upper limit of normal; *Unk*, unknown.
*History of jaundice after previous exposure to vancomycin.
†Initially, concomitant medications thought to be an unlikely cause that on re-review was considered at least probable.
‡Black, fatal outcome after reexposure after onset of DRESS syndrome and acute exacerbation of liver and renal injury.

Part 2: Phenytoin SCAR

- How to interpret HLA and other genetic information – caveats and implications
- Population based pharmacogenomic screening/testing/research not “race”-based
- General future concepts relevant to all medications

HLA as a Screening Test

If a risk allele is present it has the same implications across race/ethnicity

The performance as a screening test may differ across race (negative predictive value)

Different HLA risk alleles may be present in different populations

What Determines Number Needed to Test to Prevent one Case?

HLA risk allele frequency in the specific population

Prevalence of drug-specific phenotype

Positive predictive value of the HLA risk allele for the drug-specific phenotype

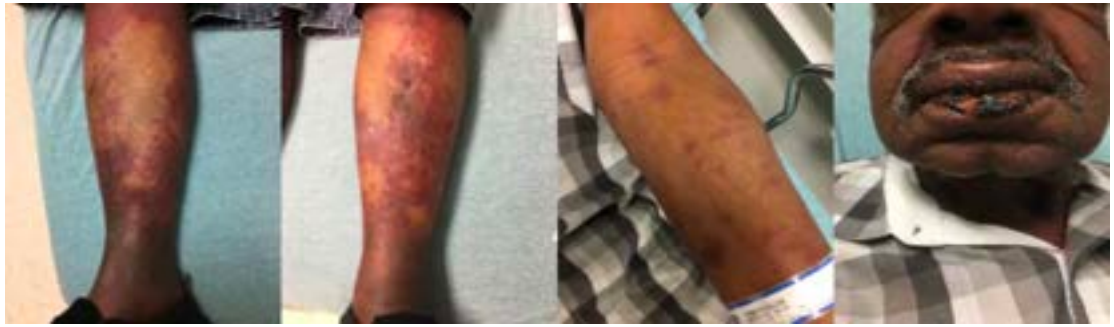
HLA Class I Strongly Associated with SCAR

DRUG	CAUSES SCAR	SYNDROME	Risk HLA-	100% Negative Predictive Value Across Populations	Positive Predictive Value	Number Needed to test to prevent "1"	Screening and/or diagnosis?
Abacavir	N	Abacavir hypersensitivity	B*57:01	Y	55%	13	**Pre-prescription screening**
Allopurinol	Y	DRESS or SJS/TEN	B*58:01	N	3%	250	Screening or diagnosis
Carbamazepine	Y	SJS/TEN only DRESS >>> SJS/TEN	B*15:02 A*31:01	N N	3% <0.5%	1000 5000	Screening or diagnosis Risk stratification/diagnosis
Dapsone	Y	DRESS or SJS/TEN	B*13:01	N	7.8%	84	Screening or diagnosis
Nevirapine	Y	SJS/TEN	C*04:01	N	2.5%	200	Screening or diagnosis
Trimethoprim-sulfamethoxazole	Y	DRESS or SJS/TEN	B*13:01	N	3-4%	211	Screening or diagnosis
Vancomycin	Y	DRESS	A*32:01	N	20%	75	**Risk stratification or diagnosis**

Deshpande et al. Clin Pharmacol Ther 2021 Sep;110(3):607-615

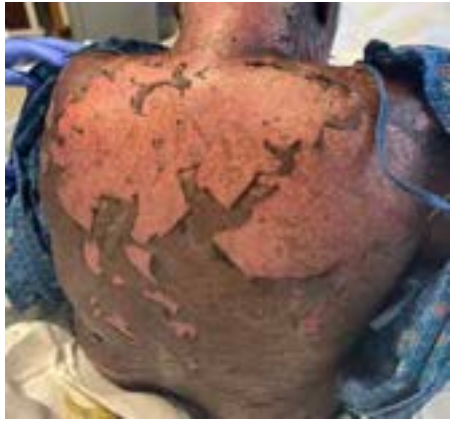
Gibson et al. J Allergy Clin Immunol 2023 Feb;151(2):289-300

HLA testing as “Secondary Prevention”

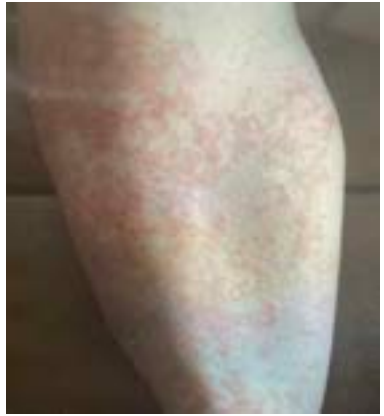


- 74 year old man gout & hypertension presented 6 weeks later having had history consistent with DRESS (RegiSCAR 6) occurring on simultaneous administration of allopurinol and ceftriaxone.

HLA-B*58:01+ DRESS and SJS/TEN related to allopurinol



- 67 year old woman transferred with SJS/TEN
- Mysterious decrease in uric acid seen in lab records
- No history of allopurinol use obtained initially from transfer or medication record



- 71 year old Caucasian man history of rash, facial swelling 3 weeks following allopurinol
- Treated with steroids weaned over 8 weeks
- Records sparse
- RegiSCAR 3

What is the HLA Roadmap in 2023 (Beyond Prevention)

Avoid the drug in a known risk population

Preemptive management to identify and monitor a high-risk population

Facilitate early recognition and discontinuation of the likely culprit medication

Diagnosis, integrated management and future drug safety

Quality assured inexpensive test

Unique niche (lack of safe/effective medication alternatives)

Eases clinical practice/ shared patient

decision-making

Provides additional information (e.g. drug causality/diagnosis) =

"secondary prevention"

Improve patient/family/healthcare provider confidence

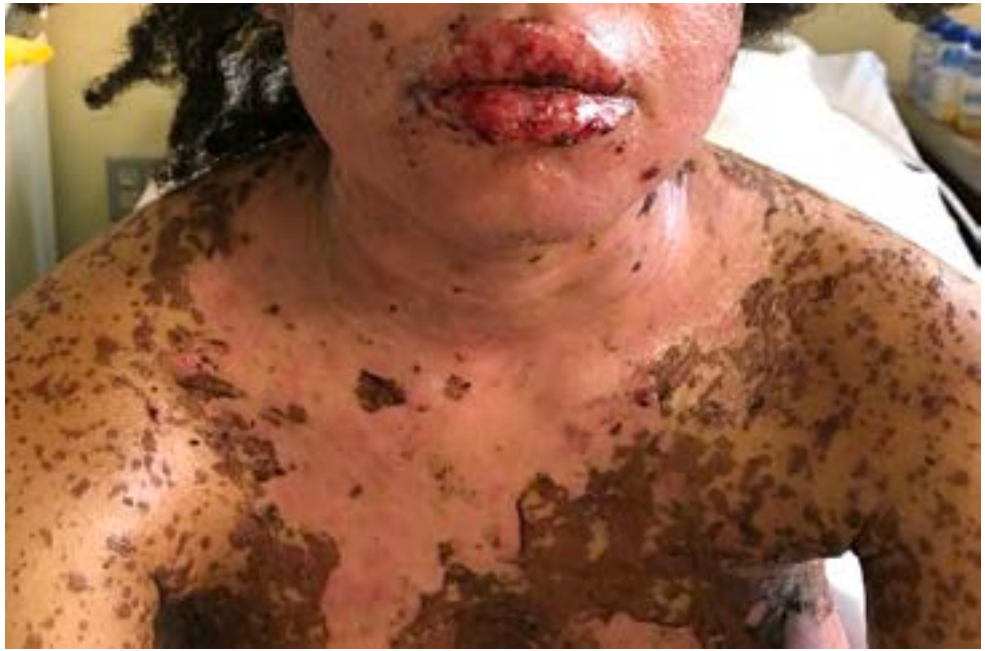
drug safety

Information transfer to community healthcare providers including pharmacy

Pharmacogenomic Implementation Toolkit

Genetic Counselling not just testing is Important

- 21 year old transferred from outside hospital
- History of starting on lamotrigine 2.5 weeks prior
- 3 days prior to admission developed throat pain and blistering rash and stopped lamotrigine but started amoxicillin and ibuprofen
- Rash progressed
- Mother said “genetic testing” was done and was negative and they had felt reassured



Lamotrigine SJS/TEN in HLA-B*15:02 Negative

Beware of how to interpret genetic information

VIEWPOINT

Race and Pharmacogenomics–Personalized Medicine or Misguided Practice?

JAMA. 2021 Feb 16;325(7):625-626

Christopher W. Goodman, MD
Department of Medicine, University of South Carolina School of Medicine, Columbia.

Allan S. Brett, MD
Department of Medicine, University of South Carolina School of Medicine, Columbia.

The use of race in clinical decision-making is coming under increasing scrutiny, in part because of growing recognition that race-based diagnosis and treatment reflect flawed social, biological, and genetic assumptions. Despite this concern, guidelines, algorithms, and advisory and regulatory bodies (including the US Food and Drug Administration [FDA]) regularly use race in ways that influence clinical decisions. For example, race-based "corrections" have been deemed problematic in algorithms, risk scores, and physiologic

Race-based pharmacogenetic screening recommendations may result in considerable practice variation and stereotyping, with unknown clinical consequences and reinforcement of preexisting beliefs about race as a biological construct.

HLA-A*3101 **Higher Risk**
T/T

This patient is homozygous for the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A*3101 allele or certain HLA-A*33 alleles. This genotype suggests a higher risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.

HLA-B*1502 **Normal Risk**
Not Present

This patient does not carry the HLA-B*1502 allele or a closely related *15 allele. Absence of HLA-B*1502 and the closely related *15 alleles suggests normal risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

Phillips et al JAMA Dermatol2022;158(6):607-608

RESEARCH ARTICLE

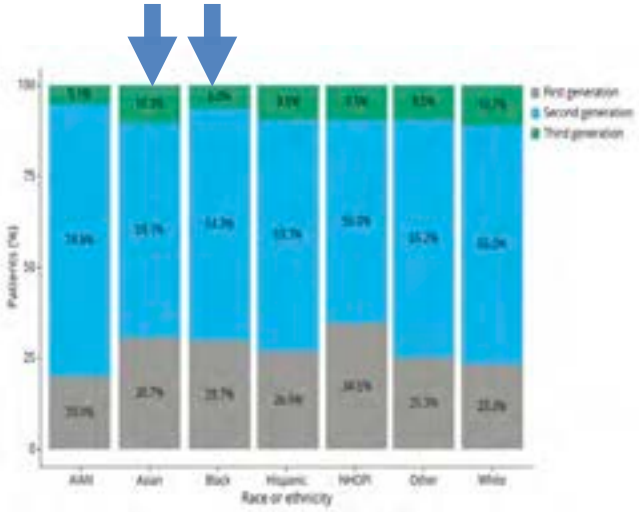
Racial and Ethnic Differences in Antiseizure Medications Among People With Epilepsy on Medicaid

A Case of Potential Inequities

Wyatt P. Bensken, PhD, Guadalupe Fernandez Baca Vaca, MD, Philip M. Alberti, PhD, Omar I. Khan, MD, Timothy H. Ciesielski, ScD, MD, MPH, Barbara C. Jobst, MD, PhD, Scott M. Williams, PhD, Kurt C. Stange, MD, PhD, Martha Sajatovic, MD, and Siran M. Koroukian, PhD

Correspondence
Dr. Bensken
wpb27@case.edu

Neurology: Clinical Practice 2023;13:e200101. doi:10.1212/CPJ.0000000000200101



- populations at risk may be more likely to be prescribed medications (e.g. first generation antiepileptics such as phenytoin) that cause SCAR
- 46% of phenytoin SCAR patients in VUMC BioVu were African American >80% sharing same class I HLA allele prevalent in AA (only 10% overall AA in VUMC BioVu)

Garon S, JACI 2017;139:2

FDA Wording

5.3 Serious Dermatologic Reactions

DILANTIN can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.4)]*. The onset of symptoms is usually within 28 days, but can occur later. DILANTIN should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCARs.

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. In addition, retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant, which has also been associated with decreased clearance of phenytoin. Consider avoiding DILANTIN as an alternative to carbamazepine in patients who are positive for HLA-B*1502 or in CYP2C9*3 carriers *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.5)]*.

The use of HLA-B*1502 or CYP2C9 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

HLA Alleles and *CYP2C9*3* as Predictors of Phenytoin Hypersensitivity in East Asians

Shih-Chi Su[1,2], Chun-Bing Chen[1,2,3,4,5,6], Wan-Chun Chang[2], Chuang-Wei Wang[2,5,6], Wen-Lang Fan[1], Lai-Ying Lu[2,3], Ryosuke Nakamura[7], Yoshiro Saito[7], Mayumi Ueta[8], Shigeru Kinoshita[8], Chonlaphat Sukasem[9,10], Kittika Yampayon[11,12], Pornpimol Kijsanayotin[12], Nontaya Nakkam[13], Niwat Saksit[13,14], Wichittra Tassaneeyakul[13], Michiko Aihara[15], Yu-Jr Lin[16], Chee-Jen Chang[17], Tony Wu[18], Shuen-Iu Hung[19,*] and Wen-Hung Chung[1,2,3,4,5,6,*]

Table 4 Calculations used for number needed to test to prevent one case of phenytoin hypersensitivity and the positive and negative predictive values with multiple susceptibility alleles

*CYP2C9*3/HLA-B*13:01/ HLA-B*15:02/ HLA-B*51:01*	Positive	Negative	Total	
ADR positive	a	b	a + b	Sensitivity = a/a + b × 100%
Control	c	d	c + d	Specificity = d/c + d × 100%
Total	a + c	b + d	a + b + c + d = 100,000	
	PPV = a/a + c × 100%	NPV = d/b + d × 100%		NNT to prevent one case = 100,000/a
Phenytoin-SCAR	323.46	126.54	450	Incidence = 0.45%
Control	22,239.47	77,310.53	99,550	Sensitivity = 71.88%,
Total	22,562.93	77,437.07	100,000	Specificity = 77.66%
	PPV = 1.43359%	NPV = 99.84%		NNT to prevent one case = 310
Phenytoin-SCAR + MPE	2412.59	1637.41	4050	Incidence = 4.05%
Control	21,435.23	74,514.77	95,950	Sensitivity = 59.57%
Total	23,847.82	76,152.18	100,000	Specificity = 77.66%
	PPV = 10.1%	NPV = 97.85%		NNT to prevent one case = 42

A theoretical population of 100,000 has been assumed, and the number of individuals with the ADR calculated based on previous reported prevalence, and the number of tolerant patients calculated by subtracting this figure from 100,000. The sensitivity and specificity of the multiple susceptibility alleles test for the phenytoin hypersensitivity have been taken from **Table 3** and the numbers in each of the four cells (a, b, c, and d) calculated. The positive and negative predictive values and numbers needed to test were then calculated from the numbers in each cell (a, b, c, and d).

CYP, cytochrome P450; ADR, adverse drug reaction; MPE, maculopapular exanthema; NNT, number needed to treat; NPV, negative predictive value; PPV, positive predictive value; SCAR, severe cutaneous adverse reactions.

HLA Alleles and *CYP2C9*3* as Predictors of Phenytoin Hypersensitivity in East Asians

Shih-Chi Su[1,2], Chun-Bing Chen[1,2,3,4,5,6], Wan-Chun Chang[2], Chuang-Wei Wang[2,5,6], Wen-Lang Fan[1], Lai-Ying Lu[2,3], Ryosuke Nakamura[7], Yoshiro Saito[7], Mayumi Ueta[8], Shigeru Kinoshita[8], Chonlaphat Sukasem[9,10], Kittika Yampayon[11,12], Pornpimol Kijsanayotin[12], Nontaya Nakkam[13], Niwat Saksit[13,14], Wichittra Tassaneeyakul[13], Michiko Aihara[15], Yu-Jr Lin[16], Chee-Jen Chang[17], Tony Wu[18], Shuen-Iu Hung[19,*] and Wen-Hung Chung[1,2,3,4,5,6,*]

Table 3 Association of phenytoin hypersensitivity reactions with single and multiple susceptibility alleles

	Positivity	OR (95% CI)	*P* value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CYP2C9*3							
Control	9/376 (0.02)	1.00					
SCAR	39/128 (0.30)	17.87 (8.35–38.24)	1.09E-17	30.47	97.61	81.25	80.48
SJS/TEN	22/65 (0.34)	20.86 (9.03–48.20)	1.22E-13	33.85	97.61	70.97	89.51
DRESS	17/63 (0.27)	16.95 (6.93–41.47)	8.83E-11	26.98	97.61	65.38	88.86
SCAR + MPE	49/235 (0.21)	10.74 (5.16–22.34)	4.66E-14	20.85	97.61	84.48	66.37
MPE	10/107 (0.09)	4.20 (1.66–10.63)	0.003	9.35	97.61	52.63	79.09
CYP2C9*3/HLA-B*13:01							
Control	48/376 (0.13)	1.00					
SCAR	63/128 (0.49)	6.62 (4.18–10.49)	4.18E-16	49.22	87.23	56.76	83.46
SJS/TEN	31/65 (0.48)	6.23 (3.51–11.05)	1.32E-02	47.69	87.23	39.24	90.61
DRESS	32/63 (0.51)	7.05 (3.95–12.6)	9.34E-11	50.79	87.23	40.00	91.36
SCAR + MPE	90/235 (0.38)	4.24 (2.84–6.33)	5.40E-13	38.30	87.23	65.22	69.34
MPE	27/107 (0.25)	2.31 (1.36–3.92)	0.004	25.23	87.23	36.00	80.39
CYP2C9*3/HLA-B*15:02							
Control	31/376 (0.08)	1.00					
SCAR	59/128 (0.46)	9.52 (5.74–15.78)	1.78E-19	46.09	91.76	65.56	83.33
SJS/TEN	36/65 (0.55)	13.82 (7.49–25.47)	2.98E-17	55.38	91.76	53.73	92.25
DRESS	23/63 (0.37)	6.40 (3.40–12.03)	3.57E-08	36.51	91.76	42.59	89.61
SCAR + MPE	81/235 (0.34)	5.85 (3.71–9.23)	9.68E-16	34.47	91.76	72.32	69.14
MPE	22/107 (0.21)	2.88 (1.59–5.22)	0.001	20.56	91.76	41.51	80.23
CYP2C9*3/HLA-B*51:01							
Control	28/376 (0.07)	1.00					
SCAR	56/128 (0.44)	9.67 (5.75–16.26)	7.38E-19	43.75	92.55	66.67	82.86
SJS/TEN	29/65 (0.45)	10.01 (5.376–18.66)	1.36E-12	44.62	92.55	50.88	90.63
DRESS	27/63 (0.43)	9.32 (4.966–17.51)	1.63E-11	42.86	92.55	49.09	90.63
SCAR + MPE	81/235 (0.34)	6.54 (4.1–10.46)	5.21E-17	34.47	92.55	74.31	69.32
MPE	25/107 (0.23)	3.79 (2.1–6.84)	1.60E-05	23.36	92.55	47.17	80.93
CYP2C9*3/HLA-B*13:01/HLA-B*15:02/HLA-B*51:01							
Control	84/376 (0.22)	1.00					
SCAR	92/128 (0.72)	8.88 (5.63–14.01)	2.12E-23	71.88	77.66	52.27	89.02
SJS/TEN	48/65 (0.74)	9.82 (5.36–17.96)	1.77E-15	73.85	77.66	36.36	94.50
DRESS	44/63 (0.70)	8.05 (4.46–14.53)	3.83E-13	69.84	77.66	34.38	93.89
SCAR + MPE	140/235 (0.60)	5.12 (3.59–7.31)	2.70E-20	59.57	77.66	62.50	75.45
MPE	48/107 (0.45)	2.83 (1.80–4.44)	8.27E-06	44.86	77.66	36.36	83.19

P values were calculated by using Fisher's exact test. The odds ratio (OR) with their 95% confidence intervals (CIs) were estimated by using a Haldane modification of Woolf's method as described in METHODS.
CYP, cytochrome P450; DRESS, drug reaction with eosinophilia and systemic symptoms ($N = 63$); MPE, maculopapular exanthema ($n = 107$); NPV, negative predictive value; PPV, positive predictive value; SCAR, severe cutaneous adverse reactions ($n = 128$); SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis ($n = 65$).

Table 3 Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

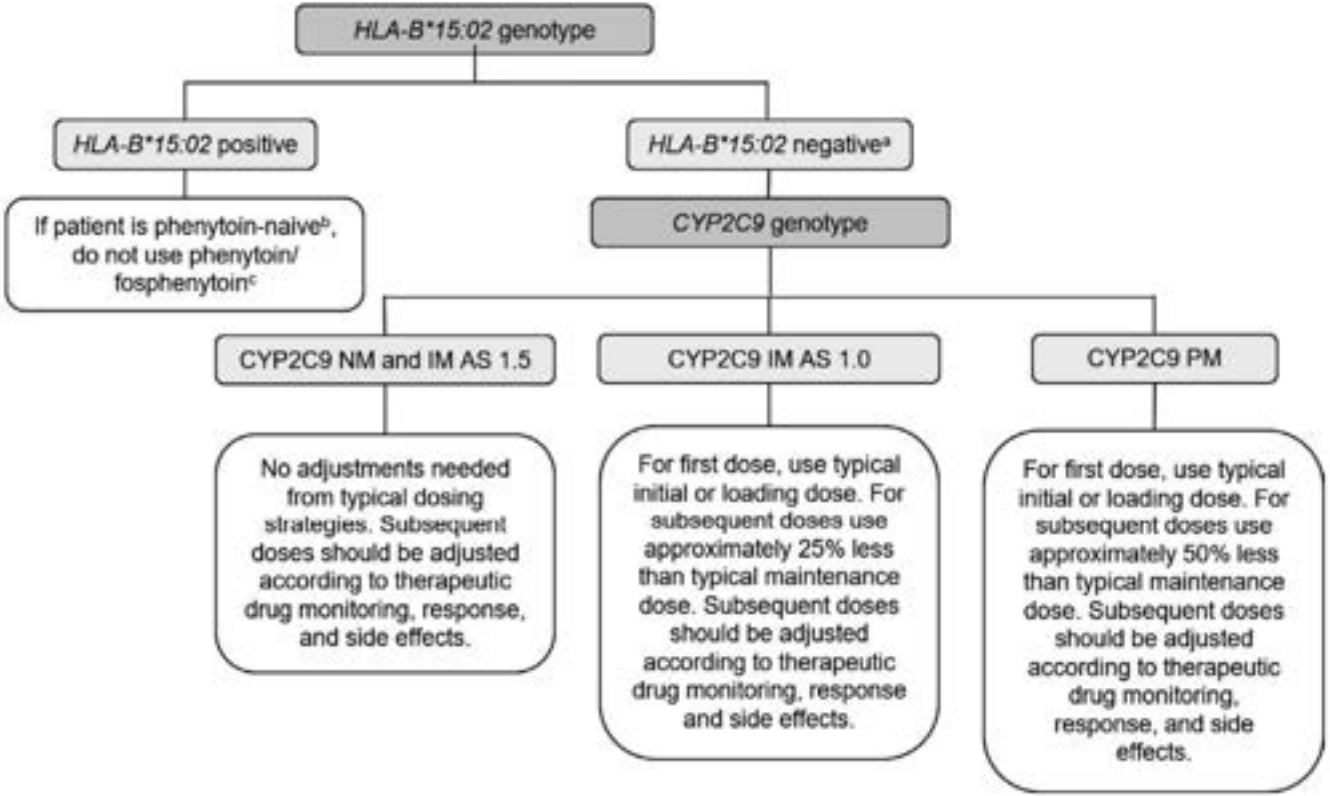
*HLA-B*15:02* phenotype	CYP2C9 phenotype	Implication	Therapeutic recommendation	Classification of recommendation	Considerations
*HLA-B*15:02* positive	Any CYP2C9 phenotype	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin-naïve, do not use phenytoin/fosphenytoin. Avoid carbamazepine and oxcarbazepine.	Strong	Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, and phenobarbital, have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.
			If the patient has previously used phenytoin continuously for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4–28 days), and cases usually occur within 3 months of dosing.	Optional	Previous tolerance of phenytoin is not indicative of tolerance to other aromatic anticonvulsants.
*HLA-B*15:02* negative	CYP2C9 NM	Normal phenytoin metabolism	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
*HLA-B*15:02* negative	CYP2C9 IM AS 1.5	Slightly reduced phenytoin metabolism; however, this does not appear to translate into increased side effects.	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Moderate	
*HLA-B*15:02* negative	CYP2C9 IM AS 1.0	Reduced phenytoin metabolism; higher plasma concentrations will increase probability of toxicities.	For first dose, use typical initial or loading dose. For subsequent doses, use ~ 25% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Moderate	
*HLA-B*15:02* negative	CYP2C9 PM	Reduced phenytoin metabolism; higher plasma concentrations will increase probability of toxicities.	For first dose, use typical initial or loading dose. For subsequent doses use ~ 50% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
*HLA-B*15:02* negative	Indeterminate	n/a	n/a	No recommendation	

AS, activity score; IM, intermediate metabolizer; n/a, not applicable; NM, normal metabolizer; PM, poor metabolizer; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

CPIC GUIDELINE UPDATE

Clin Pharmacol Ther. 2021 Feb; 109(2): 302–309.

Algorithm for suggested clinical actions based on HLA-B*15:02 and CYP2C9 genotype



Clin Pharmacol Ther. 2021 Feb; 109(2): 302–309.

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2C9 and HLA-B Genotypes and Phenytoin Dosing: 2020 Update Jason H. Karnes1 , Allan E. Rettie2 , Andrew A. Somogyi3 , Rachel Huddart4 , Alison E. Fohner5 , Christine M. Formea6, Ming Ta Michael Lee7 , Adrian Llerena8, Michelle Whirl-Carrillo4 , Teri E. Klein4,9, Elizabeth J. Phillips10, Scott Mintzer11, Andrea Gaedigk12, Kelly E. Caudle13, John T. Callaghan14

"The literature evaluating the association of the HLA-B alleles and phenytoin-induced SJS/TEN is inconsistent with respect to the specific HLA-B allele responsible for this ADR. Interpretation of literature is complicated by the studies' small sample sizes, inconsistent definition of the SJS/TEN 4 phenotype, inconsistent genotyping methodologies and the variety of race/ethnic groups in which studies were performed. The strength of the association between HLA-B*15:02 and phenytoin–induced SJS/TEN is weaker than the association between HLA-B*15:02 and carbamazepine–induced SJS/TEN and the association between HLA-B*57:01 and abacavir hypersensitivity syndrome. Even in the East Asian and Central/South Asian populations where HLA-B*15:02 carriage is prevalent, the negative predictive value (NPV) of HLA-B*15:02 falls significantly short of 100%. This lack of 100% NPV is illustrated by studies that have suggested that HLA-B alleles other than HLA-B*15:02, such as HLAB*13:01 and HLA-B*13:15, are associated with phenytoin-induced SJS/TEN (4, 5). Specific amino acid binding residues in HLA-B shared amongst risk alleles may be important and distinct drug-peptide-HLATCR interactions may also occur in patients with phenytoin SJS/TEN that do not carry HLA-B*15:02. However, this is only one of several non-mutually exclusive mechanisms to explain why different HLA alleles may be implicated in phenytoin-induced SJS/TEN (6). The observation of multiple HLA associations underscores the notion that the absence of these variants does not rule out the possibility of a patient developing phenytoin-induced SJS/TEN."

Clin Pharmacol Ther. 2021 Feb; 109(2): 302–309.

Using Population Descriptors in Genetics and Genomics Research: A New Framework for an Evolving Field (2023)

DETAILS

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LEGEND

+ Preferred population descriptor(s)
− Should not be used
? In some cases; refer to Ch. 5 text and the decision tree in Appendix D
E Descriptors could be used if appropriate proxies for environmental, not genetic, effects

GENOMICS STUDY TYPE	Race	Ethnicity/ Indigeneity	Geography	Genetic Ancestry	Genetic Similarity	Notes
1: Gene Discovery - Mendelian Traits	−	?	?	?	+	Similarity suffices as a genetic measure; at fine-scale, other variables may be useful
2: Trait Prediction - Mendelian Traits	−	E	E	?	+	No population descriptors may be necessary for analysis
3: Gene Discovery - Complex Traits	−	E	E	?	+	Similarity suffices as a genetic measure
4: Trait Prediction - Complex Traits	−	E	E	?	+	Similarity suffices as a genetic measure
5: Cellular and Physiological Mechanisms	−	E	E	−	?	No population descriptors may be necessary for analysis
6: Health Disparities with Genomic Data	E	E	E	?	+	Not all health disparities studies rely on descent-associated population groupings, so none may be necessary for analysis
7: Human Evolutionary History	−	?	+	+	+	Reconstructing genetic ancestry may be of central interest

*HLA-B*53:01* Is a Significant Risk Factor of Liver Injury due to Phenytoin and Other Antiepileptic Drugs in African Americans

Paola Nicoletti, MD, PhD[1], Andrew Dellinger, PhD[2], Yi-Ju Li, PhD[2], Huiman Barnhart, PhD[3], Elizabeth Phillips, MD[4] and Naga Chalasani, MD[5] for the Drug Induced Liver Injury Network (DILIN) investigators

INTRODUCTION: **To investigate human leukocyte antigen alleles associated with liver injury due to antiepileptic drugs (AEDs) in African Americans (AA).**

METHODS: **In this study, 21 AA with AED drug-induced liver injury (DILI), 176 AA with DILI due to non-AEDs, and 5816 AA population controls were included.**

RESULTS: ***HLA-B*53:01*** **was significantly associated with aromatic AED-DILI (odds ratio: 4.52, 95% confidence interval: 2.42–8.44, $P = 1.46 \times 10^{-5}$). Phenytoin DILI showed the strongest association with *HLA-B*53:01* (odds ratio: 9.17; 95% confidence interval: 3.61–23.28, $P = 1.1 \times 10^{-5}$). The *HLA-B*53:01* allele was carried by 8 of 9 AA phenytoin DILI cases.**

DISCUSSION: ***HLA-B*53:01*** **is a significant risk factor of liver injury due to antiepileptics, particularly phenytoin, in AA.**

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Table 1. Association of AED drug-induced liver injury with human leukocyte antigen alleles across drug classes in African American patients

Drug	Allele	OR (95% CI)	*P*	FDR	AF cases	AF controls	CF cases	% Carriers with DRESS
Phenytoin (N = 9)	**B*53:01**	**9.17 (3.61–23.28)**	**1.1×10^{-5}**	**0.0006**	**0.56**	**0.12**	**0.89**	**100**
	A*03:01	6.12 (2.29–16.34)	0.002	0.04	0.33	0.08	0.44	100
Lamotrigine (N = 4)	A*32:01	26.97 (5.40–134.8)	0.004	0.07	0.25	0.01	0.50	100
All AEDs (N = 21)	**B*53:01**	**4.52 (2.42–8.44)**	**1.46×10^{-5}**	**0.001**	**0.38**	**0.12**	**0.57**	**75**
	A*32:01	6.22 (1.90–20.38)	0.01	0.28	0.07	0.01	0.14	67
Aromatic AED (N = 17)	**B*53:01**	**4.54 (2.27–9.09)**	**8.7×10^{-5}**	**0.006**	**0.38**	**0.12**	**0.59**	**90**
	A*32:01	7.83 (2.37–25.91)	0.009	0.14	0.09	0.01	0.18	67

HLA B*53:01 is bolded to highlight its statistical significance in phenytoin, All AEDs, and aromatic AEDs.
AED, antiepileptic drugs; AF, allele frequency; CF, carriage frequency; CI, confidence interval; DRESS, drug reaction with eosinophilia and systemic symptom; FDR, false discovery rate; OR, odds ratio.

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Erika Lee (Toronto)
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Michelle Goh (Australia)
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Nontaya Nakkam (Thailand)
Dean Naisbitt (Liverpool)

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elizabeth.j.phillips@vumc.org

THANK YOU FOR YOUR ATTENTION!