Chilean Society of Hematology
XX Congress of the Chilean Society of Hematology
X Congress of Transfusion Medicine

Drug Induced Hemolytic Anemia (DIIHA)

Sandra J. Nance, MS, MT(ASCP)SBB
Senior Director, IRL, American Red Cross
Adjunct Assistant Professor, University of Pennsylvania
Senior Director, American Rare Donor Program
Philadelphia, Pennsylvania, USA

American Red Cross Headquarters

Washington, DC

American Red Cross

American Red Cross Immunohematology Reference Laboratories

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Disclaimers

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Abbreviations

- AIHA – Autoimmune Hemolytic Anemia
- DAT – Direct Antiglobulin Test
- DIIHA- Drug-Induced Immune Hemolytic Anemia
- IRL – Immunohematology Reference Laboratory
- NRLBGS – National Reference Laboratory for Blood Group Serology
- RBC – Red Blood Cells

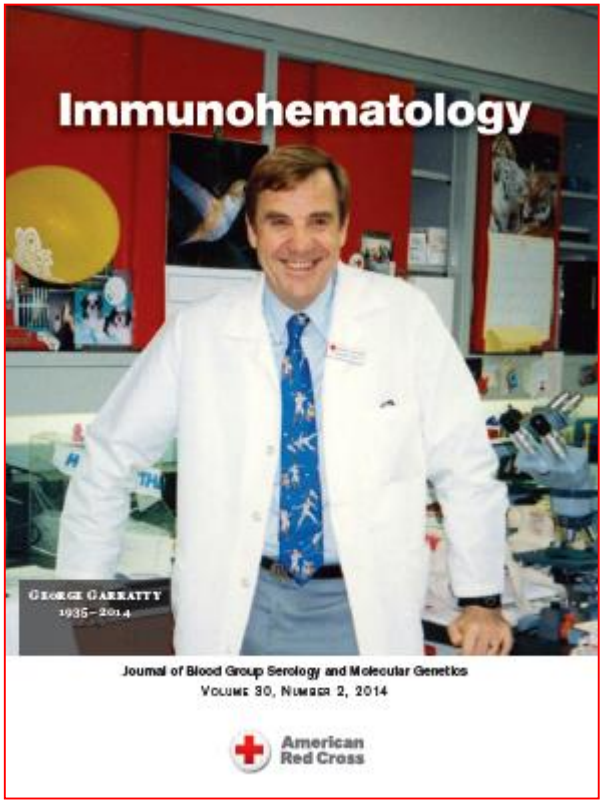
Drug-Induced Immune Hemolytic Anemia (DIIHA)

- First suspected in 1953 by Snapper et al (Ann Int Med, 619)
- First documented in 1956 by Harris (J Lab Clin Med, 760)
- By 1967, 34 published cases involving 15 drugs

DIIHA Reports by G Garratty

Number of Drugs reported to cause DIIHA or positive DAT

- 1980 – 33 drugs
- 1989 – 70 drugs
- 2003 – 100 drugs
- 2014 – 138 drugs



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DIIHA Case Documentation

Some reports are not so well documented for the drug as causative agent, often reported as:

- Hemolytic Anemia starts after starting a drug
- Hemolytic Anemia resolves after stopping drug
- Positive DAT

DIIHA Documentation

To prove that hemolytic anemia is due to drug:

- Drug required to be present in test media to demonstrate antibody reactivity
- Or, prove that hemolytic anemia was induced by drug with clinical documentation

DIIHA Documentation

- How to prove that drug must be present in order for antibody to react
  - Can be difficult to prove with testing
  - Preferred to show antibody in eluate
  - Antibody in serum supports but does not prove as drug antibodies have been detected in “normal” donors and patients

DIIHA Information

- Why would drug antibody be in serum of healthy person?
  - May be present due to past exposure
  - May be a feature of the particular drug – cells coated with cephalosporins non-specifically take up antibody
- Some drugs do not require presence of drug to react – look like autoantibody

DIIHA - How to Prove?

- Proof Positive: Clinical and Serologic evidence
  - Patient has clinical evidence of hemolysis
  - Stop the drug
  - Observe that Hemolytic Anemia stops, DAT becomes negative and no eluate reactivity
  - Start the drug
  - Observe that Hemolytic Anemia and serologic evidence is present

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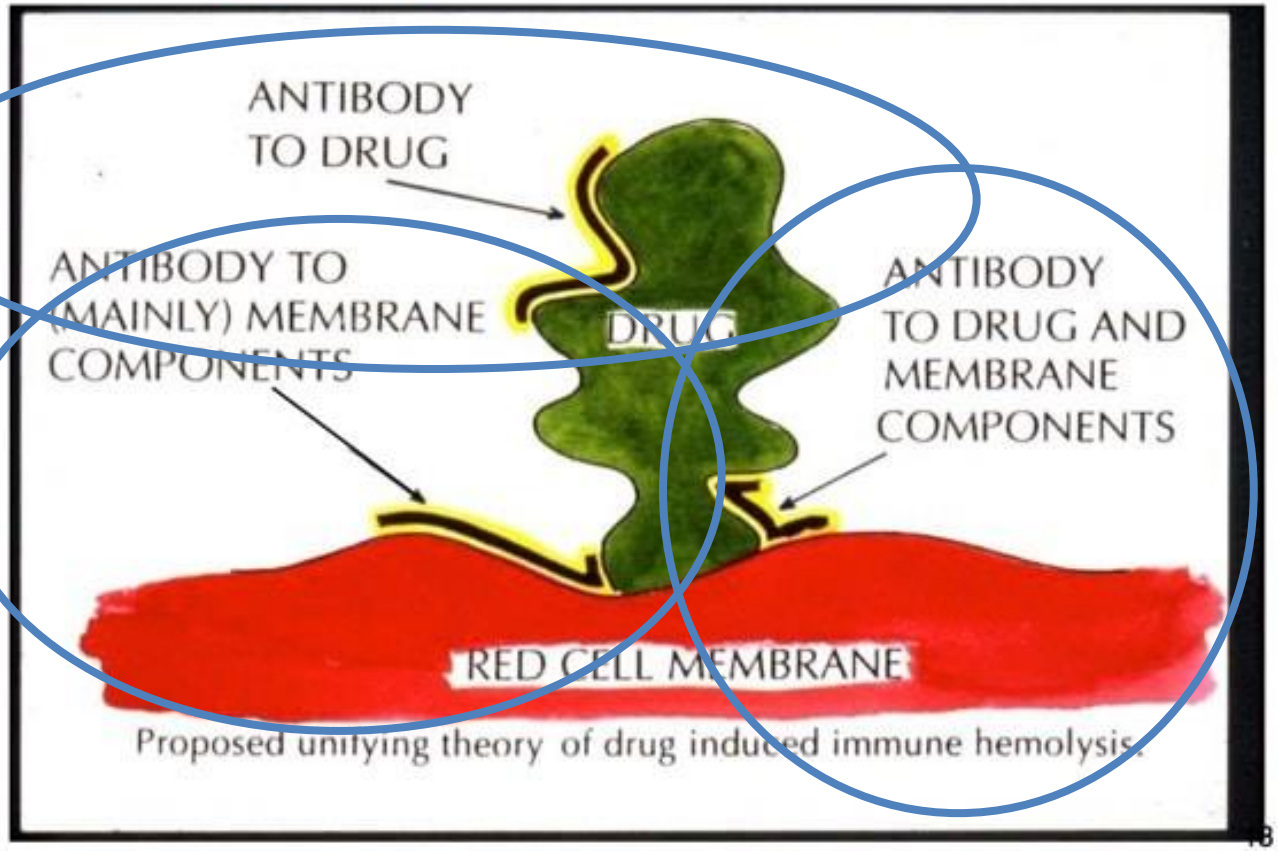
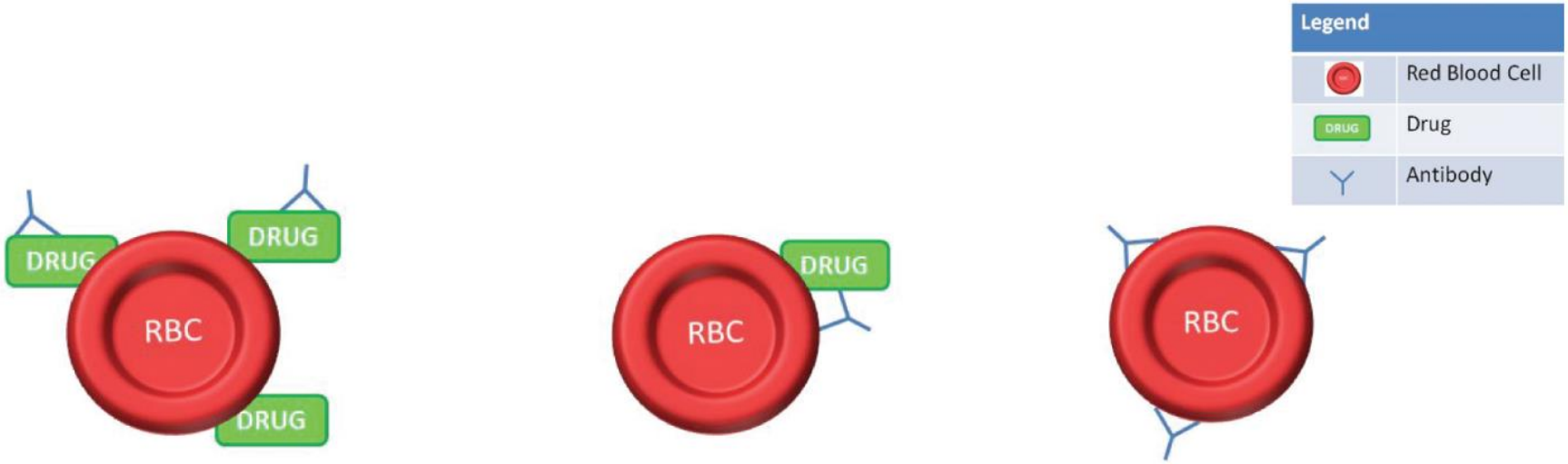
RARELY DONE ON PURPOSE - SOMETIMES DONE BY ACCIDENT

Proposed Mechanisms for Drug-dependent Antibodies



From Petz and Garratty Acquired Immune Hemolytic Anemias, Churchill Livingstone NY 1990

Another way to think about this



A. Drug-dependent Antibody
Mechanism: *drug is bound to RBC and antibody is directed against drug epitope e.g. penicillin*

B. Drug-dependent Antibody
Mechanism: *antibody is directed against neoantigen variably composed of drug and RBC membrane proteins e.g. ceftriaxone*

C. Drug-independent Antibody
Mechanism: *drug results in generation of RBC auto-antibodies e.g. methyldopa*

Cambridge University Press

American Red Cross

Technical aspects

Two ways that drug antibody investigations originate

- Clinically requested - Specific request from patient's physician suspecting DIIHA due to clinical symptoms and laboratory results
- Laboratory discovery
  - Hemolysis in serum tube
  - Positive DAT, negative eluate
  - Positive antibody screen with all cells reactive

Indications for DIIHA Testing if Laboratory Discovered

- Positive antibody screen (variable)
  - Could be positive if drug currently being administered
  - Could be negative if antibody is all on patient's RBCs
- If autocontrol tested with screen or panel, expected to be positive (or DAT positive)
- If Eluate tested – expected to be negative which is the clue that positive DAT is not due to warm AIHA

Pertinent Facts of DIIHA Samples

- Reactivity variable generally according to sensitivity of method, except for Solid Phase
  - Gel, Ficin, PEG IAT> SPRCA, Saline IAT> 37C or IS
- Reactivity wanes as time elapsed since drug administered
- Some cases reported blood group specificities
- Normal donors and patients may have drug antibodies

DIIHA Antibodies with Blood Group Specificity

Antibody Specificity	Drug Implicated
Anti-e or relative anti-e	Diclofenac, Latanoxef, Nabumetone, Piperacillin, Teniposide, Tolmetin,
Anti-C	Rifampicin
Anti-E	Nomifensine
Anti-f	Cefotetan, Sulindac
Anti-Jk^{a}	Chorpropamide
Anti-H	Sulfamethoxazole
Anti-Rh17	Sulindac

Normal Sera may have Drug Antibodies

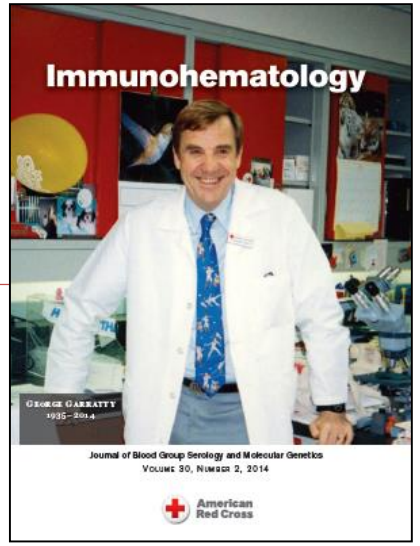


Table 5. Percentage of agglutinins reacting with drug-treated red blood cells found in our laboratory when screening blood donors' and random patients' sera*

Drug	Blood donors	Random patients
Penicillin (unpublished results)	5%	6%
Cephalothin[58]	39%	NT
Ticarcillin[68]	33%	NT
Cefotetan[59] (and unpublished results)	80%	78%
Piperacillin[72]	91%	49%
Oxaliplatin[73]	16%	4%
Cisplatin[73]	7%	NT
Meropenem[74]	93%	60%

*It is interesting to note that, for some drugs, fewer patients than donors have antibodies.

NT = not tested.

Immunohematology 2014;30:44–54.

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DIIHA – Four Categories

- Drug dependent antibodies – Penicillin type
  - Detection method – drug coated cells
- Drug dependent antibodies – non-penicillin type
  - Detection method – drug solution addition
- Nonimmunologic adsorption of proteins onto RBCs
  - Detection method – compare with normal serum, difficult to prove
- Drug independent antibodies – autoantibodies
  - Detection method – routine antibody screen, eluate

DIIHA

DRUG DEPENDENT ANTIBODIES

PENICILLIN TYPE

(DRUG COATED RBCs)

DIIHA - Drug dependent antibodies

- Penicillin type
  - Ampicillin, amoxicillin, piperacillin, ticarcillin (cross react with Penicillin)
  - Methicillin, nafcillin (do not cross react with Penicillin)
- Detection method
  - Drug coated cells
- Drugs in this category include:
  - Carbromal
  - Cefotaxime
  - Cefotetan
  - Cefoxitin
  - Cisplatin
  - Erythromicin
  - Isoniazid
  - 6-mercaptopurine
  - Penicillins
  - Streptomicin
  - Tolbutamide
  - Azopropazone
  - Carbimazole
  - Cephalothin
  - Cianidanol

DIIHA – Drug Coated Cells

- Commonly, antibodies to Penicillin can be detected with drug-coated cells
- Normal people can have antibody to penicillin
- Most patients who have penicillin antibody also have antibody to the b-lactam nucleus thus are cross reactive with semi-synthetic penicillins that have different side chains but still have the b-lactam nucleus
- Some patients have antibody to the side chains only and thus do not cross-react with other penicillins

DIIHA – Drug Coating Method

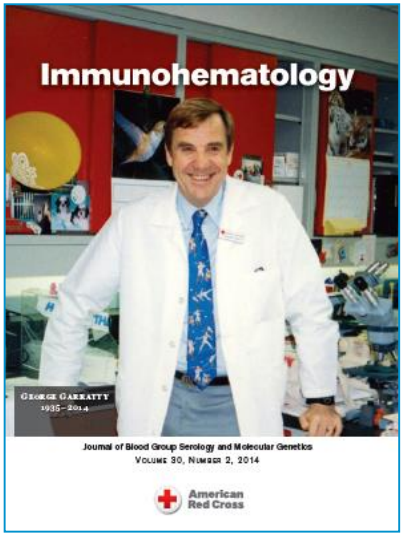
- Prepare drug coated cells using appropriate drug solution (Ag negative if needed)
- Test coated and uncoated RBCs in parallel with serum and eluate of patient, and normal inert serum.
- If normal serum is positive, dilute normal serum and patient serum 1:20 or 1:100 for cefotetan
- Test
  - 2 drops serum/eluate and 1 drop 4% RBCs
  - 37C 60 minutes
  - Wash, add AHG, read macro and micro

Table 2. Expected results when drug antibody reacts with drug-treated RBCs

Sample tested	Drug-treated RBCs: 60 min at 37°C	Drug-treated RBCs: AHG	Untreated RBCs: 60 min at 37°C	Untreated RBCs: AHG
Patient's serum	+/0	+	0	0
Patient's serum diluted 1 in 20*	+/0	+	0	0
Eluate	+/0	+	0	0
Last wash	0	0	0	0
Normal sera (pooled or 4–6 individuals)	0	0/+*	0	0
Normal sera diluted 1 in 20*	0	0	0	0
Positive control	+/0	+	0	0
PBS	0	0	0	0

*If drug causes nonimmunologic protein adsorption, normal sera will react at the antiglobulin test; a 1 in 20 dilution should not react.

AHG = antihuman globulin; PBS = phosphate-buffered saline; RBCs = red blood cells.



Immunohematology 2014;30:85–94

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DIIHA – Drug Hapten Inhibition

Prepare:

- Titer patient's serum versus drug coated RBCs
- Prepare Inhibition solution (10mg/mL)
- Prepare master dilution of patient's serum one tube past titer end-point
- Prepare 2 sets of tubes, "test" and "control"

Test set of titration tubes:

  - 0.1 mL serum dilution
  - 0.1 mL drug solution

- Control set of tubes:
  - 0.1 mL serum dilution
  - 0.1 mL PBS
- 37C, 60 minutes
- Add drug coated RBCs
- 37C, 60 minutes, read
- Wash, add AHG, Read

DIIHA – Drug Hapten Inhibition

- Interpretation
  - Serum + Drug solution same titer as PBS
    - No inhibition- antibody not inhibited by drug
  - Serum + Drug solution lower titer than PBS
    - Inhibition – proving drug antibody present
  - Serum + Drug solution higher titer than PBS
    - Drug antibody reacts preferentially by Drug Solution Addition method

DIIHA

DRUG DEPENDENT ANTIBODIES

NON-PENICILLIN TYPE
(DRUG SOLUTION ADDITION)

DIIHA - Drug Dependent Antibodies – Non Penicillin Type

- Detection method – drug solution addition
  - "Immune Complex"
- Drugs in this category include:
  - Carbimazole
  - Tolmetin
  - Cefotaxime
  - Cetazidime
  - Cianidanol
  - Carboplatin
  - Cefotetan
  - Teniposide
  - Glafenine
  - Nomifensine
  - Latamoxef
  - Diclofenac
  - Zomepirac

DIIHA Drug Solution Addition Method (also called "Immune Complex")

- Most drugs are not bound to RBCs and cannot be prepared in vitro
- Not well understood how they act in vivo to cause hemolytic anemia
- Thought to cause Hemolytic Anemia by activating complement
- Small amount of drug needed

Drug Solution Addition Type

- Acute complement-mediated hemolysis
  - Up to 50% have renal failure
- C3 is present on RBCs, but IgG and IgM can also be present
- Antibodies are often IgM, but can be IgG
- In vitro, in presence of drug, can see hemolysis, agglutination and sensitization
- Stop drug, hemolytic anemia resolves

DIIHA – Drug Solution Addition Method

Prepare Drug Solution (1mg/mL) and test tubes as follows:

Serum	Drug Solution	Fresh Complement	PBS
2 drops	2drops	-----	-----
2 drops	2 drops	2 drops	-----
2 drops	-----	2 drops	-----
2 drops	-----	-----	2 drops
-----	2 drops	2 drops	-----
-----	-----	2 drops	2 drops

DIIHA – Drug Solution Addition Method

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2 drops	-----	2 drops	-----
2 drops	-----	-----	2 drops
-----	2 drops	2 drops	-----
-----	-----	2 drops	2 drops

Test

Controls

DIIHA – Drug Solution Addition Method

- Prepare two sets of tests, one with untreated and one with enzyme treated RBCs, 6% -10% suspension
- 37C, 60 minutes incubation
- Read for hemolysis and agglutination
- Wash, add Polyspecific AHG, read

DIIHA

NONIMMUNOLOGIC ADSORPTION OF PROTEINS ONTO RBCs

DIIHA -Nonimmunologic Adsorption of Proteins onto RBCs

- Detection method:
  - Comparison to normal serum
  - Clinical/temporal relationship to hemolytic anemia
- Drugs in this category include:
  - Cephalosporins
  - Suramin
  - Diglycoaldehyde (INOX)
  - Cisplatin/Oxaliplatin
  - Tazobactam (in Zosyn)
  - Sulbactam (in Unasyn)
  - Clavulanate (Augmentin and Timetin)

DIIHA Non-immunologic Adsorption of Protein on RBCs

- Proteins adsorb to RBCs causing positive DAT
- Detected because normal plasmas react with RBCs incubated with drug, but eluates from those RBCs are negative
- AHG tests with anti-albumin standardized for use with RBCs are positive
- Different sources of AHG may or may not contain anti-albumin, thus detection may be variable

DIIHA Non-immunologic Adsorption of Protein on RBCs

- Positive DAT may be due to IgG, IgM, IgA, C3, or Albumin
- Eluate from patient's RBCs is negative with drug-coated or uncoated RBCs, even in presence of drug
- Patient's serum and normal donor serum may react with drug coated but not with untreated RBCs, Patient's serum may be stronger
- Patients may have +DAT but no hemolytic anemia

DIIHA

DRUG INDEPENDENT ANTIBODIES

DIIHA
Drug Independent Antibodies

- Autoantibodies
  - Detection method – routine antibody screen, eluate
- Drugs in this category include:
  - Methyldopa
  - Levodopa
  - Procainamide
  - Mefenamic acid
  - Fludarabine
  - Cladrabine
  - Cianidanol
  - And others reactive by this and other mechanisms

DIIHA - Drug Independent Antibodies Drug Induced Autoantibodies

- Antibodies do not require drug to be present
- Serologic and clinical features similar to idiopathic AIHA
- Methyldopa first and best studied
  - Positive DAT post therapy 3-6 mo, hemolytic anemia rarely before 18 weeks
  - No anamnestic response upon re-administration
  - Up to 15% on drug make autoantibodies
  - Less than 0.5% with positive DAT have DIIHA
  - Commonly have Rh specificity
  - If have DIIHA and removed from drug, positive DAT can persist for 2 years

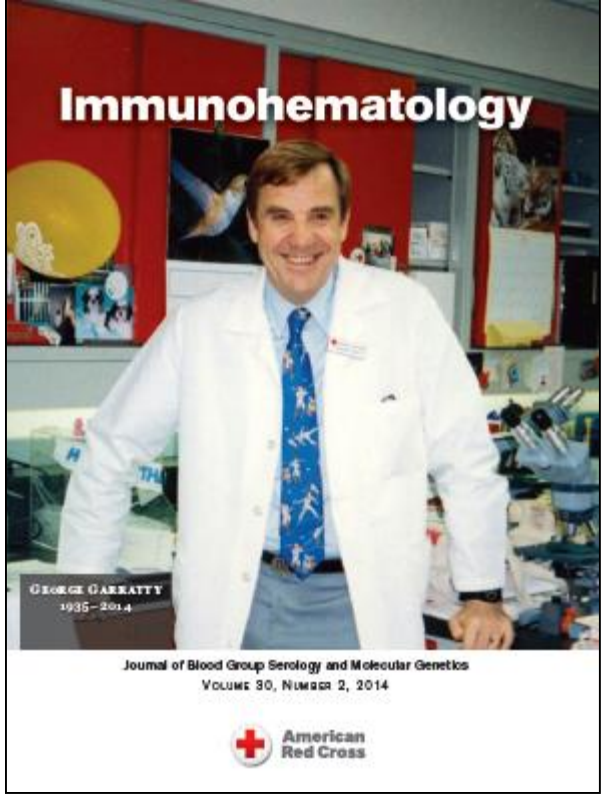
DIIHA

CEPHALOSPORINS

Table 3. Drug-induced immune hemolytic anemia caused by cephalosporins: summary of methods used and results (number positive/number tested) in references in which data on methods were given

Cephalosporin	Reference	Drug-treated RBCs	Serum + RBCs + drug	No in vitro drug
First-generation				
Cephalothin	5	5/5	1/1	0/5
Cefazolin	2	2/2	0/1	0/2
Cephalexin	1	1/1	0/0	?
Second-generation				
Cefoxitin	4	4/4	1/2	0/3
Cefamandole	1	1/1	0/0	0/1
Cefotetan	31	31/31	20/22	12/25
Cefuroxime	2	2/2	0/2	0/2
Cefotaxime	4	3/4	3/4	1/4
Third-generation				
Ceftazidime	4	2/4	3/4	0/4
Ceftriaxone	28	0/12	28/28	5/19
Ceftizoxime	4	2/4	3/4	2/4
Cefixime	1	1/1	1/1	0/1

RBCs = red blood cells.



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DIIHA - Cephalosporins

- Pharmacologic Aspects:
  - Most administered by injection
    - Plasma half life of 1-2 hours
    - Metabolites not common
  - Most orally administered are less of a risk for DIHA due to relatively lower dose

    Cephalexin, Cefadroxil, Cefaclor, Cefuroxime Axetil, Cefixime, Cephradine

DIIHA
Cephalosporins - Viraraghaven et al,

- US- FDA reviewed 85 cases of HA associated with Cefotetan
  - 5 were published
  - +DAT in 50 of 52 tested
  - Cefotetan antibodies in 30 of 30 tested
  - Renal dysfunction in 7 patients
  - 15 fatalities
  - Prev. administered Cefotetan – 15 (4 died)
  - 32 for treatment, 47 prophylaxis

Adv Drug React Toxicol Rev 2002;21:101-107

DIIHA – Cephalosporins

- Cefotetan data from multiple references (n=31)
  - 80% for surgery, one single 2 gm dose used
  - HA evident 1-13 days after drug administered
  - Nadir Hb S/P drug – mean 4.8 g/dL
  - Fatal HA 19%
  - Renal Failure 19%
  - All had Cefotetan Ab vs drug coated RBCs (median titer 512, normal less than 20)
  - 30/31 positive with drug solution added
  - 40% reacted with RBCs without drug present

Petz and Garratty, Immune Hemolytic Anemias, p 296

Summary – Investigation of DIHA

- DIIHA is rare
- If have positive DAT and negative eluate, more common to have anti-A or anti-B coating the RBCs
- 80% of all positive DATs yield negative eluates
- Investigate when evidence of Hemolytic Anemia and treatment with a drug in same time frame
- If drug never reported, use both serum and eluate and test with Drug coated and Drug solution method

Drugs Implicated in DIIHA

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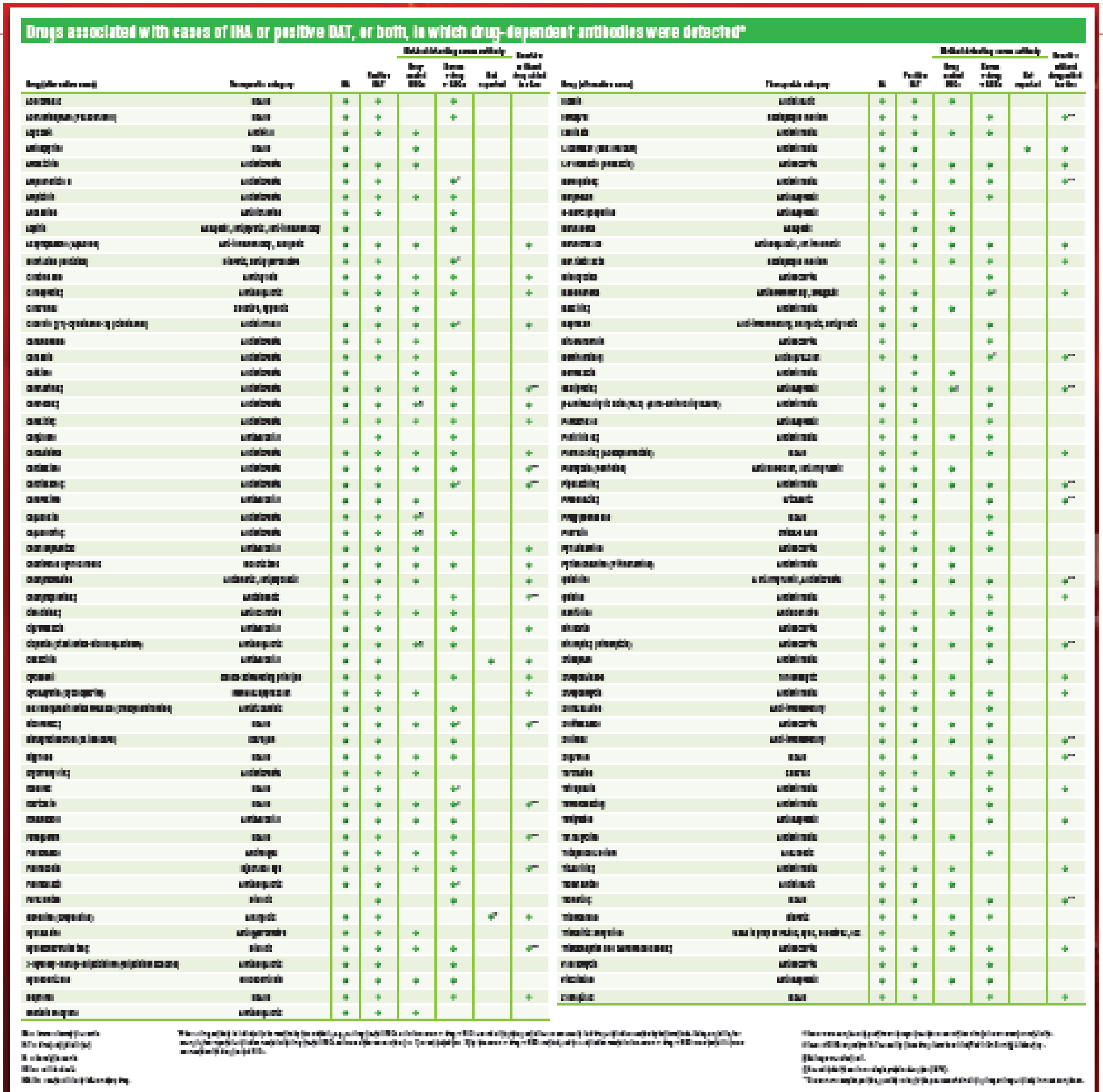
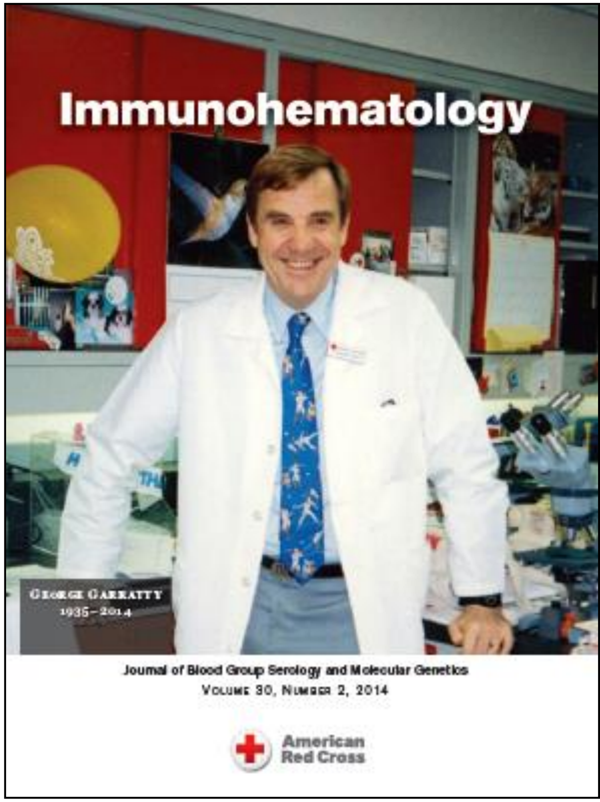

Drugs associated with cases of IHA or positive DAT, or both, in which drug-dependent antibodies were detected*



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Drug (alternative name)	Therapeutic category	HA	Positive DAT	Method detecting serum antibody: Drug-coated RBCs	Method detecting serum antibody: Serum + drug + RBCs	Method detecting serum antibody: Not reported	Reactive without drug added in vitro
Aceclofenac	NSAID	●	●		●		
Acetaminophen (Paracetamol)	NSAID	●	●		●		
Acyclovir	Antiviral	●	●	●			
Aminopyrine	NSAID	●		●			
Amoxicillin	Antimicrobial	●	●	●			
Amphotericin B	Antimicrobial	●	●		●†		
Ampicillin	Antimicrobial	●	●	●	●		
Antazoline	Antihistamine	●	●		●		
Aspirin	Analgesic, antipyretic, anti-inflammatory	●			●		
Azapropazone (Apazone)	Anti-inflammatory, analgesic	●	●	●			●
Buthiazide (Butizide)	Diuretic, antihypertensive	●	●		●†		
Carbimazole	Antithyroid	●	●	●	●		●
Carboplatin‡	Antineoplastic	●	●	●	●		●
Carbromal	Sedative, hypnotic		●	●			
Catechin [(+)-Cyanidanol-3] (Cianidanol)	Antidiarrheal	●	●	●	●†		●
Cefamandole	Antimicrobial	●	●	●			
Cefazolin	Antimicrobial	●	●	●			
Cefixime	Antimicrobial	●		●	●		
Cefotaxime‡	Antimicrobial	●	●	●	●		●**

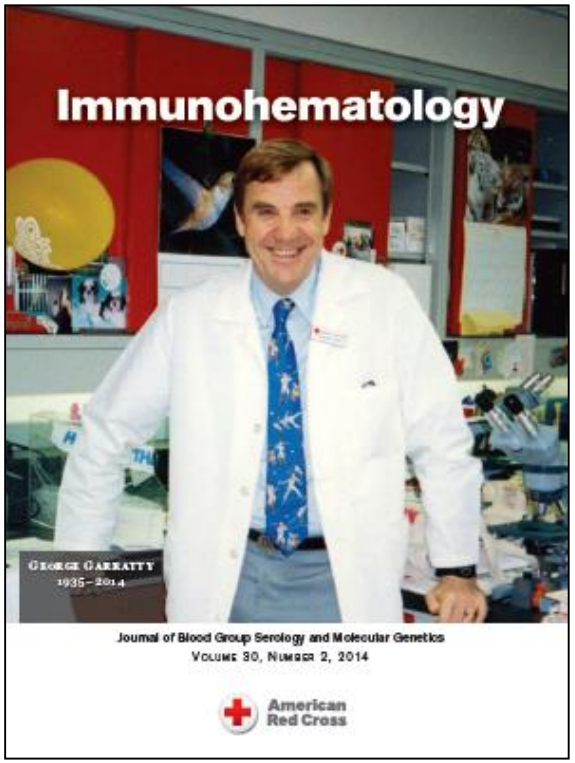
Drug (alternative name)	Therapeutic category	HA	Positive DAT	Method detecting serum antibody: Drug-coated RBCs	Method detecting serum antibody: Serum + drug + RBCs	Method detecting serum antibody: Not reported	Reactive without drug added in vitro
Cefotetan‡	Antimicrobial	●	●	●¶	●		●
Cefoxitin‡	Antimicrobial	●	●	●	●		●
Cefpirome	Antibacterial		●		●		
Ceftazidime	Antimicrobial	●	●	●	●		●
Ceftizoxime	Antimicrobial	●	●	●	●		●**
Ceftriaxone‡	Antimicrobial	●	●		●†		●**
Cefuroxime	Antibacterial	●	●	●			
Cephalexin	Antimicrobial	●	●	●¶			
Cephalothin‡	Antimicrobial	●	●	●¶	●		
Chloramphenicol	Antibacterial	●	●	●			●
Chlorinated hydrocarbons	Insecticides	●	●	●	●		●
Chlorpromazine	Antiemetic, antipsychotic	●	●	●			●
Chlorpropamide‡	Antidiabetic	●	●		●		●**
Cimetidine‡	Antiulcerative	●	●	●	●		
Ciprofloxacin	Antibacterial	●	●		●		●
Cisplatin (Cisdiamino-dichloroplatinum)	Antineoplastic	●	●	●¶	●		
Cloxacillin	Antibacterial	●	●			●	●
Cyclofenil	Gonad-stimulating principle	●	●		●		●
Cyclosporin (Cyclosporine)	Immunosuppressant	●	●	●			●

Drug (alternative name)	Therapeutic category	HA	Positive DAT	Method detecting serum antibody: Drug-coated RBCs	Method detecting serum antibody: Serum + drug + RBCs	Method detecting serum antibody: Not reported	Reactive without drug added in vitro
Dexchlorpheniramine maleate (Chlorpheniramine)	Antihistaminic	●	●		●		
Diclofenac‡	NSAID	●	●	●	●†		●**
Diethylstilbestrol (Stilboestrol)	Estrogen	●	●		●		
Dipyrone	NSAID	●	●	●	●		
Erythromycin‡	Antimicrobial	●	●	●			
Etodolac	NSAID	●	●		●†		
Etoricoxib	NSAID	●	●	●	●†		●**
Ethambutol	Antibacterial	●	●	●	●		
Fenoprofen	NSAID	●	●		●		●**
Fluconazole	Antifungal	●	●	●	●		
Fluorescein	Injectable dye	●	●	●	●		●**
Fluorouracil	Antineoplastic	●	●		●†		
Furosemide	Diuretic		●		●		
Glafenine (Glaphenine)	Analgesic	●	●			●?	●
Hydralazine	Antihypertensive	●	●	●			
Hydrochlorothiazide‡	Diuretic	●	●	●	●		●**
9-Hydroxy-methyl-ellipticinium (elliptinium acetate)	Antineoplastic	●	●		●		
Hydrocortisone	Glucocorticoid	●	●	●	●		
Ibuprofen	NSAID	●	●		●		●
Imatinib mesylate	Antineoplastic	●	●	●			

Drugs associated with cases of IHA or positive DAT or both in which only drug-independent antibodies (autoantibodies) were detected

Drug (alternative name)	Therapeutic category	HA	Positive DAT	More evidence needed
Alemtuzumab	Antineoplastic; immunosuppressant	●	●	●
Bendamustine	Antineoplastic	●	●	●
Captopril	Antihypertensive	●	●	●
Chaparral	Herbal		●	●
Cimetidine	Antiulcerative	●	●	●
Cladribine (2-chloro-deoxyadenosine)	Antineoplastic	●	●	
Fenfluramine	Anorexic	●	●	●
Fludarabine*	Antineoplastic	●	●	
Interferon	Antineoplastic, antiviral	●	●	●
Interleukin-2	Antineoplastic	●	●	●
Ketoconazole	Antifungal	●	●	●
Lenalidomide	Immunomodulatory	●	●	●
Levodopa (L-dopa)	Antiparkinsonian	●	●	
Mefenamic acid	NSAID	●	●	
Mesantoin (Mephenytoin)	Anticonvulsant	●	●	●
Methyldopa*	Antihypertensive	●	●	
Nalidixic acid	Antibacterial	●	●	●
Procainamide*	Antiarrhythmic	●	●	●
Rituximab	Antineoplastic	●	●	●
Tacrolimus	Immunosuppressant	●	●	●
Weidean	Chinese herbs	●	●	●

IHA = immune hemolytic anemia; DAT = direct antiglobulin test; HA = hemolytic anemia; NSAID = nonsteroidal anti-inflammatory drug.
*Cases of drug-induced immune hemolytic anemia or positive DAT caused by these drugs have been identified in Dr. Garratty's laboratory.



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Drugs associated with the detection of nonimmunologic protein adsorption onto RBCs

Drug (alternative name)	Therapeutic category	HA	Positive DAT	Drug-dependent antibody(ies) also detected
Cefotetan*	Antimicrobial	●	●	●
Cephaloridine	Antimicrobial		●	
Cephalothin*	Antimicrobial	●	●	●
Cisplatin	Antineoplastic	●	●	●
Clavulanate potassium* (Clavulanic acid)	ß-Lactamase inhibitor		●	
Diglycoaldehyde (INOX)	Antineoplastic		●	
Oxaliplatin*	Antineoplastic	●	●	●
Sulbactam*	ß-Lactamase inhibitor	●	●	
Suramin	Antihelminthic, antiprotozoal			
Tazobactam*	ß-Lactamase inhibitor	●	●	

RBCs = red blood cells; HA = hemolytic anemia; DAT = direct antiglobulin test; IHA = immune hemolytic anemia.

*Cases of drug-induced immune hemolytic anemia or positive DAT caused by these drugs have been identified in Dr. Garratty's laboratory.

Data on Drug Antibodies Dr Garratty's Laboratory

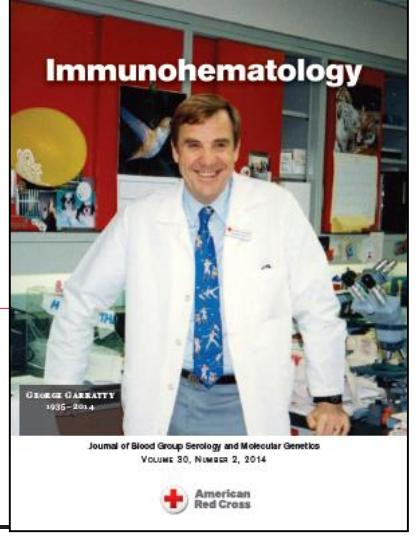

Table 4. Drug antibodies detected by the Research Lab at the American Red Cross in Pomona, CA, from 1978 to 2013

Years	Ceftriaxone	Cefotetan	Piperacillin	Platinum-based drugs	Other drugs
1978–83	0	0	0	0	7
1984–89	2	0	0	0	4
1990–95	2	20	0	0	7
1996–2001	6	45	2	0	6
2002–07	7	15	6	3	7
2008–13	14	13	30	5	6
Total	**31**	**93**	**38**	**8**	**37**

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American Red Cross

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Muchas Gracias

Sandra.Nance@redcross.org