



Clinical Pharmacology & Toxicology Pearl of the Week

~ Drug-induced Lupus ~

- ✓ **Definition:** Drug induced lupus occurs in individuals after exposure to the causative drug for a few weeks to more than a year. It most commonly occurs in older patients (> 50 years), Caucasians, and equally in males and females.
- ✓ **Pathophysiology:**
 - Genetics – slow acetylator status; certain HLA subtypes (HLA-DR4, HLA-DR0301 and Complement C4 null allele)
 - Epigenetics – procainamide and hydralazine can decrease T cell DNA methylation leading to over-expression of LFA-1 causing immune dysregulation.
 - Biotransformation – procainamide and hydralazine can serve as substrate for methyl peroxidase in activated neutrophils. The reactive metabolite, procainamide hydroxylamine can affect the immune system.
 - Drugs may also function as haptens or agonists for drug specific T cells.
- ✓ **Manifestations (typically come on abruptly):**
 - Fever and/or other constitutional symptoms (50%)
 - Arthritis and arthralgias (80-95%)
 - Myalgias
 - Serositis (50% with procainamide, 25% with quinidine)
 - Hepatomegaly (5-25%)
 - Erythematous papular rashes (20%) (most commonly occurring with hydralazine)
 - Discoid lesions or malar erythema (2%)
 - Pulmonary infiltrate (especially with procainamide)
 - Severe manifestations of SLE, such as cytopenia, nephritis, and CNS involvement are exceedingly rare in drug induced lupus, as is the presence of dsDNA and hypocomplementemia.

Drug-induced Lupus versus SLE

@Lupusreference

		SLE	Drug-induced lupus (DIL)
Epidemiology	Prevalence Age F:M sex-ratio	10-180/100 000 Typically 20-40 9:1	≈10% of all lupus cases drug-dependent 4:1 to 1:1
Clinical manifestations		Malar rash Photosensitivity Alopecia, oral ulcers Lupus nephritis NPSLE	Constitutional symptoms Arthritis, myalgia, serositis Kidney & NPSLE rare Malar rash is rare in DIL SCLE-DIL (terbinafine, thiazidic, PPI, ACE, calcium-b)
Laboratory Manifestations	CRP Cytopenia	Usually normal (except with serositis) Common	Usually normal (except with serositis) Less common (drug-dependent)
Immunological workup	ANA Anti-ENA Anti-dsDNA Anti-histone Low complement pANCA anti-MPO	>95% Positive in up to 30% Positive in 60-80% of cases Positive in 60-80% 50-60% Negative	>95% (IgG anti-chromatin) Rare (SSA+ for cutaneous DIL), anti-Sm rare Rarely positive (common with anti-TNF) Positive in >90% Rare (<5%) Seen with PTU (50%) and minocycline (65-100%)
Prognosis		Minor to life-threatening	Usually mild forms with constitutional symptoms
Treatment		Usual therapeutic management of SLE	Discontinuation of causal drug +++ Hydroxychloroquine csDMARDs and/or bDMARDs (rare) Topics for cutaneous-DIL
Evolution		Chronic disease	Disappearance of manifestations (weeks to months) and of autoantibodies (months to years)

✓ Autoantibodies most commonly seen in Drug induced lupus

- ANA - virtually all patients have positive ANA.
- **Anti-histone antibodies** - Most patients (95%) with symptomatic drug induced disease due to procainamide, hydralazine, chlorpromazine, and quinidine demonstrate elevated levels of IgG Anti-histone antibodies.
- dsDNA is rarely found in drug induced lupus.
- Antibodies to Sm, RNP, Ro/SS-A, LA/SS-B are common in idiopathic SLE but are unusual or unlikely to persist in drug induced lupus.
- APLA: can be seen in both DIL and idiopathic SLE.

✓ Top 10 drugs associated with Drug-Induced Lupus

- Procainamide
- Hydralazine
- Quinidine
- D-Penicillamine
- Isoniazid
- Methyldopa
- Chlorpromazine
- Minocycline (5/10,000 patients)
- Anti-TNF Agents (2/1000 patients)
- Terbinafine

✓ **List of other drugs implicated in drug induced lupus**

✓ Definite	✓ Probable	✓ Possible
<ul style="list-style-type: none"> ✓ Procainamide ✓ Hydralazine ✓ Penicillamine ✓ Quinidine ✓ Isoniazid ✓ Minocycline ✓ Diltiazem (subacute cutaneous lupus) ✓ Anti-TNF agents ✓ Interferon-alpha ✓ Methyldopa ✓ Chlorpromazine ✓ Practolol 	<ul style="list-style-type: none"> ✓ Anti-convulsant agents (mephenytoin, phenytoin, carbamazepine, others) ✓ Propylthiouracil ✓ B- adrenergic blocking agents ✓ Sulfasalazine ✓ Anti-microbials (sulfonamides, nitrofurantoin) ✓ Lithium ✓ Captopril ✓ Docetaxel ✓ Hydrochlorothiazide ✓ Glyburide ✓ Amiodarone 	<ul style="list-style-type: none"> ✓ Statins ✓ Valproate ✓ Gemfibrozil ✓ Griseofulvin

✓ **Treatment of Drug induced Lupus**

- Discontinue the offending agent! The disease typically resolves after the drug has been discontinued within a few weeks of medication discontinuation.
- NSAIDs will help control the symptoms of arthralgias.
- Patients with severe symptoms, such as pericarditis or pleuritis, often require a short course of corticosteroids to control their disease.
- In more prolonged cases, anti-malarials (hydroxychloroquine) can be used.
- Further immunosuppression with azathioprine and cyclophosphamide is almost never required.

References:

Solhjo M, Goyal A, Chauhan K. Drug-Induced Lupus Erythematosus. [Updated 2023 Apr 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441889/>

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The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).