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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

from bedside to the bench…

Adverse Drug Reaction (ADR)

Any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy

World Health Organization. 1966.

Adverse Drug Reaction (ADR)

- ADR is **frequent**
  - 0.1 – 1 % pre-marketing trials
  - 2 – 6 % hospitalized patients
- Severe ADRs lead to **substantial morbidity, hospitalization** and even **death**

**** As the largest organ in the body, skin is the commonest target for ADRs***

Dermatology Consultations in a Tertiary Hospital (QMH)

Diagnosis	No. of patients (N)	Percentage (%)
1. Eczema	311	18.9
2. Drug eruption	**220**	**13.4**
3. Fungal infection	114	6.9
4. Bacterial infection	110	6.7
5. Viral infection	107	6.5
6. Scabies infestation	103	6.3
7. Contact dermatitis	96	5.8
8. Psoriasis	65	4.0
9. Blistering eruption	61	3.7
10. Vasculitis	50	3.0

Yeung *et al*. 2008

Adverse Drug Reactions

- Patterns of drug eruption are **heterogenous**

Severe Cutaneous Adverse Reactions (SCARs)

1. Stevens Johnson Syndrome / Toxic Epidermal Necrolysis (SJS / TEN)
2. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
3. Acute Generalized Exanthematous Pustulosis (AGEP)

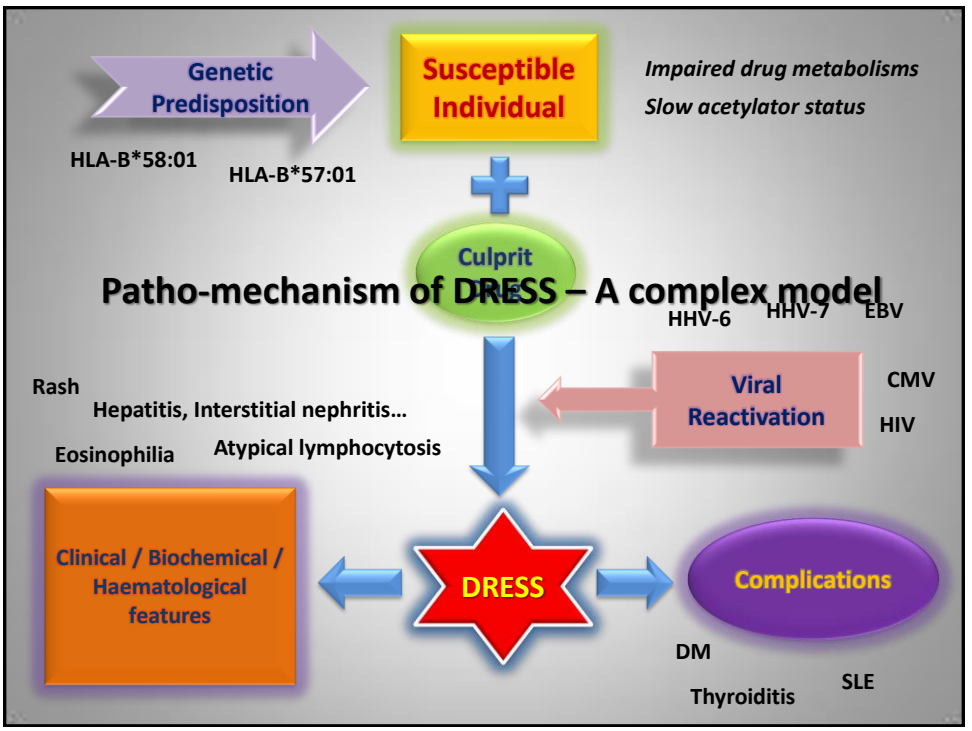
Drug **R**eaction with **E**osinophilia and **S**ystemic **S**ymptoms **(DRESS)**

- Synonym: **Drug-Induced Hypersensitivity Syndrome**
- **Acute, distinct, idiosyncratic drug-induced hypersensitivity reaction**
- **Clinical Significance**
  - *Mortality (10 – 20%)*
    - Fulminant hepatitis; Myocarditis
  - *Long term autoimmune complications*
    - Thyroiditis, DM, SLE

Eshki M *et al.* Arch Dermatol. 2009;145(1):67-72.
Peyriere H *et al*. Br J Dermatol 2006; 155: 422–8.
Proudfoot LE *et al*. Br J Dermatol 2009; 161:5.

The Unique DRESS syndrome

- ***Delayed onset*** (2 – 6 wks after initiation)
- *Triad of (1)* ***rash****; (2)* ***fever****; (3)* ***visceral insult***
- ***Diversified*** *cutaneous manifestations*
- ***Internal organs*** *involvement*
- ***Persistence, aggravation, relapse*** *of symptoms*

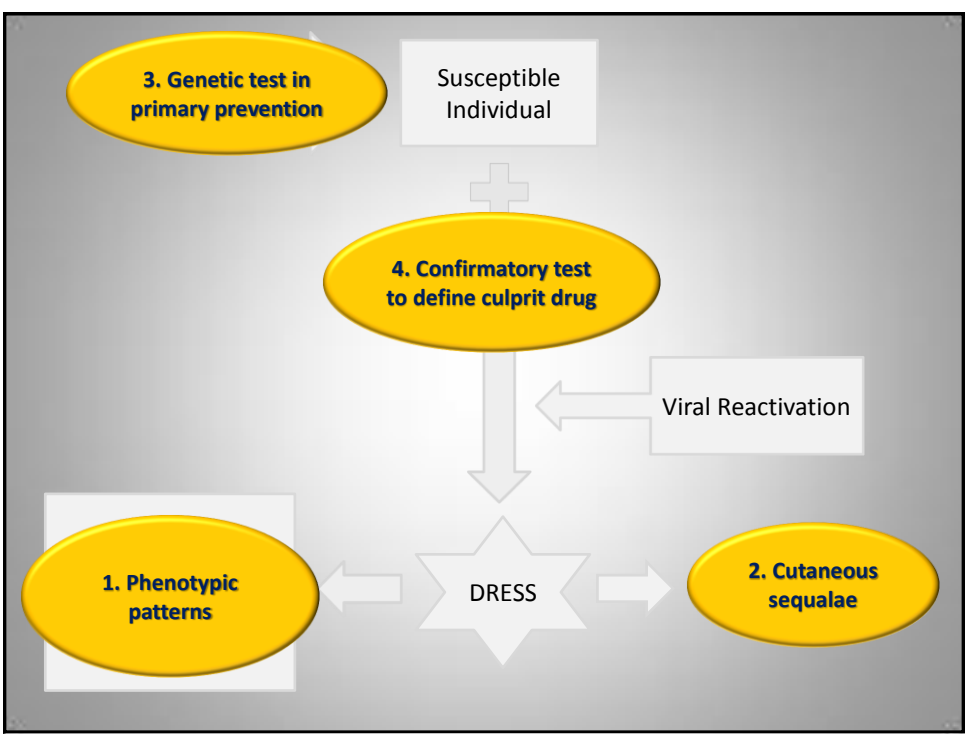


DRESS - Research Hurdles

- **Uncommon** (Incidence: 1 / 10000)
- **Under-diagnosis**
  - Lack of awareness
  - Under-developed hospital-based dermatology

**** Knowledge derived from case reports / series***

DRESS - Knowledge gap



Single-centered, Five-year Retrospective Review of DRESS in Chinese patients

I. Clinical, biochemical, histopathological and pharmaco-genetic characteristics
II. Treatment, outcome and complications

Method

- Retrospective study
- 60-month period (2007 – 2011)
- Pts dx with DRESS (fulfill RegiSCAR criteria)

Single-centered, Five-year Retrospective Review of DRESS in Chinese patients

Outcomes

- Demographics
- Culprit agents
- Clinical / laboratory / histopathological features
- Serological tests for HLA-B*58:01(allopurinol)
- Treatment and prognosis

Inclusion criteria (RegiSCAR)

Criteria must be fulfilled

- Hospitalization
- Reaction suspected to be drug-related
- Acute rash

Three of the following four criteria are required for diagnosis

- Fever > 38 oC
- Enlarged lymph nodes at a minimum of two sites
- Involvement of at least one internal organ
- Blood count abnormalities; defined either by:
  - Lymphocytes above or below normal limits; or
  - Eosinophils above the laboratory limits; or
  - Platelets below the laboratory limits.

Kardaun SH *et al.*Br J Dermatol 2007;156:609–611.

Single-centered, Five-year Retrospective Review of DRESS in Chinese patients

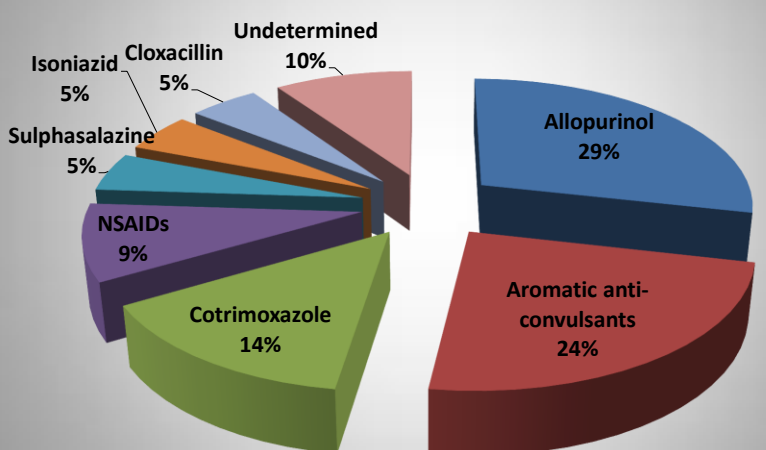
I. **Clinical, biochemical, histopathological & pharmaco-genetic characteristics**

II. Treatment, outcome and complications

Demographics

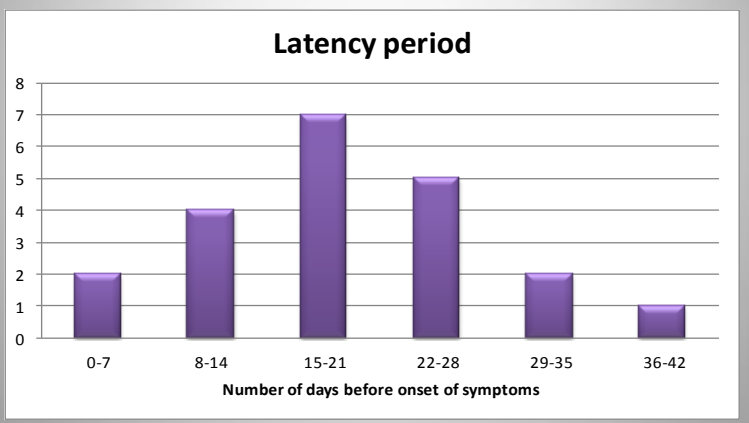
- 21 patients
- F = M (1.1 : 1)
- Mean age: 49.9 yrs (14 – 77 yrs)
- **Major comorbidities**
  - Gout (29%; n = 6)
  - Hypertension (29%; n = 6)
  - Hyperlipidemia (29%; n = 6)
  - Brain tumors (19%; n = 4)
  - Chronic kidney diseases (19%;n = 4)

Culprit agents

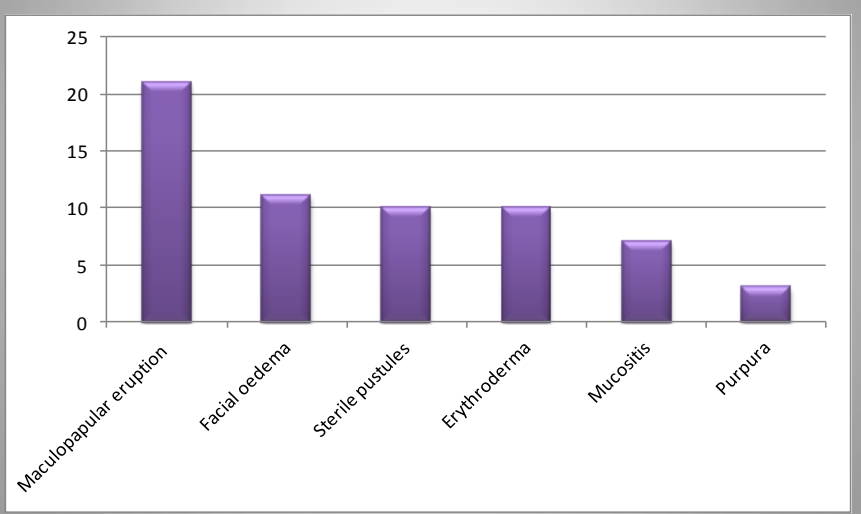


Latency period

- Mean: **21.6 days** (S.D. 9.5; 4 – 42 days)

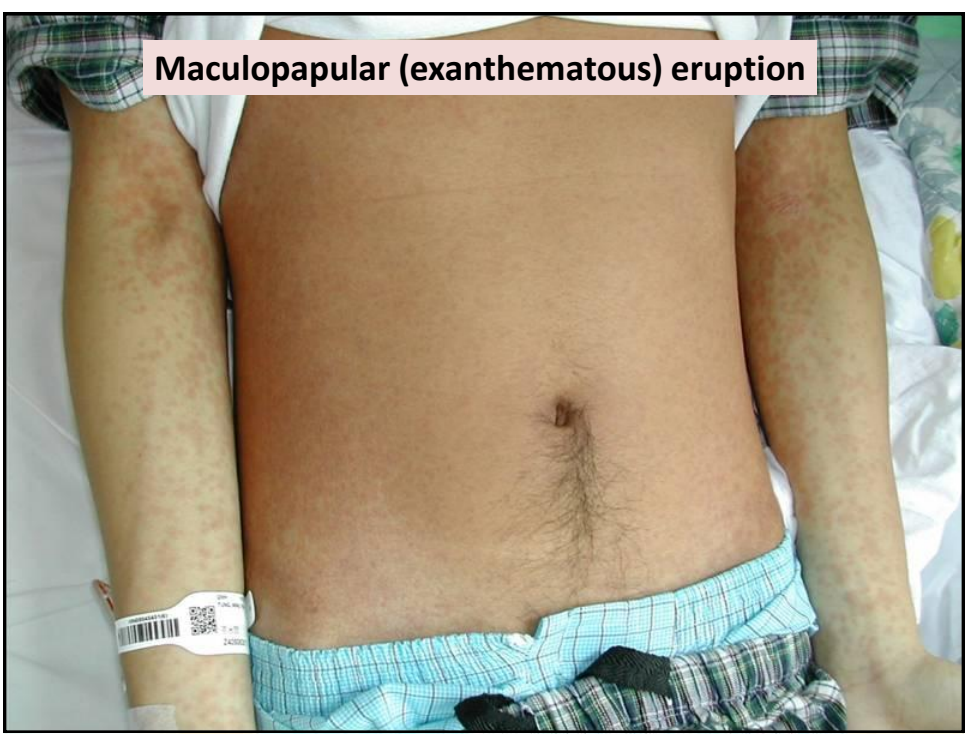


Cutaneous Manifestations

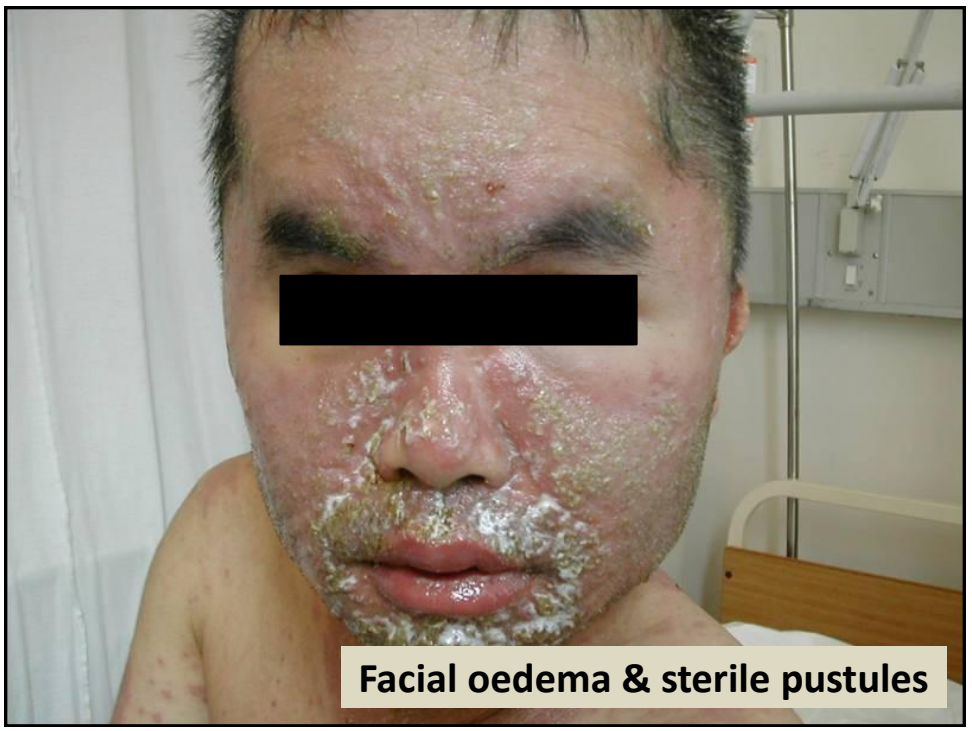


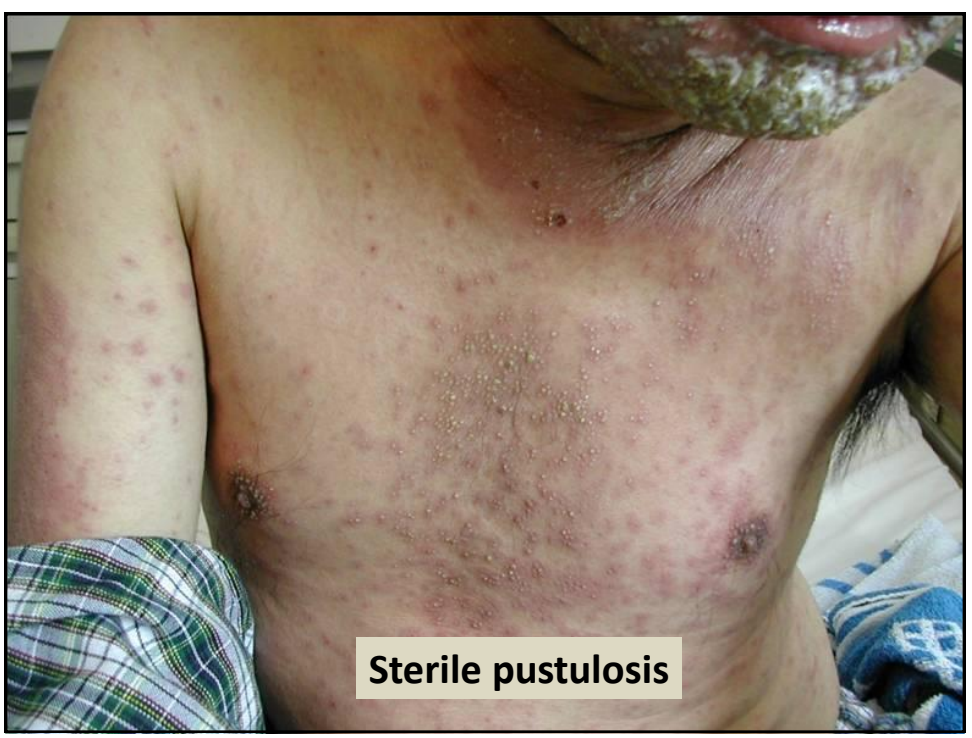
Cutaneous Manifestations

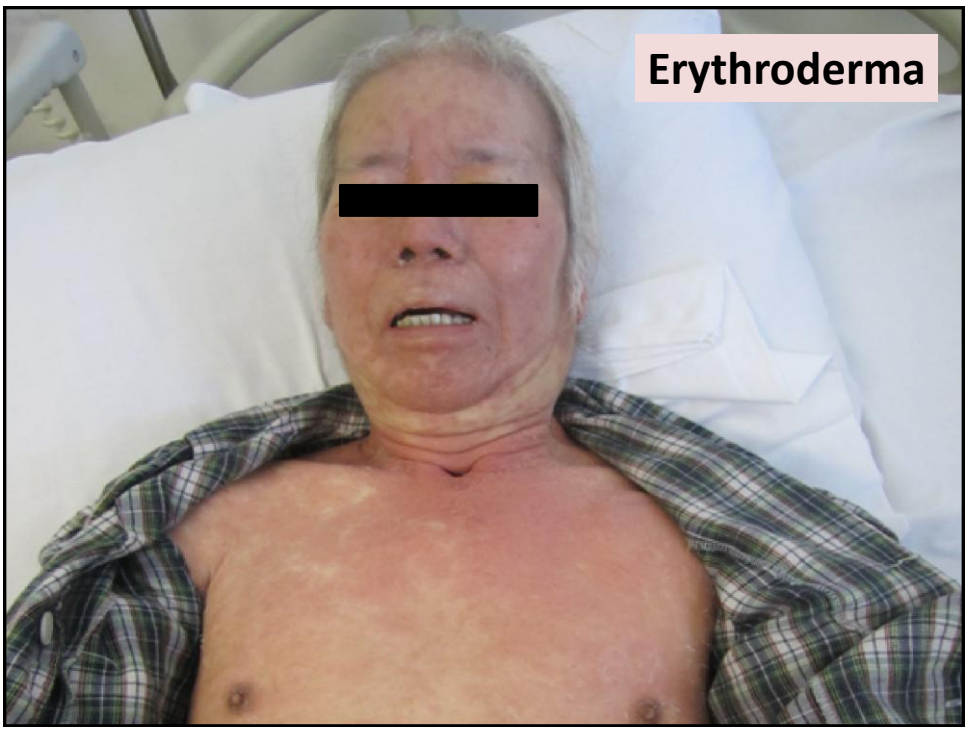
- Patients might have **> 1 skin findings**
- **Maculopapular** (**exanthematous**) eruption is the commonest finding (100%)
- Other common patterns:
  - **Facial oedema** (52%; n = 11)
  - **Sterile pustulosis** (48%; n = 10)
  - **Erythroderma** (48%; n = 10)



Maculopapular (exanthematous) eruption


Facial oedema & sterile pustules


Sterile pustulosis



Internal organs involvement

1. Liver

- ***Most frequently affected*** (100%)
- Pattern: ***Raised parenchymal enzymes*** (91%; n = 19)
  Raised ductal enzymes (57%; n = 12)
  Cholestatsis (38%; n = 8)
- Peak levels observed at median of ***4d after admission*** (3–20d)
- Pts with raised parenchymal enzymes (n=19):
  - 68% (n=13) had ***mild hepatitis*** (peak ALT $\leqq$ 500 U/L)
  - 21% (n=4) had severe hepatitis (peak ALT $\geqq$ 1000 U/L)

Internal organs involvement

2. Kidney

- 7 pts (33%)
- Defined by (i) ***elevated serum creatinine*** levels (n=7); or (ii) ***abnormal urinalysis*** (n=1)

- Pts with ***pre-existing renal insufficiency*** appeared more prone to develop further renal impairment during the course of DRESS syndrome, as compared to those with normal baseline renal functions (75% [3 of 4] versus 24% [4 of 17]) (P=0.09)

Internal organs involvement

3. Other visceral insults

- Myositis (n = 3)
- Pneumonitis (n = 2)
- Pancreatitis (n = 1)

Haematological abnormalities

- **Eosinophilia** (100%)
  - Eos: 0.56 - 22.4 x 10^9/L
- **Atypical lymphocytosis** (67%; n = 14)
- Lymphocytosis (52%; n = 11)
- Thrombocytopenia (24%; n = 5)
- Leucopenia (5%; n = 1)
- Pancytopenia (5%; n = 1)

Histopathological features

- Skin biopsies in 11 pts
- **Histological patterns**

1. ***Lichenoid dermatitis*** **(**91%; n=10)
   - Basal vacuolar degeneration
   - Subepidermal blister
   - Melanin incontinence
2. ***Presence of dermal eosinophils*** **(**82%; n=9)
3. ***Presence of cytoid bodies*** **(**73%; n=8)
4. Superficial perivascular mononuclear infiltrate **(**55%; n=6)

*Are there **phenotypical patterns** in such **highly heterogenous** syndrome?*

Allopurinol-induced DRESS

1. **Longer latency period** (days)
   - Mean 27.2 ± 9.1 vs 19.3 ± 9.0 (p=0.01)
2. **Higher rate of renal involvement**
   - 83% [5 of 6] vs 13% [2 of 15] (P<0.01)
   - Multi-variate analysis
     - OR: 23.1 (95% CI: 1.5 – 356.2) (P=0.02)
3. **Commonest culprit agent**
   - High prevalence in Han-Chinese population

Allopurinol – Pharmaco-genetic basis

- **Genetic predisposition** in Han-Chinese
  - Higher ***carrier rate*** of HLA-B*58:01 alleles
  - Higher ***odds ratio*** in developing SCARs in carries

Hung *et al*. Proc Natl Acad Sci U S A 2005;102:4134–9.

* ***In the present study, all 6 pts (100%) with allopurinol-induced DRESS were tested +ve for carrying the HLA-B*58:01 allele***

Prevalence and odds ratio of HLA-B*58:01 carriers in different populations

Population	Prevalence of HLA-B*58:01	OR of allopurinol-induced SCARs in carries
Han-Chinese	**20%**	**580**
European	0.8-6%	80
Japanese	<1%	40
Thai	8.1%	348

dbMHC Database.
Aihara *et al*. J Dermatol. 2011 ;38(3):246-54.
Kaniwa *et al*. Pharmacogenomics 2008; 9:1617–1622.
Hung *et al*. Proc Natl Acad Sci U S A 2005;102:4134–9.

CLINICAL AND LABORATORY INVESTIGATIONS

BJD
British Journal of Dermatology

Association between *HLA-B*58:01* allele and severe cutaneous adverse reactions with allopurinol in Han Chinese in Hong Kong

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- **Case-control study**
- 50 subjects tested (HLA-B*58:01)
  - 20 cases with allopurinol-induced SCARs
  - 30 controls tolerant to allopurinol
- **OR: 124**, 95% CI: 12.8 – 1195.1 **(P < 0.01)**
- **Sensitivity: 100%; Specificity: 86.7%**

*Is there a role of **Genetic screening** in prevention of **DRESS?***

Prospective Study of HLA-B*58:01 Screening to reduce Allopurinol-induced SCARs in Patients with Chronic Kidney Disease (CKD)

1. Background

- Allopurinol: Tx of gouty arthritis & complicated hyperuricaemia, often present in pts with CKD
- To date, no effective test to predict & prevent occurrence of allopurinol-induced SCARs
- Genetic screening before starting Abacavir has proven effective in reducing the risk of hypersensitivity reaction

Jung *et al*. Nephrol Dial Transplant. 2011 Mar 10.
Hughes *et al*. Pharmacogenetics. 2004;14:335-42.

Prospective Study of HLA-B*58:01 Screening to reduce Allopurinol-induced SCARs in Patients with Chronic Kidney Disease (CKD)

2. Objectives

- ***Primary*** To determine whether use of HLA-B*58:01 screening can prevent allopurinol-induced SCARs by prospectively identifying subjects at genetic risk
- ***Secondary*** To confirm the association between HLA-B*58:01 allele and allopurinol-induced SCARs in Chinese patients with CKD

3. Study design

- 3-year prospective study
- Subject inclusion
  - Han-Chinese
  - Pts with CKD (QMH, TWH renal clinics)
  - Planned to start allopurinol
- Eligible pts undergo test for HLA-B*58:01

Prospective HLA-B*58:01 Screening

- HLA-B*58:01 carriers: Not for allopurinol
- Historical controls collected from CMS
- Compare the incidence of allopurinol-induced SCARs prior and after prospective screening

**** Provide evidence to justify implementation of genetic screening programme***

Prospective Study of HLA-B*58:01 Screening to reduce Allopurinol-induced SCARs in Patients with Chronic Kidney Disease (CKD)

Progress

- 80 pts participated
- 16.3% (n=13) HLA-B*58:01 carrier

DRESS - Management

- **Early recognition, prompt withdrawal** of culprit
- **Hospitalization** is recommended
  - close monitoring of vital signs
  - Investigate organ dysfunctions
- **Supportive care alone** may suffice in **mild cases**
- Regular blood biochemistry monitoring
- Appropriate tests to exclude the uncommon involvement of pancreas, lungs, heart and muscles, if clinically indicated

Culprit agents

- **Drug history** & **temporal relationship**
- Newly introduced drug, administered within **three months** before the onset of symptoms
- Criteria by **Naranjo *et al.*** to determine the causality for suspected reactions
- Associations with the suspected medications were defined as definite, probable, possible, unlikely and undetermined.

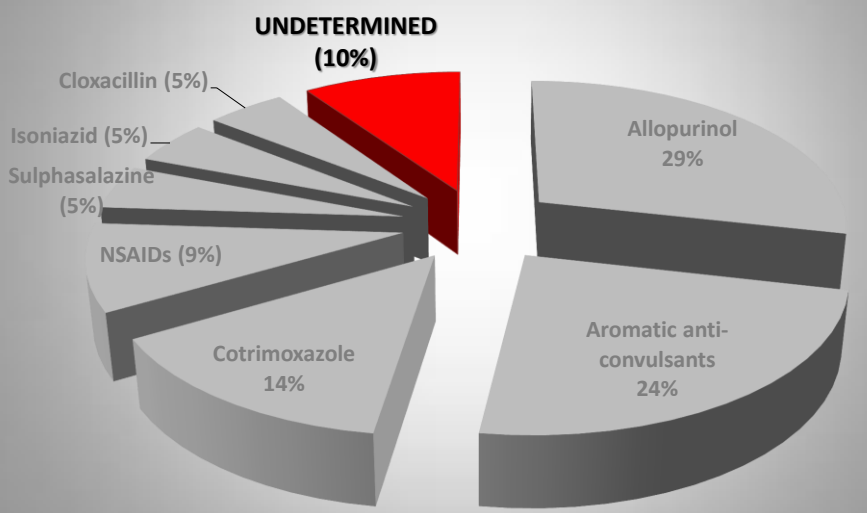
Naranjo *et al*. Pharmacol Ther 1981;30:239–245.

Naranjo Criteria

	Score
Previous reports on the reaction	0 or 1
Temporal illegibility in the onset of the reaction	-1 or -2
Improvement after drug withdrawal	0 or 1
Positive re-challenge	-1 or -2
Exclusion of alternative causes for the ADR	- 1 or -2
Placebo response	0 or 1
Drug concentration and monitoring	0 or 1
Dose relationship	0 or 1
Previous exposure and cross reactivity	0 or 1
Presence of any objective evidence	0 or 1

Results: $\geqq$ 9 definitive; 5 – 8 probable; 1 – 4 possible; $\leqq$ 0 unlikely

Culprit agents



Culprit agent - Practical difficulties

- **Undetermined in 10%**

  → **Multiple drug history**
  - Anti-convulsants
  - Antibiotics
  - Haematological / Oncological pts

  → Unclear drug history

*Any **confirmatory test** in defining **Culprit agent** of DRESS?*

Lymphocyte transformation test (LTT)

- Detect circulating drug-specific memory T cells
- *In vitro* proliferation upon drug stimulation
- Concludes *in vivo* reaction due to sensitization

* ***Safe, reproducible***
* *DRESS –* ***strong T-cell activation***
* *Simultaneous assessment of* ***multiple drugs***

Lymphocyte transformation test (LTT)

- Peripheral blood mononuclear cell (PBMC)
- **Incubation** (Culture medium + Drug [△conc.])
- **Controls** Positive: Tetanus toxoid (TT)
  Negative: Culture medium ONLY
- Uptake of radiolabelled thymidine
  - count per minutes (c.p.m.)

- **Stimulation index (SI)**
  - c.p.m. with drug / c.p.m. without drug
  - Positive test: SI > 2

LTT - Current knowledge (1)

1. **Sensitivity**
- Variable among drugs
- Overall 60 – 70%
- False +ve (NSAIDs)

2. **Specificity**
- 85 – 100%
- ↑in aromatic anti-convulsant & β-lactam

Pichler *et al*. Allergy 2004: 59: 809-20.

LTT - Current knowledge (2)

3. Timing (+ve LTT)

	Acute (1 – 4 wks)	Recovery (5 – 16wks)	> 1 yr
Exanthem	+	-	-
DRESS	-	+	+
SJS / TEN	+	-	-

Kano et al. Allergy 2007: 62: 1439-44.

Prospective study on the Efficacy of Lymphocyte Transformation Test (LTT) in determining the Culprit drug in DRESS

1. Background

- Under-utilization of LTT (availability / cost)
- Previous research included different types of cutaneous adverse reactions
- Existing knowledge based on small series
- Efficacy and optimal timing of LTT unclear

Prospective study on the Efficacy of Lymphocyte Transformation Test (LTT) in determining the Culprit drug in DRESS

2. Objectives

- ***Primary*** To determine the sensitivity & specificity of LTT in DRESS
- ***Secondary*** To determine the optimal timing for LTT and to assess the impact of systemic immunosuppression on LTT

Prospective study on the Efficacy of Lymphocyte Transformation Test (LTT) in determining the Culprit drug in DRESS

- Pilot study
- Collaboration with Div. of Clinical Immunology, Dept. of Pathology (QMH)
- Prospective collection of serial blood samples
- Acute (1-4 wk) & Recovery (>4 wks) phase

DRESS - Treatment

- Systemic corticosteroid recommended in pts with significant internal organ involvement
- Moderate to high dose (0.5-1mg/kg/d)
- To date, no prospective, randomized placebo-controlled trials existed to demonstrate the efficacy of corticosteroid therapy in DRESS
- Other treatment options with reported success
  - Pulsed IV methylprednisolone, IVIG, plasmapheresis, cyclosporine A and cyclophosphamide

Single-centered, Five-year Retrospective Review of DRESS in Chinese patients

I. Clinical, biochemical, histopathological & pharmaco-genetic characteristics

II. Treatment, outcome and complications

Corticosteroid therapy (71%; n = 15)

	Mean	Median	Range
Time to starting systemic corticosteroid (days)	13.7		3 - 36
Duration of corticosteroid therapy (weeks)		17	4 - 202
Starting prednisolone dose (mg/day)	54.6		30 - 200
Starting prednisolone/body weight (mg/kg/day)	1.0		0.5 - 4
Prednisolone dose at **1 month** (mg/day)	16.4		0 - 30
Prednisolone/body weight at **1 month** (mg/kg/day)	0.3		0 - 0.5
Prednisolone dose at **3 month** (mg/day)	5.6		0 - 25
Prednisolone/body weight at **3 month** (mg/kg/day)	0.1		0 - 0.5

DRESS - Treatment

- **Steroid-sparing agent**
  - 29% (n=6)
  - Average time to start: 5.4 ± 2.6 wk (2 - 8 wk)
  - Median duration: 16 wks (8 - 198 wk)

Prognosis

- **Mortality:** 5% (n=1)
  - Died from acute renal failure 1 month after Dx
  - Initial clinical improvement with supportive treatment
  - Not treated with systemic corticosteroid
- **Relapse**
  1. Relapse of **rashes** in 7 patients (33%)
     - Mean time of relapse : 8.4 ± 2.7 wks (2 - 20 wks)
     - No difference between pts with or without steroid (P=0.39)
  2. Relapse of **hepatitis** in 1 patient (5%) in five weeks
  3. Relapse of **eosinophilia** in 3 patients (14%)

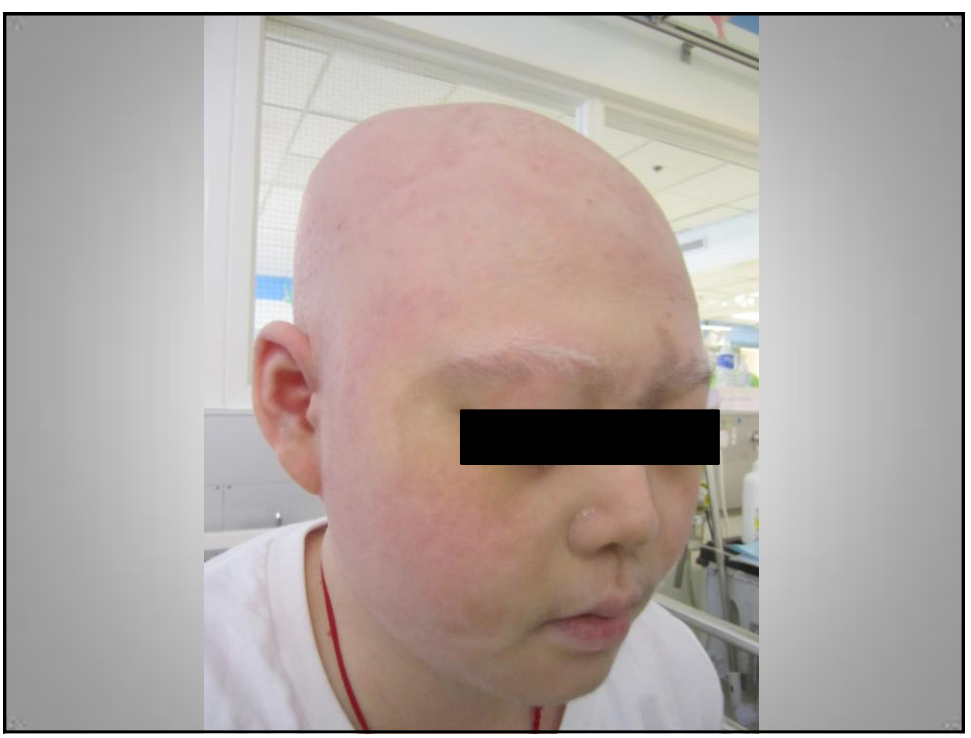
Autoimmune Complications

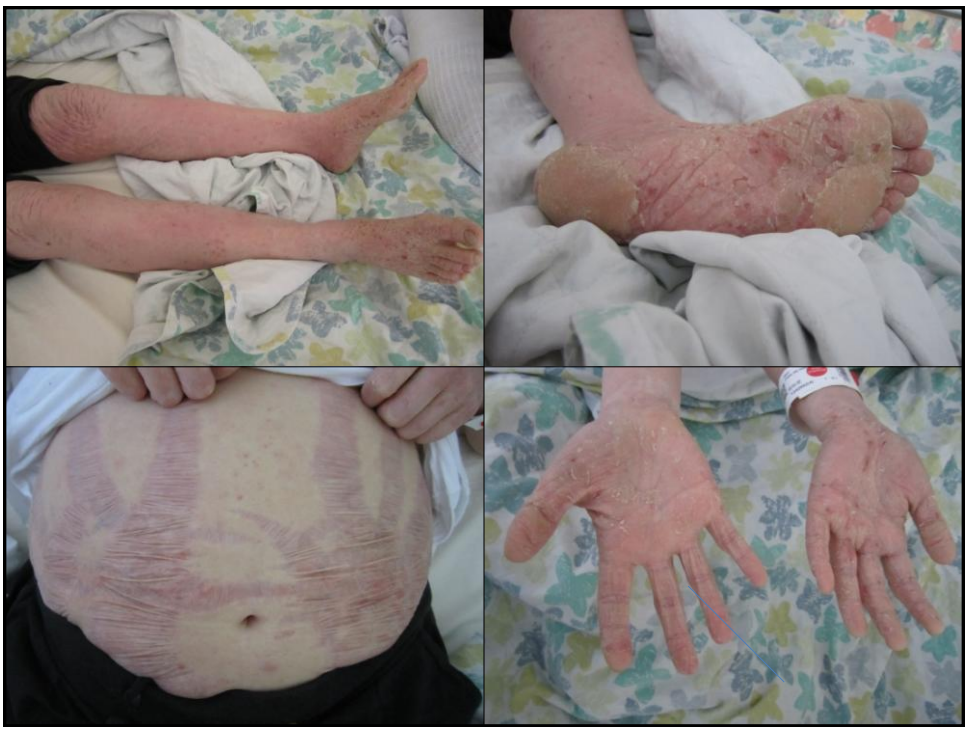
1. **Insulin-dependent diabetes mellitus** (10%; n=2)
2. **Thyroiditis** (10%; n=2)
3. **Bronchiolitis obliterans with organizing pneumonia (BOOP)** (5%; n=1)

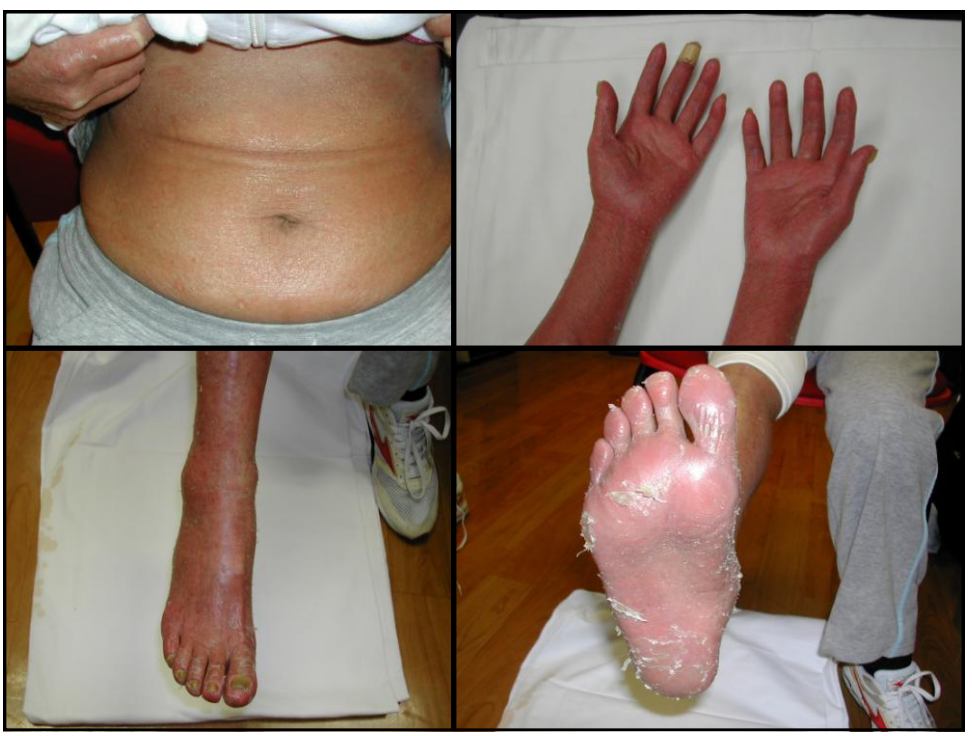
- 22 months after Dx of DRESS
- Hx of interstitial penumonitis during course of DRESS
- Culprit agent: Naproxen

Long term cutaneous sequalae

- ***Never been described in literature***
- One patient developed alopecia totalis and vitiligo 3 years after diagnosis
- **Chronic psoriasiform eruption**
  - Persistent erythroderma
  - Refractory to multiple immunosuppressants
  - Cotrimoxazole as culprit in both cases







Summary (1)

1. DRESS is an uncommon, but potentially fatal severe cutaneous adverse reaction
2. Heterogenous clinical, biochemical and histological features are found in DRESS
3. Phenotypical differences exist in DRESS caused by various culprit drugs

Summary (2)

4. HLA-B*58:01 screening may be efficacious in prevention of allopurinol-induced DRESS
5. Lymphocye transformation test may help in identification of culprit drugs
6. DRESS is associated a variety of long term autoimmune and cutaneous complications

Thank you