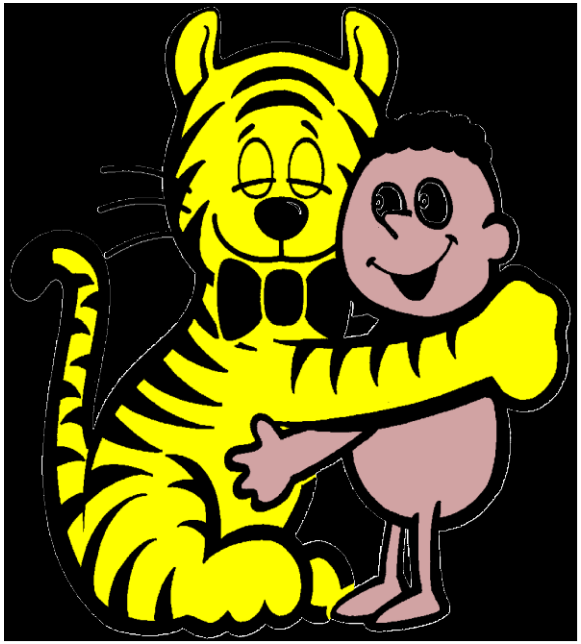
Update - Kawasaki disease

Mark Cotton
& Simone Nicol
Stellenbosch University
(SU), South Africa

ID Workshop, SAPA Conference
CTICC 9 Sept 2014



Children's Infectious Diseases Clinical Trial Unit

Tygerberg Children's Hospital

Tomisaku Kawasaki - 1st description of Kawasaki syndrome (disease)

アレルギー，16（3）
178～222，1967(昭42)

指趾の特異的落屑を伴う小児の急性熱性皮膚粘膜淋巴腺症候群

（自験例50例の臨床的観察）

日本赤十字社中央病院小児科（部長：神前章雄博士）
川　崎　富　作

（受付：1月19日，1967）

1. 緒　言

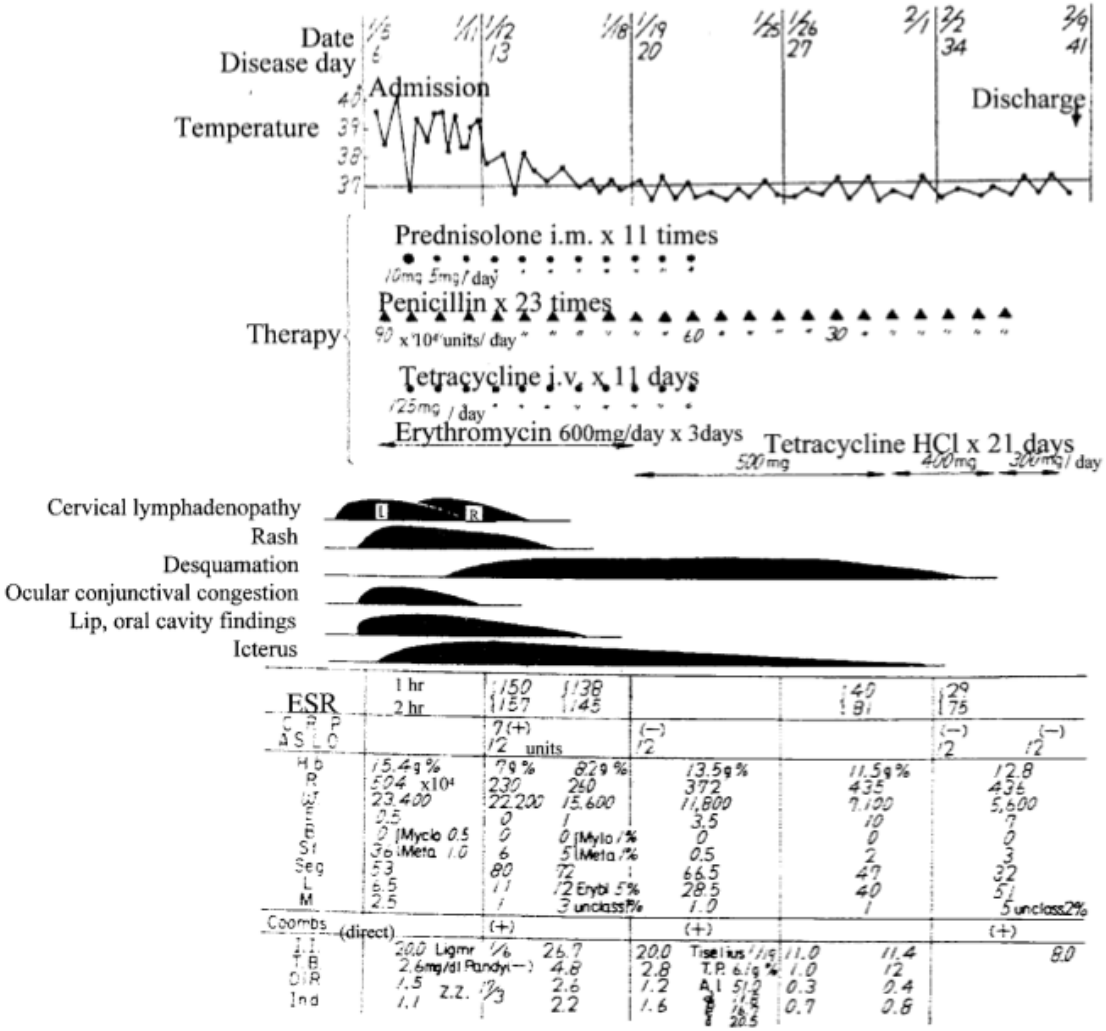
1876年 Fuchs[1] の発表した Herpes iris conjunctivae 以来，多数の学者によつて，眼，皮膚，粘膜を侵す一連の

6） 両手，両足が血管神経性浮腫状を呈する……22例（44%）

7） 指趾先の爪皮膚移行部よりの膜様落屑が主として

Kawasaki T. Infantile acute febrile mucocutaneous lymph node syndrome with specific desquamation of the fingers and toes. Clinical observation of 50 cases. Jpn J Allerg. 1967;178–222 (English abstract)

1st case – 4y boy



1st & only case of Coombs +ve anaemia

Tomisaku Kawasaki's timeline -

- Saw 1st case - Jan 1961
- 2nd case 1 year later
- Suspected a syndrome
  - 1st 7 cases reported as "non-scarlet fever with desquamation" at a meeting in 1962
  - 50 cases reported in 1967
  - Published in an Allergy Journal
    - "New syndrome" disputed by colleagues
- Self-limiting and benign or serious?
- Infantile polyarteritis nodosa = KD?
- !970 – 1st nationwide KD survey
  - 10 autopsy cases of sudden death after KD
- 1st English language publication - 1974

Dr Takajiro Yamamoto

Independently collected cases from 1950's

1968 – patient with KD developed gallop

Yamamoto T, Kimura J.

Acute febrile mucocutaneous lymph node syndrome (Kawasaki): subtype of mucocutaneous ocular syndrome of erythema multiforme complicated with carditis

Shonika Rinsho (Jpn J Pediatr). 1968;21:336 –339

1963 – visiting professor at Cornell, USA – shown a case at Prof. Eichenwald's grand rounds

In retrospect, 1st cases documented in 1950's

- Sakurai K. Mucocutaneous ocular syndrome: report of a case [in Japanese]. *Shonika Rinsho (Jpn J Pediatr).* 1954;7:787–790
- Hanawa K. Two cases of pericardial hematoma in infancy [in Japanese]. *Shonika Shinryo (J Pediatr Pract).* 1959;22:820

1st identification outside Japan: Hawaii- 1970's

Asian children similar clinical picture

KD identified KD from photographs from Japan

Dr. Marian Melish

Dr. Raquel Hicks

Vd Merwe PL, Gie RP et al

Mucocutaneous lymph node syndrome (Kawasaki disease). A report of 2 cases

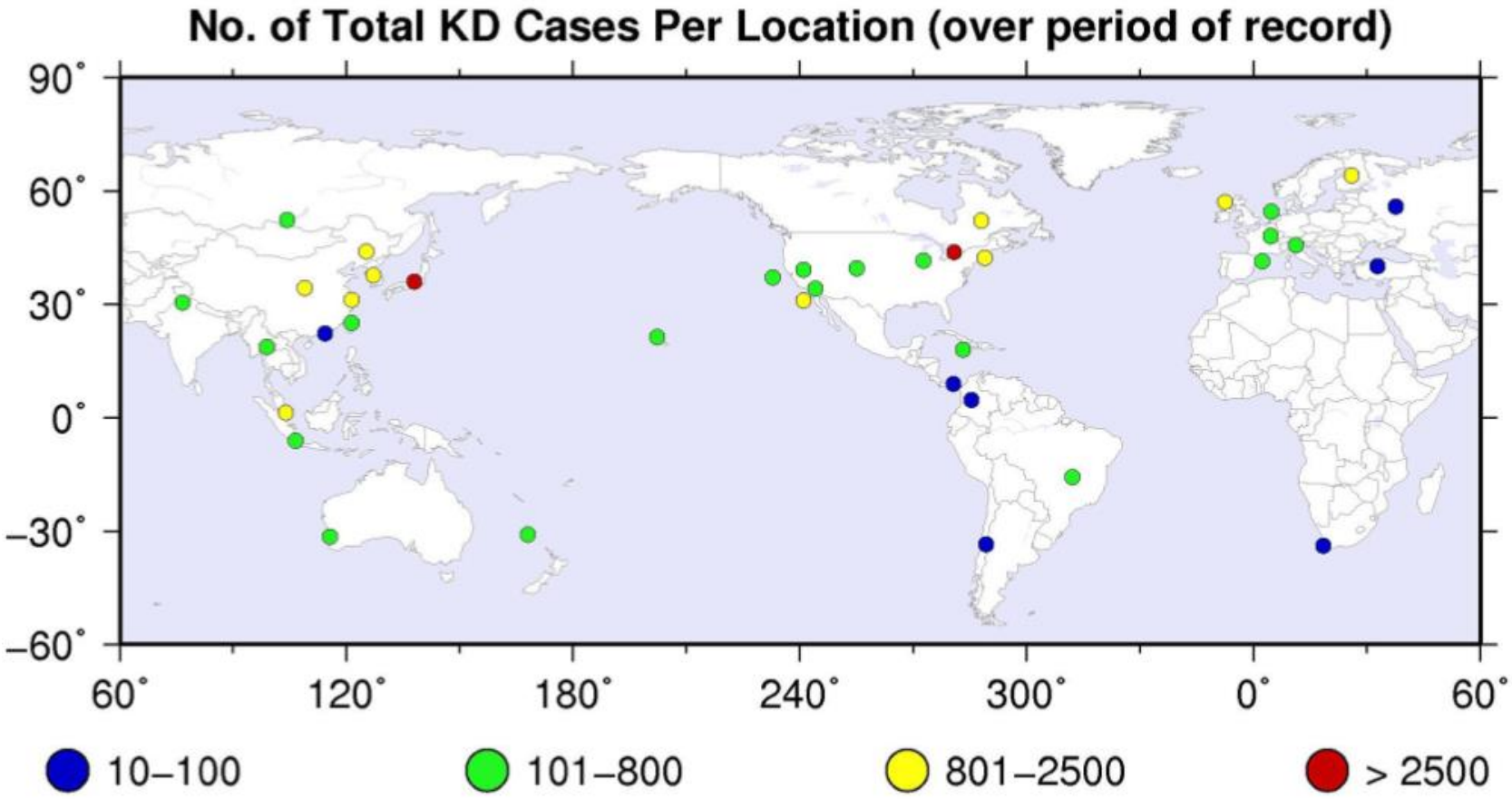
S Afr Med J 1980; 581014-6

- Pt 1: ECG inferior myocardial infarction
- Pt 2: aneurysm left coronary artery at postmortem

Epidemiology

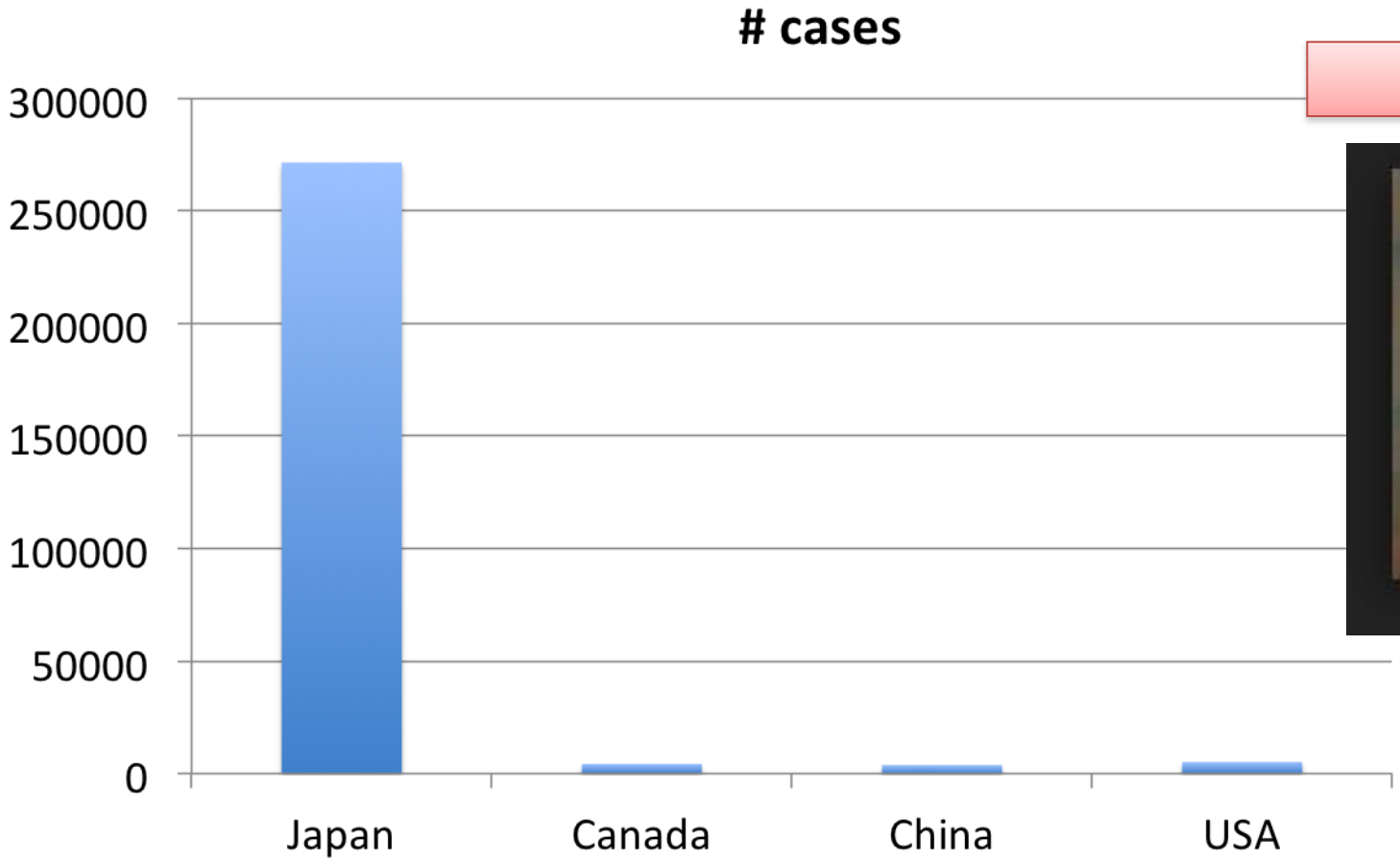
- **US**
  - Epidemics late winter and spring with 3-year intervals
  - Children from the middle and upper-middle classes
  - ~ 3000 children hospitalized annually
  - More common in Japanese-American
- Japan
  - 5000-6000 per year
  - Epidemics 1979, 1982, and 1985
- Sex: male-to-female 1.5:1
- Genetic: Japan 10x increase risk if affected sibling, 2x increase if parent,
  - similar in US (unpublished)

Cases collected 1970-2012



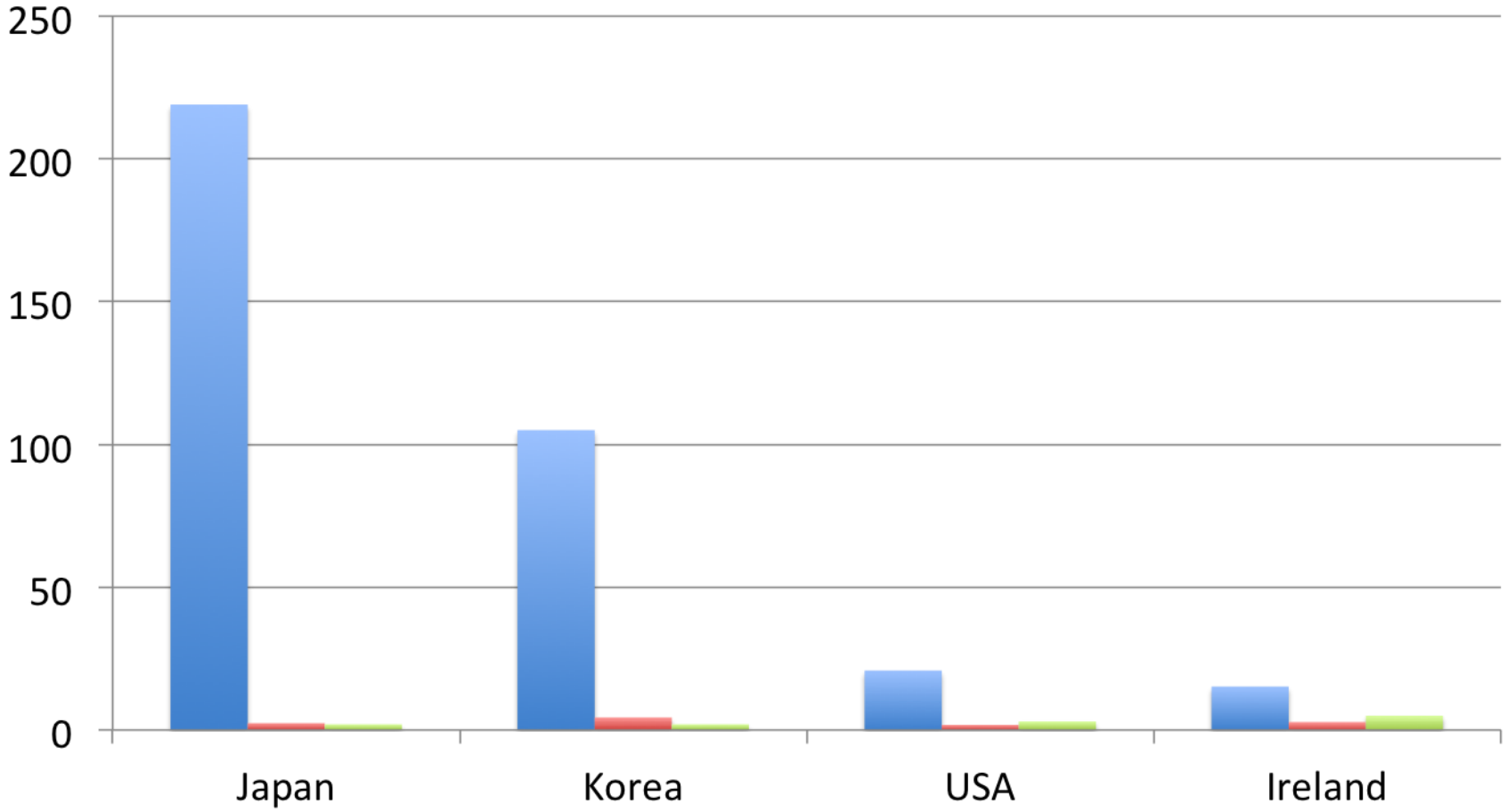
Burns JC et al Seasonality of KD PLOSOne 2013; 8: e75429

Cases in top 4 countries

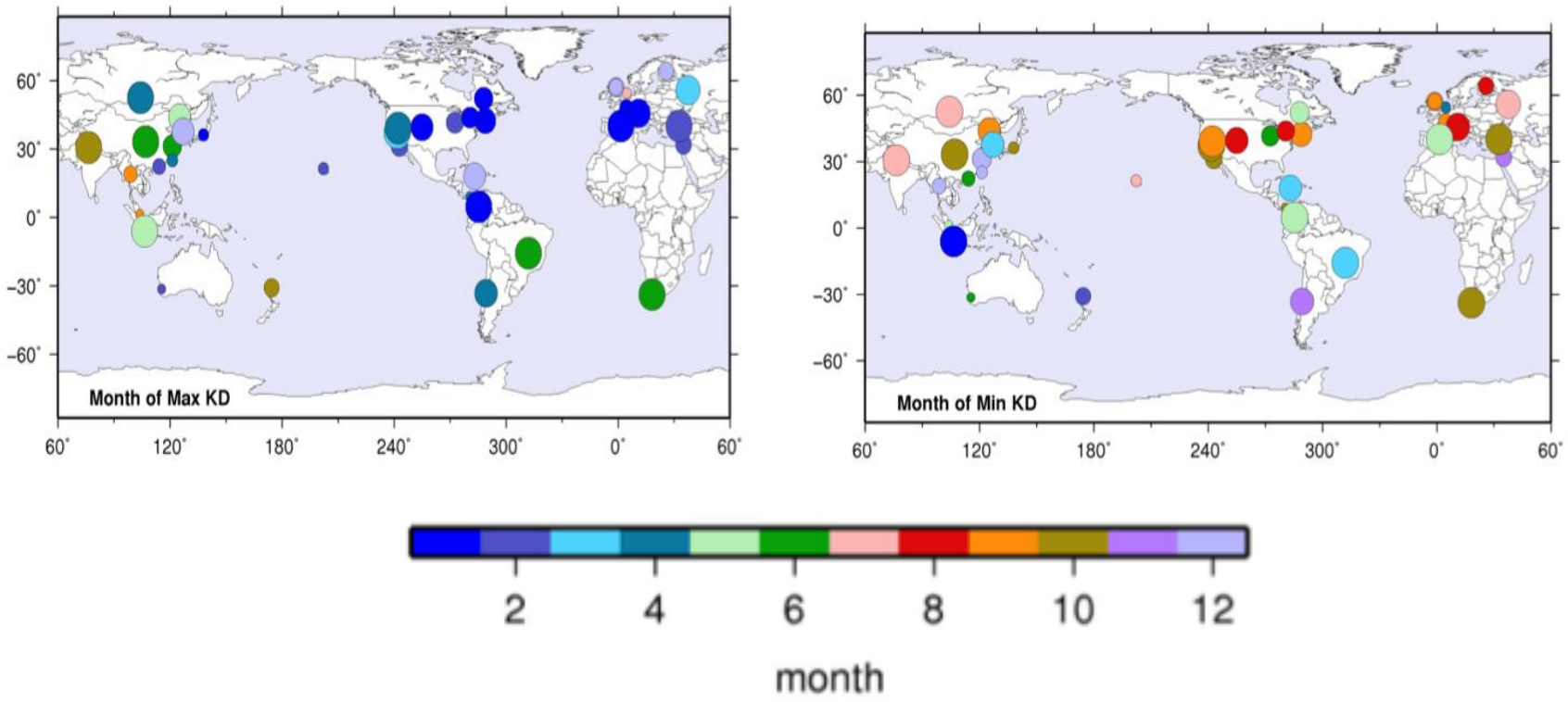


Jane C Burns

Incidence per 100,000 <5y of age



Northern Hemisphere – transmissable agent in winter



Age

- **USA –** 80-90% of admissions < 5 years, median age 3.14 years (1mo-21yrs), 10% under 6 months
- Japanese – Incidence boys 0-4 years old 240 per 100 000 (2007-2008) peak in children 6-11 months
- England - Incidence in children <5 yrs. 8 in 100 000 (1998-2003)
- Also < 6 months or > 5 years

Stanley TV, Grimwood K.

Classical Kawasaki disease in a neonate

Arch Dis Child Fetal Neonatal 2002 Mar;86(2):F135-6

- Infant <2 weeks of age
- Echo: coronary artery aneurysm day 5
- IVIG - rapid improvement

KD = leading cause acquired heart disease in the USA ≤ 5y

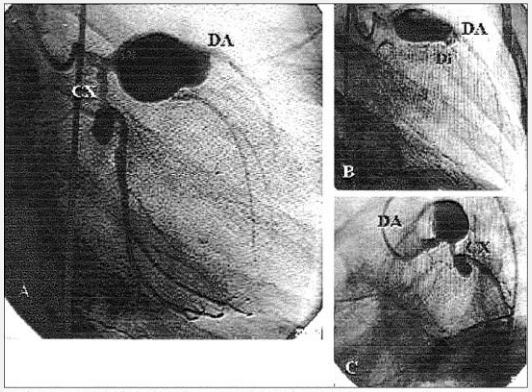


Fig. 3 – Coronary angiography performed 80 days after anti-inflammatory treatment showed a significant involution in the coronary aneurysms of the circumflex (CX), diagonal (Di), and distal part of the anterior interventricular (DA) arteries, in right (A, B) and left (C) anterior oblique views. A residual giant aneurysm persisted at the beginning of the anterior interventricular artery, though smaller than the one previously observed

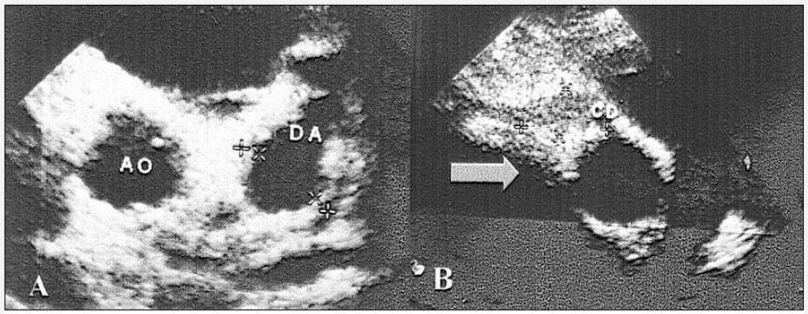


Fig. 1 - Echocardiogram, cross-sectional sections, performed 33 days after the beginning of Kawasaki disease, showing giant aneurysms 14 mm in diameter in the anterior interventricular artery (DA-A) and in the right coronary artery (CD-B), with an occlusive thrombus inside (arrow) and normal cardiac cavities.

ECHO

- asymptomatic coronary artery ectasis
- aneurysm incl giant coronary artery aneurysms with thrombosis

Coronary aneurysms in 25% untreated patients

Mortality

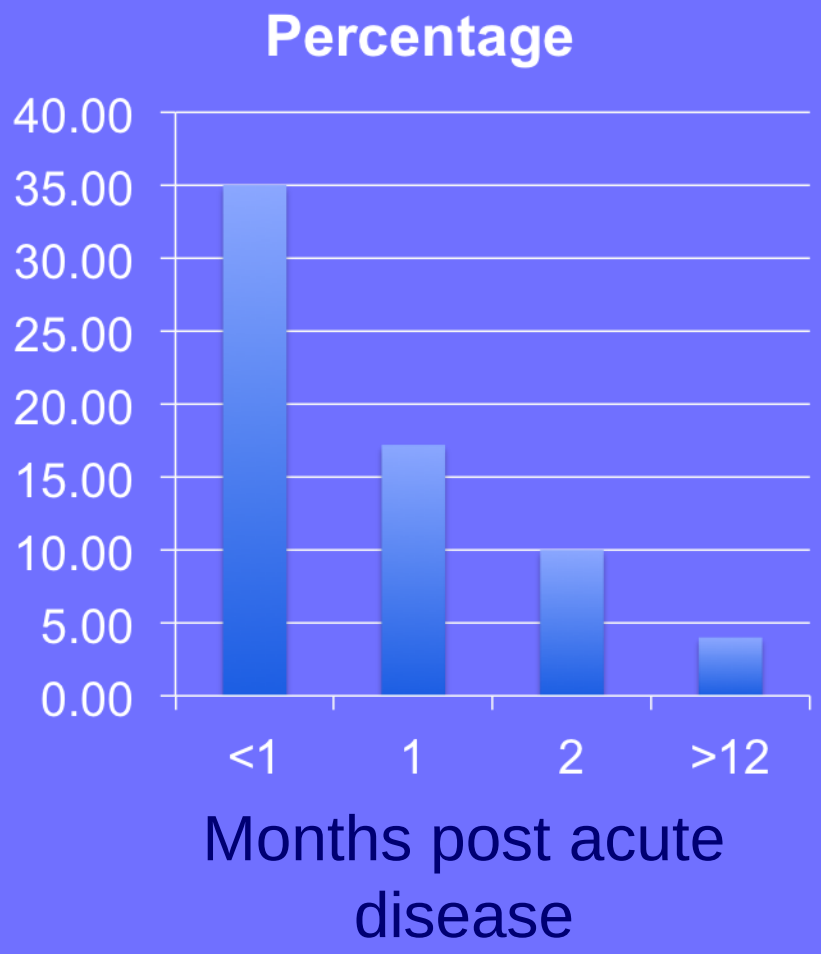
- Japanese registry of 6576 patients - increased mortality in 1st 2 months
- During improvement or recovery phase
- Postmortem - thrombotic occlusion of coronary artery aneurysms & myocardial infarction

Coronary artery lesions

Dilatation

- Internal diameter
  - <5y >3mm
  - >5y >4mm

Persistence abnormalities



Morbidity

- Giant CA >8mm greatest risk for myocardial infarction
- ⑩↓ left ventricular function in ~ 50%
- Despite healing in smaller CA, vascular reactivity doesn't return to baseline: follow up indefinitely
- Arthritis may persist

CA = coronary aneurysm

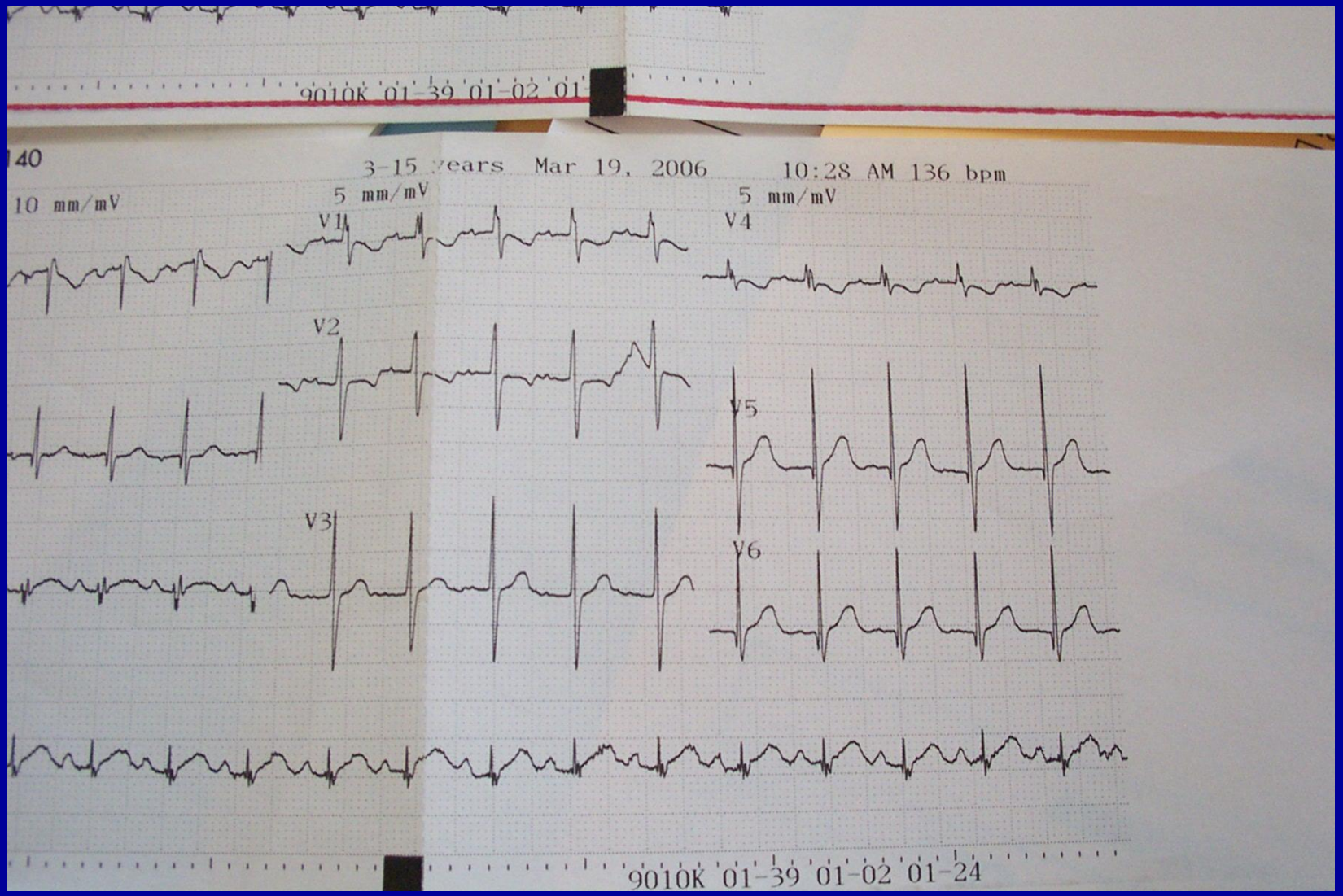
Risk of aneurysm

- Predicted by the severity of the disease
- increased fever > 16 days
- Recurrence of fever after afebrile ≥ 48 hours
- Males, < 1 year
- Cardiomegaly
- Laboratory values
  - low hematocrit
  - Thrombocytopenia
  - elevated neutrophil/band counts

Coron Artery Dis. 1995 6:857-64

Thrombocytopenia: a risk factor for acute MI - acute phase KD Niwa K et al

- 10 patients
- Coronary aneurysms & acute MI
- Platelet count: 4-12 x 10^4/mm3
- low ESR with high CRP in 7


9010K 01-39 01-02 01
140
3-15 years Mar 19, 2006 10:28 AM 136 bpm
10 mm/mV
5 mm/mV
V1
V2
V3
5 mm/mV
V4
V5
V6
9010K 01-39 01-02 01-24

Kawasaki Disease - Dx

Fever >5 days with no other explanation & ≥4 of the 5 following criteria:
Bilateral bulbar conjuctival injection
Oral mucous membrane changes, injected or fissured lips, injected pharynx or strawberry tongue
Peripheral extremity changes: erythema palms or soles, edema of hands & feet (acute phase) & periungual desquamation (convalescent stage)
Polymorphous rash
Cervical lymphadenopathy (at least one LN >1.5cm in diameter)

American Heart Association 2004

>5 of 6 with no other explanation
Fever
Bilateral bulbar conjuctival injection
Oral mucous membrane changes, injected or fissured lips, injected pharynx or strawberry tongue
Peripheral extremity changes, incl erythema palms or soles, edema of hands & feet (acute phase) & periungual desquamation (convalescent stage)
Polymorphous rash
Cervical lymphadenopathy (at least one LN >1.5cm in diameter)

Japanese Circulation Society 2008

Incomplete KD <5/6 criteria

supplementary lab criteria

Fever of >5 d associated with 2 or 3 clinical criteria,
C-reactive protein ≥3.0 mg/dL and/or erythrocyte sedimentation rate ≥40 mm/h with the following criteria
(1) albumin ≤ 3.0 g/dL
(2) anemia for age
(3) elevation of alanine aminotransferase
(4) platelets after 7 d ≥ 450,000/mm^3
(5) white blood cell count ≥15,000/mm^3
(6) urine ≥10 white blood cells/high-power field

Atypical vs Typical

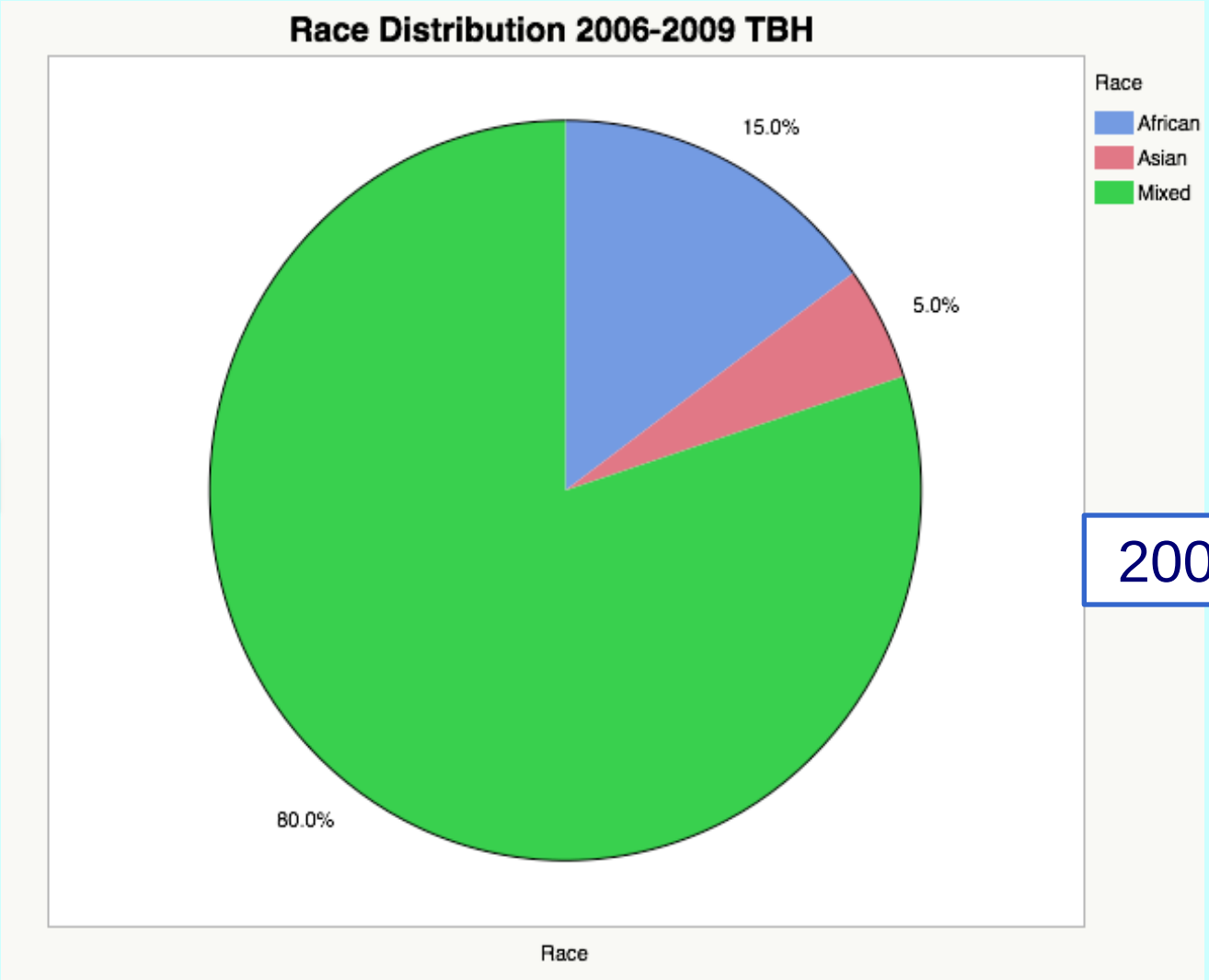
Features of Typical KD	Features of Atypical KD
Cervical LAD 60%	Cervical LAD 10%
Rash 90%	Rash 10%
Peripheral extremity changes 85%	Peripheral extremity changes 60%
>90% mucous membrane changes	>90% mucous membrane changes

LAD = lymphadenopathy

Tygerberg Children's Hospital (TCH)

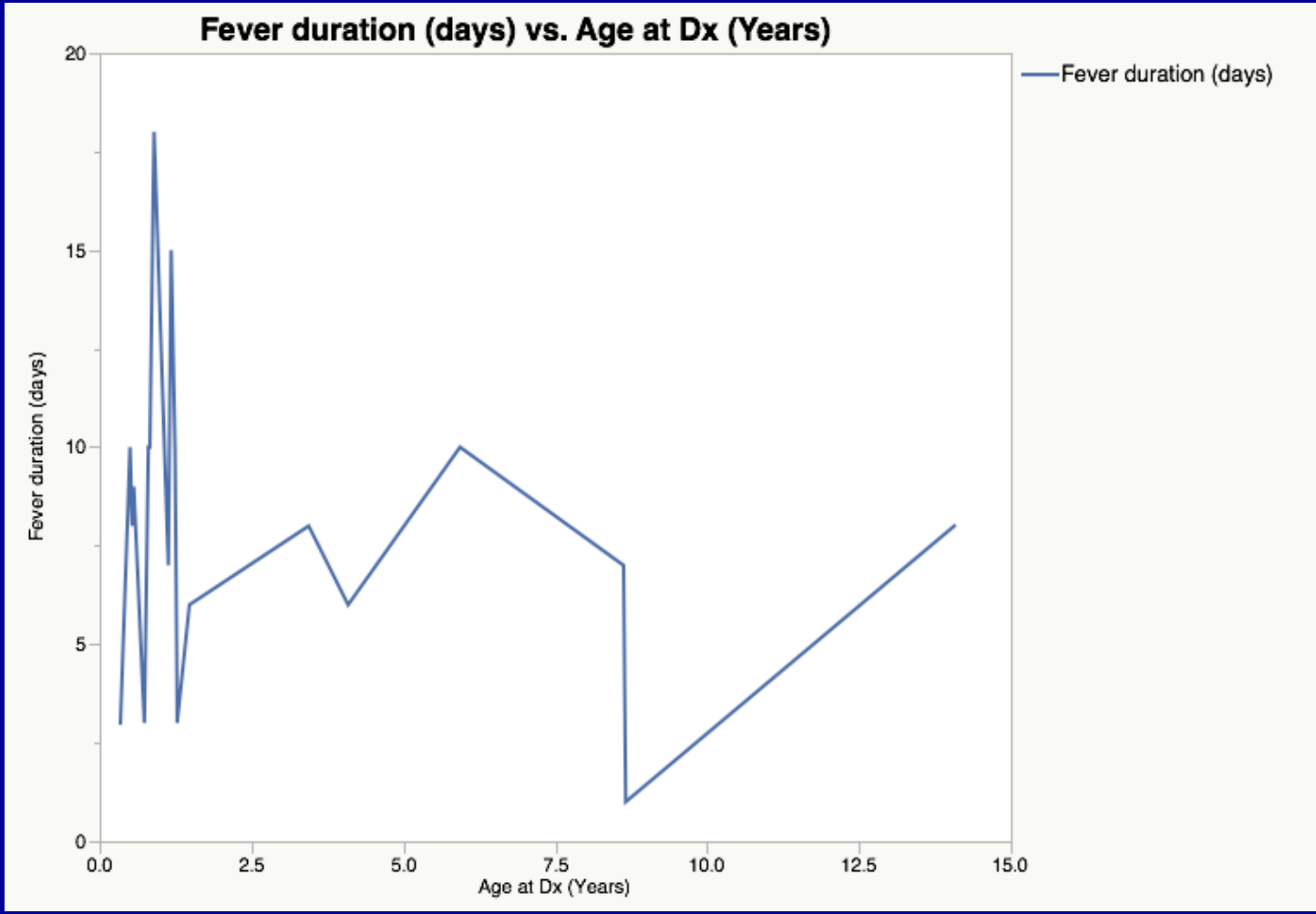
Racial breakdown

N = 21



2006-2009

Longer fever in younger patients (days)



What causes KD?

- Unusual response to infectious agent?
- Seasonality & age
  - Novel retrovirus
  - EBV
  - Parvovirus
  - Coronavirus
- Staphylococcal toxin mediated ?

Autoimmune rather than infectious agent?

Immune dysregulation

- DNA microarrays – upregulation neutrophil response genes (adrenomedullin, grancalcin and granulin)
- Evolving disease - upregulation of CD8 and NK responses & decreased neutrophil response
- Oligoclonal IgA in respiratory tract arteries: respiratory agent?

Polymorphisms with KD

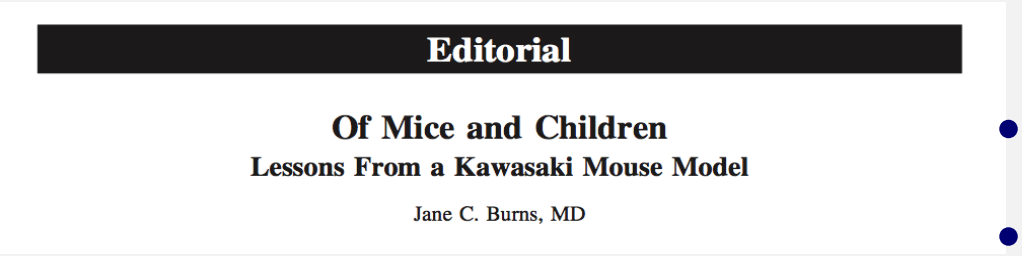
- Inositol 1,4,5- triphosphate 3-kinase
  - Negative regulator of T cell activation
- Angiopoetin up-regulation & vascular endothelial growth factor down-regulation
  - disrupting vascular homeostasis
- Adenosine triphosphate binding cassette
  - Cellular efflux of prostaglandins
- CCR5 gene

  Chemokine receptor

Hematological & cytokine & immunological events

- Persistent monocytosis post IVIG – coronary artery lesions
- Eosiniphilia
- Upregulation apoptosis genes

Animal models



Editorial

Of Mice and Children

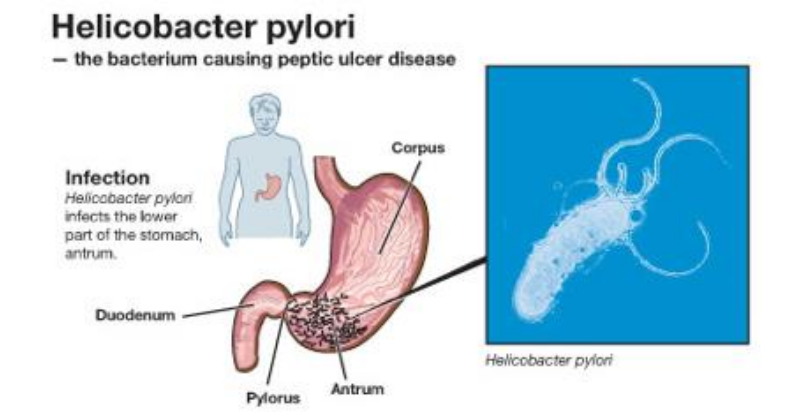
Lessons From a Kawasaki Mouse Model

Jane C. Burns, MD

- Intraperitoneal extract of *Lactobacillus casei*
- Coronary disease
- IVIG-responsive

Circulation 2012; 125: 1480

The Dr. who drank infectious broth, gave himself an ulcer, & solved a medical mystery



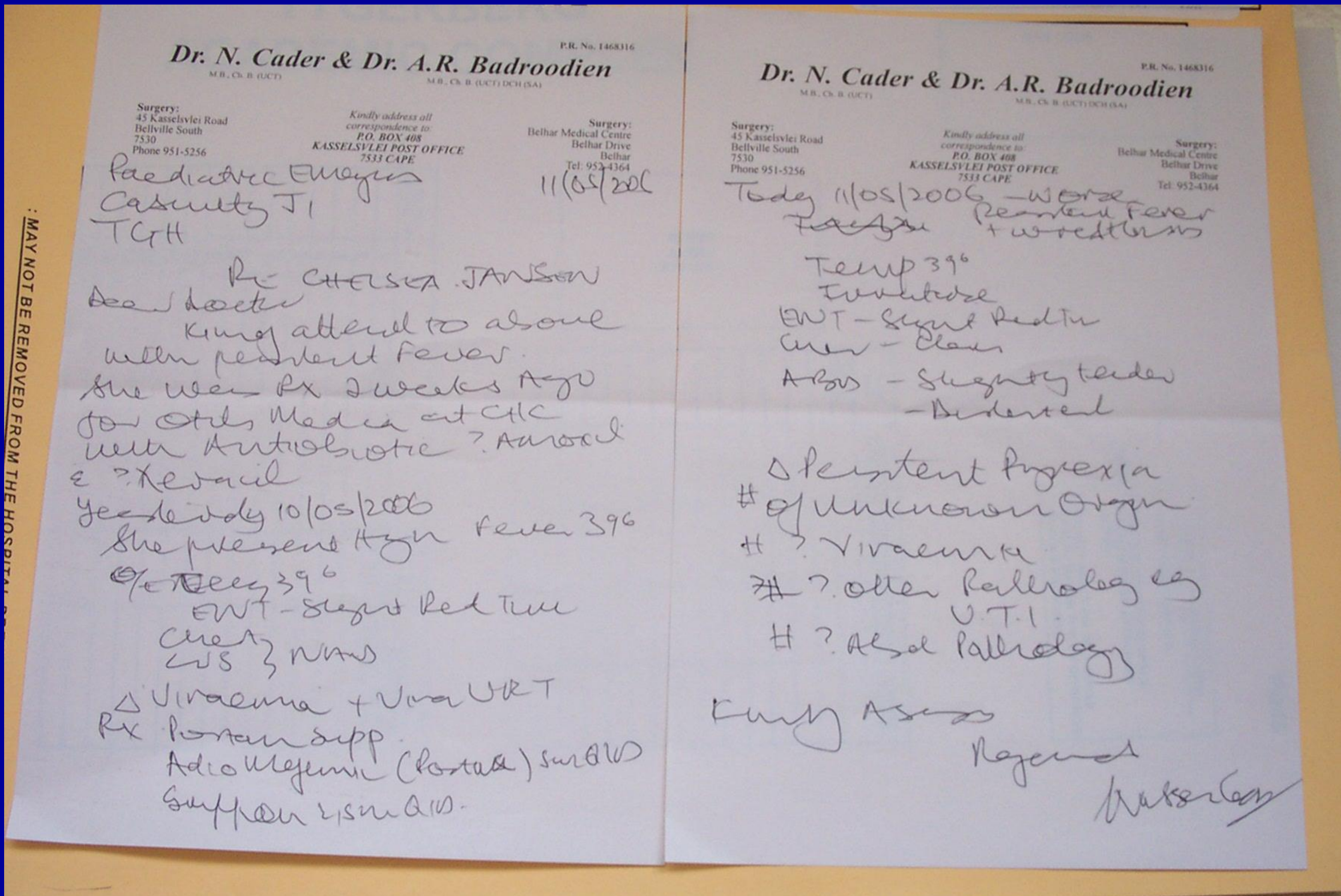
http://discovermagazine.com/2010

J Robin Warren & Barry J Marshall
Noble prize - 2005

Clinical syndrome

Can be sequential

Always ask for features on history



MAY NOT BE REMOVED FROM THE HOSPITAL

P.R. No. 1468316

Dr. N. Cader & Dr. A.R. Badroodien

M.B., Ch. B (UCT) M.B., Ch. B. (UCT) DCH (SA)

Surgery:
45 Kasselsvlei Road
Bellville South
7530
Phone 951-5256

Kindly address all correspondence to:
P.O. BOX 408
KASSELSVLEI POST OFFICE
7533 CAPE

Surgery:
Belhar Medical Centre
Belhar Drive
Belhar
Tel: 952-4364

Paediatric Emergency
Casualty J1
TGH

11/05/2006

Re: CHELSEA JANSON

Dear Doctor

Kindly attend to above with persistent fever.
She was Rx 2 weeks ago for Otitis Media at CHC with Antibiotic ? Amoxil & ? [illegible]
Yesterday 10/05/2006 she present again fever 39.6
O/E Temp 39.6
ENT - Slight Red TM
Chest / CVS } NAD

Δ Viraemia + Viral URT
Rx Panado supp
Adco Mefenamic (Ponstan) susp QID
[illegible] syrup QID.

P.R. No. 1468316

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KASSELSVLEI POST OFFICE
7533 CAPE

Surgery:
Belhar Medical Centre
Belhar Drive
Belhar
Tel: 952-4364

Today 11/05/2006 — worse
Persistent fever + restlessness

Temp 39.6
Irritable
ENT - Slight Red TM
Chest - Clear
ABDO - Slightly tender
- Distended

Δ Persistent Pyrexia
# of Unknown Origin
? Viraemia
? other Pathology eg U.T.I
? Abd Pathology

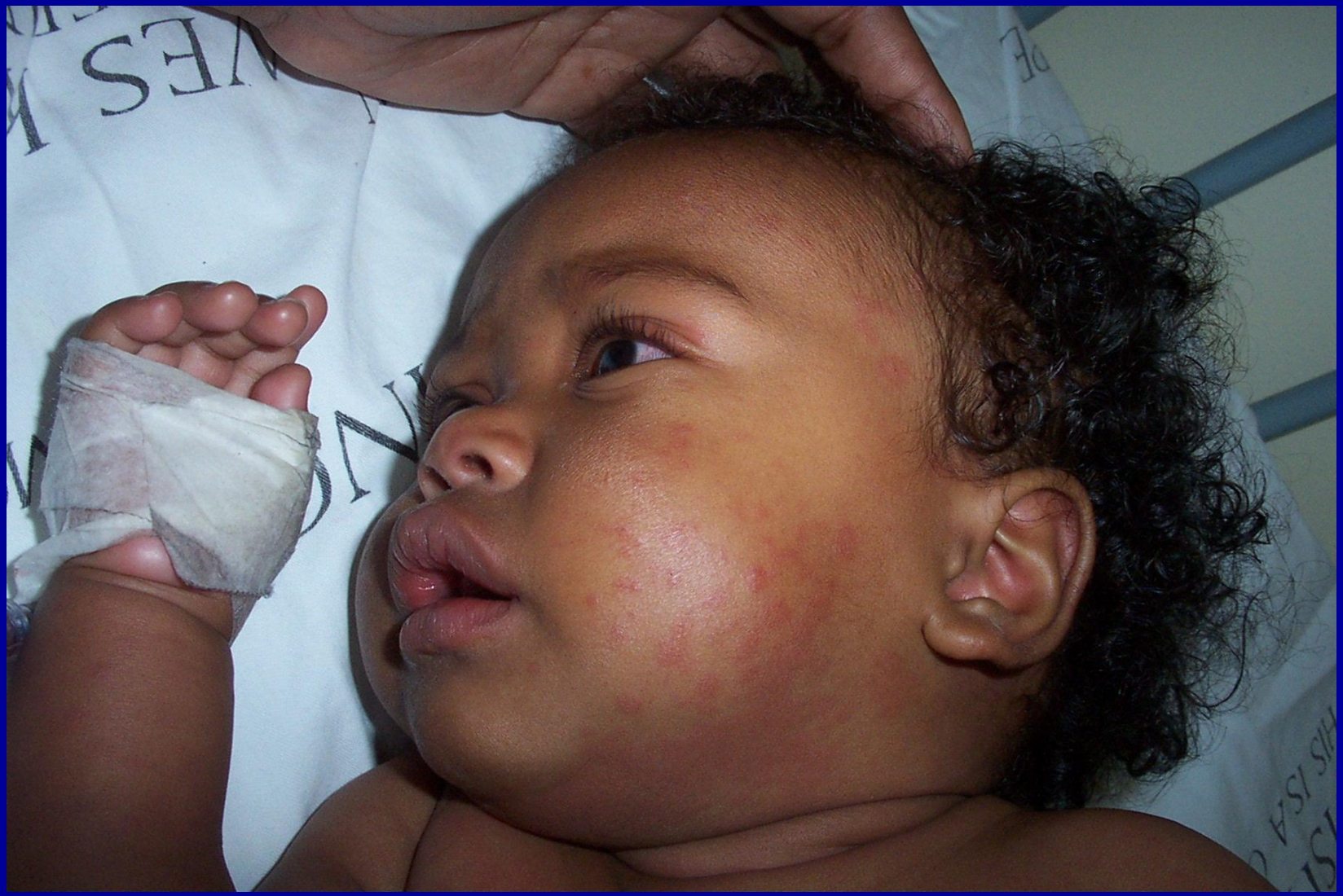
Kindly Assess

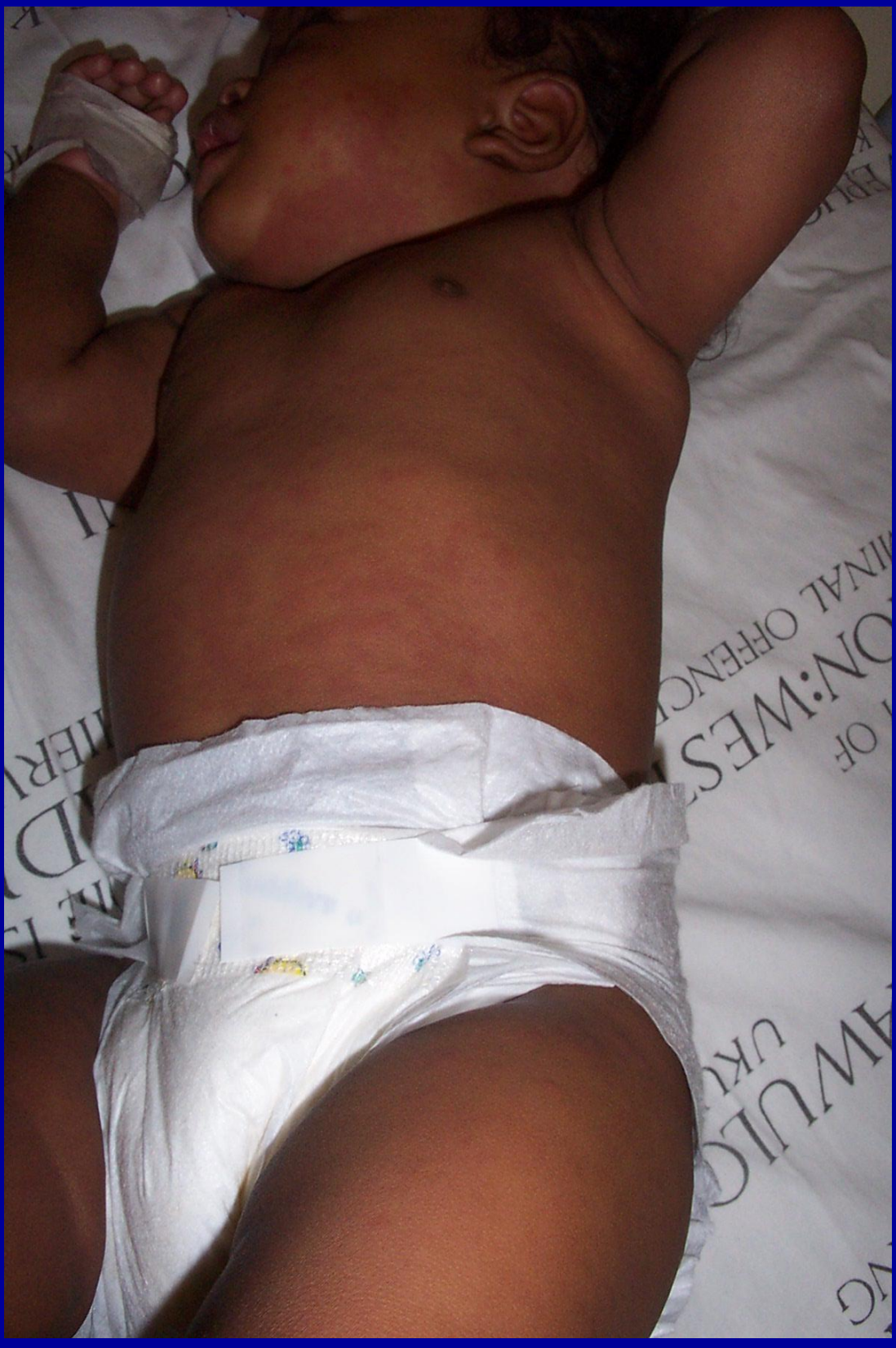
Regards

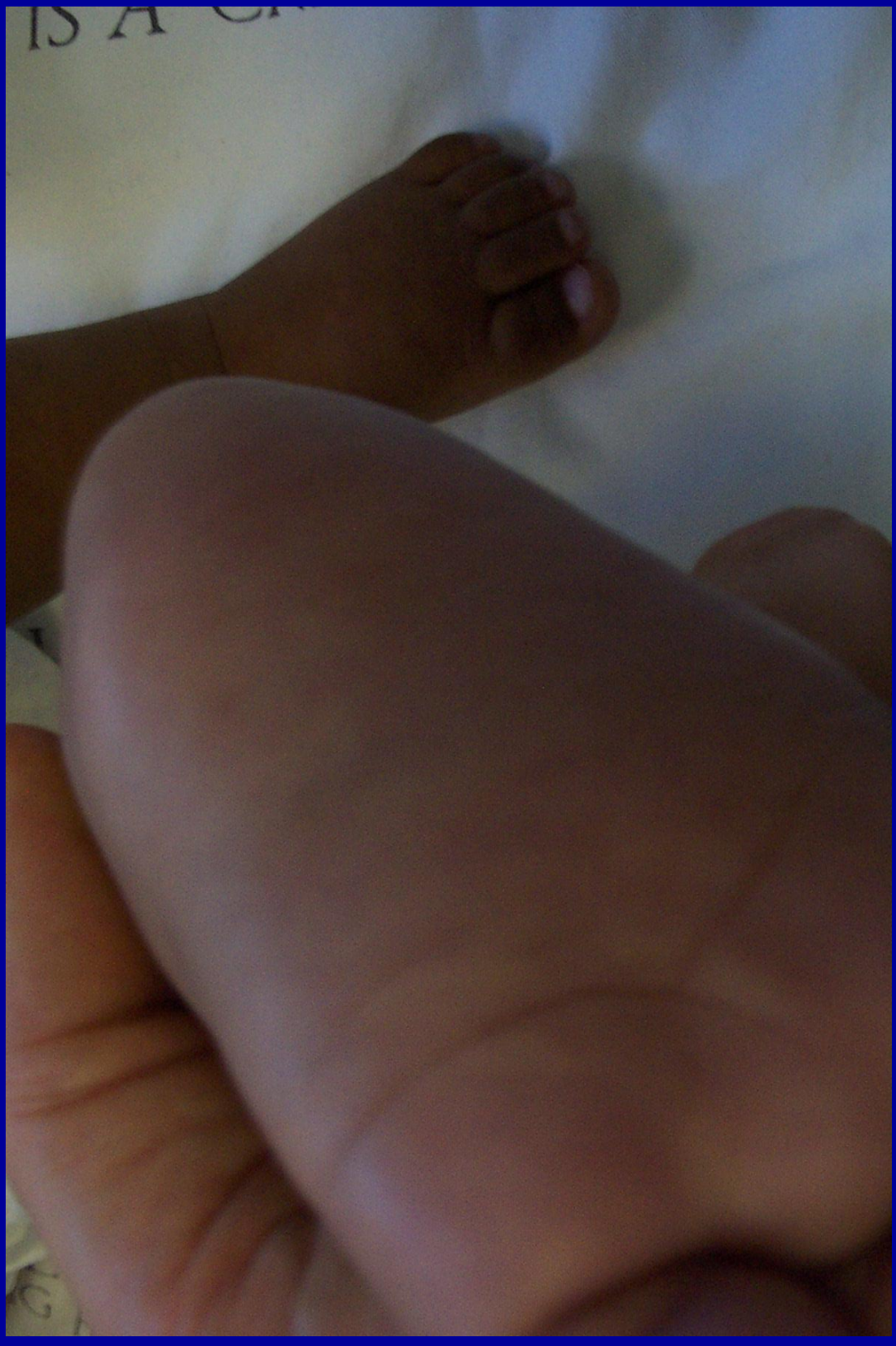
[illegible]

Clinical Course

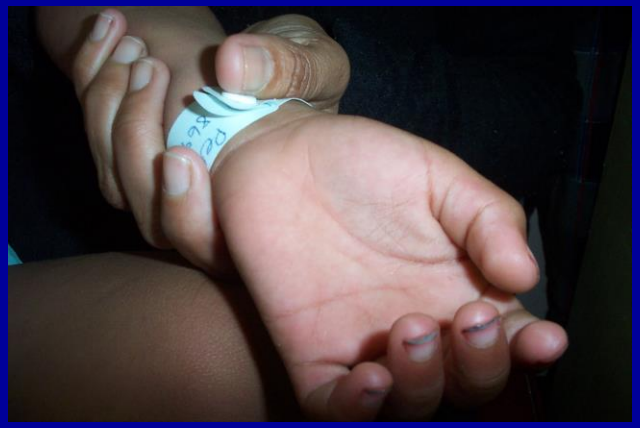
- Prodrome - respiratory or gastrointestinal illness
- Abrupt onset fever
- Usually receive abx - no response
- Irritable +++







Hands

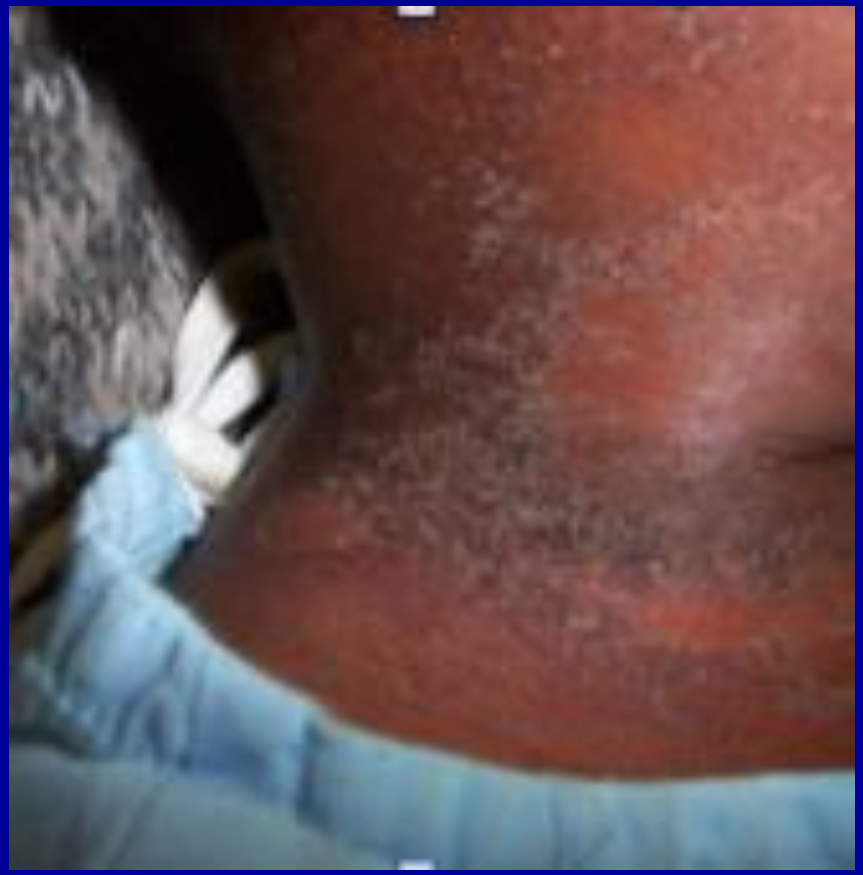


- Warm inflammatory oedema
- Periungual desquamation

Painful cracked lips

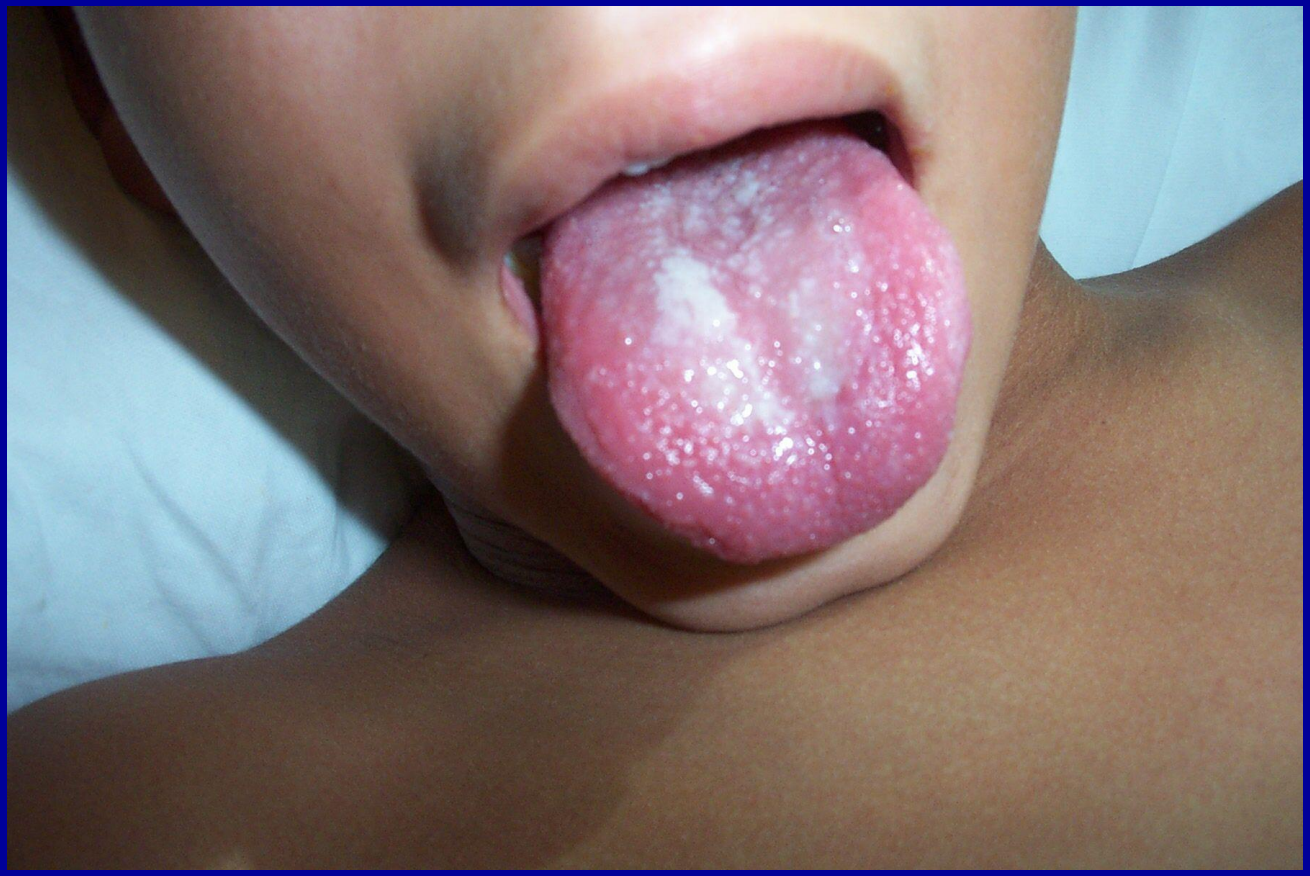
Desquamation

Perineal
Urethritis



Cervical

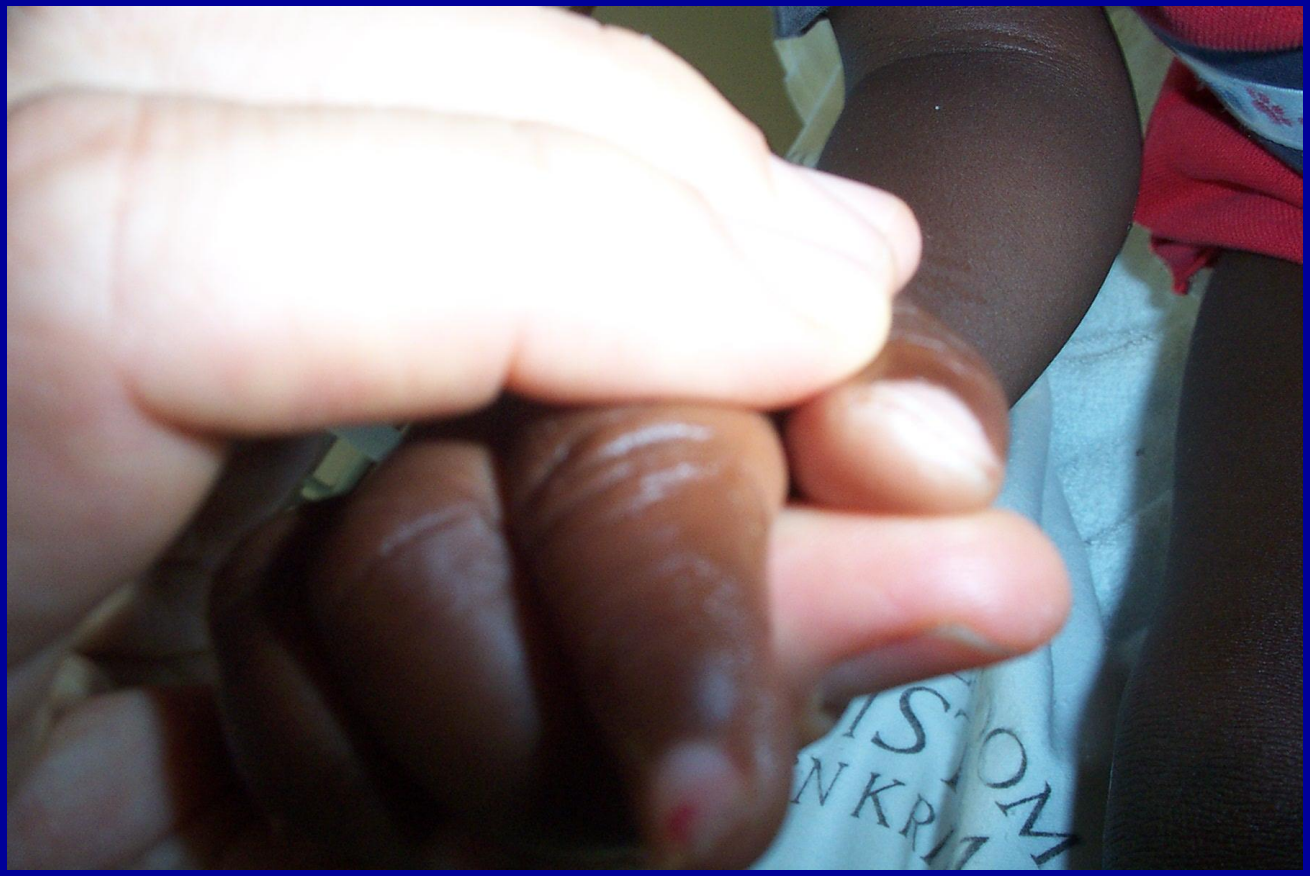
Strawberry tongue



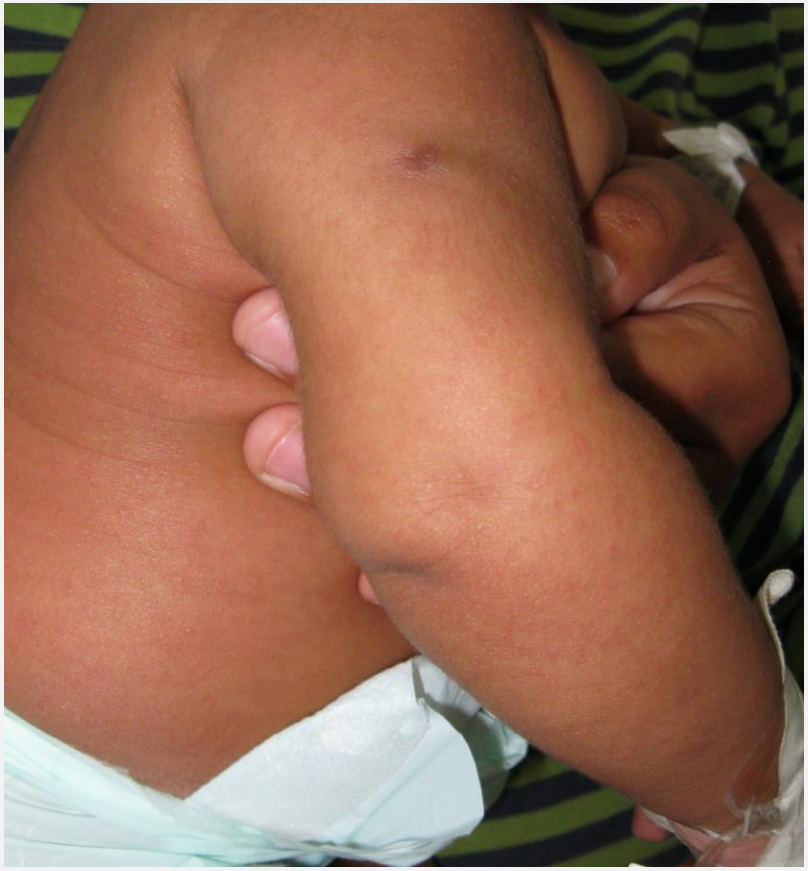
22 months of age

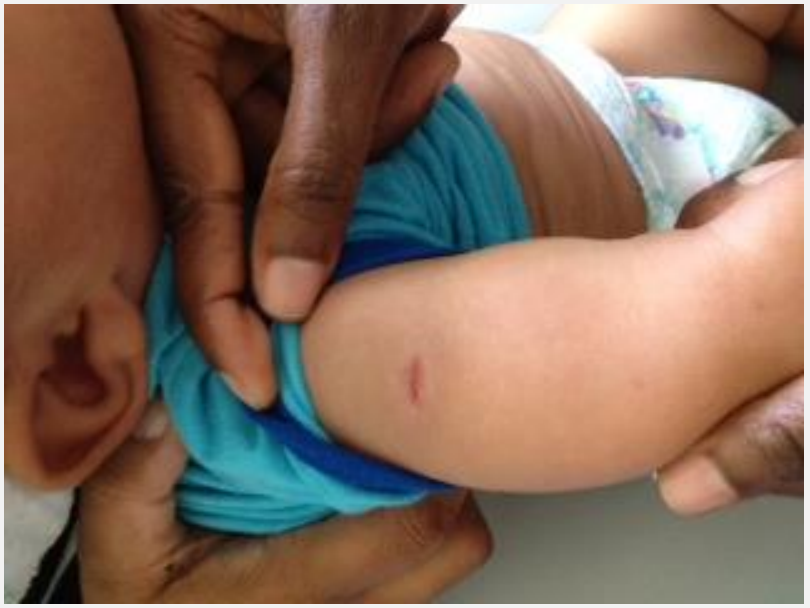
- Fever for 5 days
- Red eyes
- Lt cervical lymph node enlarged

3 days post polygam



BCG scar reactivation





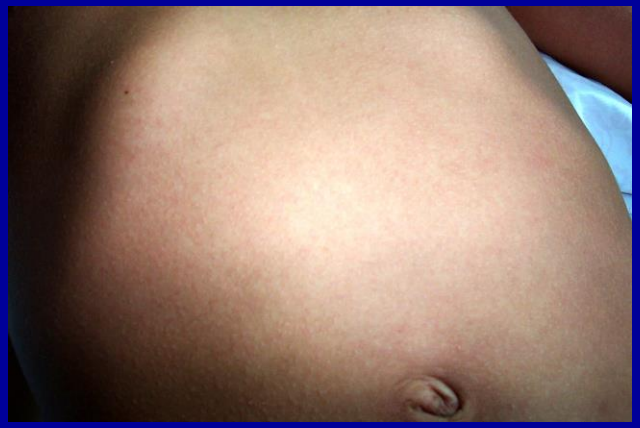
Unusual features

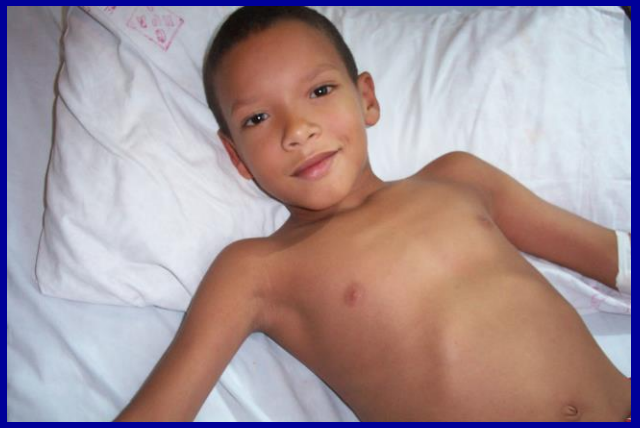
- Hepatitis
- Hydrops gall bladder
- Meningism
- Interstitial pneumonitis
- Urethritis
- Diarrhoea
- Arthritis

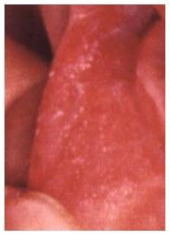
Phases

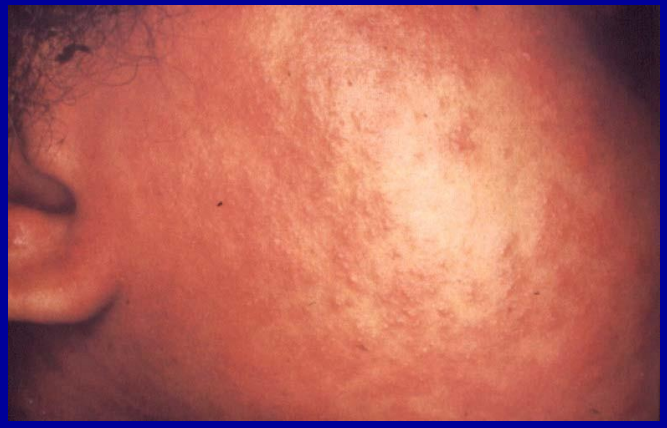
- Acute febrile (days 1-11)
  - myocarditis and pericarditis
- Subacute (days 11-21) **sudden death**
  - Persistent irritability, anorexia, conjunctival injection
  - Fever usually resolves by this stage
    - If persists, greater risk of cardiac complications
  - Thrombocytosis 1 million range
  - Desquamation of the fingertips and toes
  - Aneurysms
- Convalescence (days 21-60) - labs normalize

Differential diagnosis

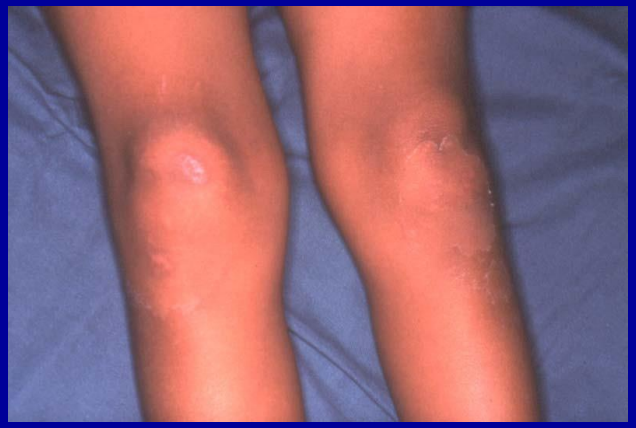


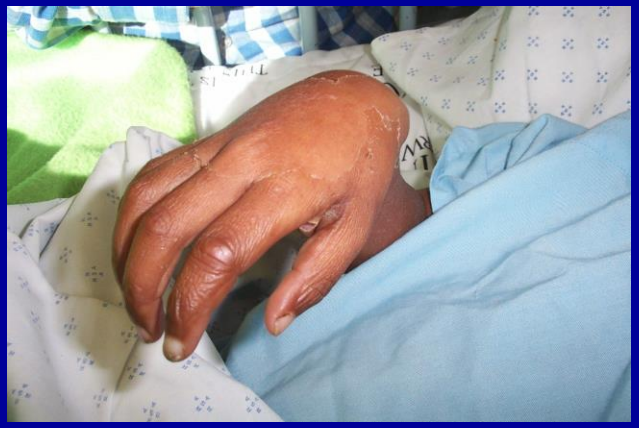


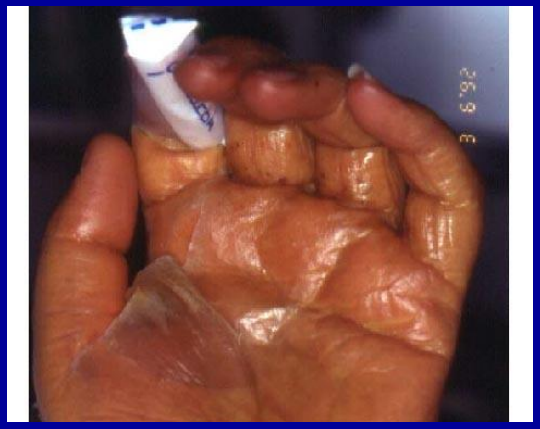




Differential







Differential

- Drug reaction
  - incl Stevens-Johnson syndrome
- Strep pharyngitis & Scarlet fever
- Toxic shock syndrome
- Measles
- Adenovirus
- Periodic syndrome
- Polyarteritis nodosa
- Hg poisoning

Treatment - effective

- IVIG 2g/kg IVI 12hrs
- Aspirin
  - 80 - 100mg/kg'day - 4 doses X 2w
  - 3 to 5mg/kg 6-8w or longer if coronary arteries

Treatment

- Terai et al (1997), prevalence of CA assessed by blinded echo at 30days and >60 days
  - Aspirin alone: CA 26% (30 days) 18% (>60 days)
  - IVIG 2mg/kg and aspirin: CA 4% (30 days) and 4% (>60 days)
- Oates-Whitehead 2003 Meta-analysis
  - RR of IVIG + aspirin versus aspirin 0.35 95% CI 0.15-0.83
  - 2g much better than 400mg

Timing of Treatment

- IVIG most effective early
- <5 days = 5 – 9 days
- <5 days - ↑ relapse?
- Expert consensus – treat within 4 days
- After day 10 – still treat if any inflammation

J Pediatr June 2003
S Shulman

IS THERE A ROLE FOR CORTICOSTEROIDS IN KAWASAKI DISEASE?

"The arrival of a good clown exercises more beneficial influence upon the health of a town than twenty asses laden with drugs." —*Thomas Sydenham (1624-1689)*

issue of The Journal, evaluates corticosteroids as an adjunct to IVIG and salicylates for primary therapy of KD.[8]

In reviewing the published experience with corticosteroids in KD, it is important to distinguish between its use as *primary therapy* and as "*rescue therapy*" for KD. Most previous

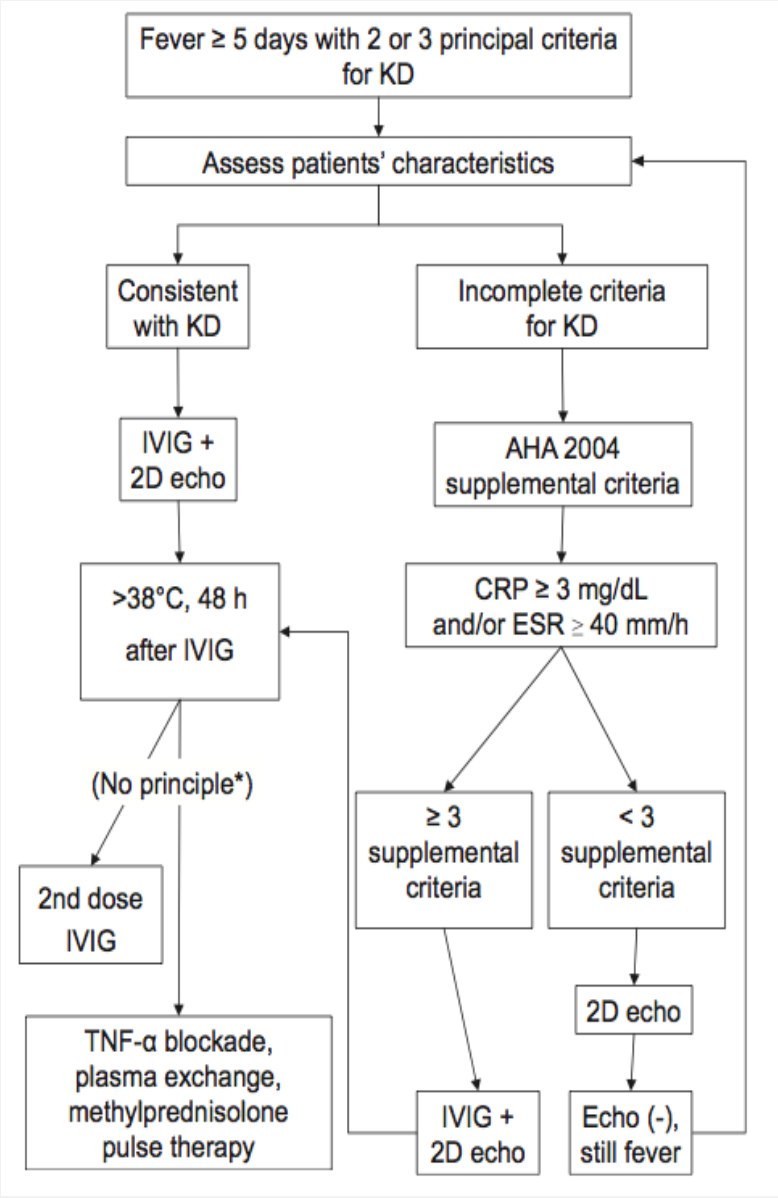
No response / Relapse

- IVIG resistance: 9 – 34%
- T >38^{o}C post 48 hours

⑩↑risk CA abnormalities

- Modalities
  - Pulsed steroids
  - TNFα blockade
  - Immunosupression
    - Cyclophosphamide
    - Cyclosporin A

Kuo et al
Pediatrics & Neonatology 2012; 53: 4-11



TNF inhibition

Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial

Adriana H Tremoulet, Sonia Jain, Preeti Jaggi, Susan Jimenez-Fernandez, Joan M Pancheri, Xiaoying Sun, John T Kanegaye, John P Kovalchin, Beth F Printz, Octavio Ramilo, Jane C Burns

TNF inhibition in acute Rx No benefit

- 196 children KD
  - 1 dose infliximab 5mg/kg plus standard therapy
  - Placebo plus standard therapy
- No difference in treatment resistance (temp >38^{o}C: 36 hours to 7 days post IVIG), both groups 11%
- No effect on CA development

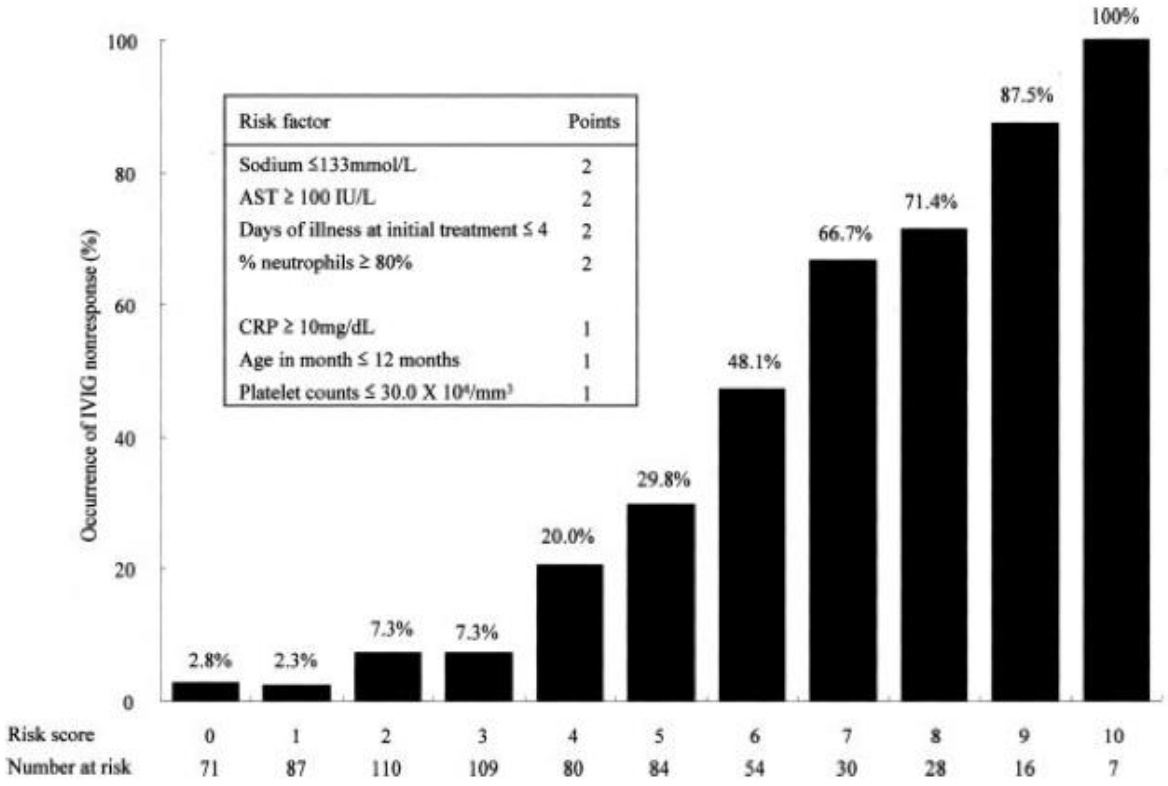
Experimental

- Ulinastatin- urinary trypsin inhibitor with anti-inflammatory properties (neutrophil targeted)
  - Not effective as monotherapy

KD shock

- In acute phase
- Hypotension & shock
- LV systolic dysfunction
- mitral regurgitation
- CA
- Resistant to Rx

Predicting IVIG non-responsiveness



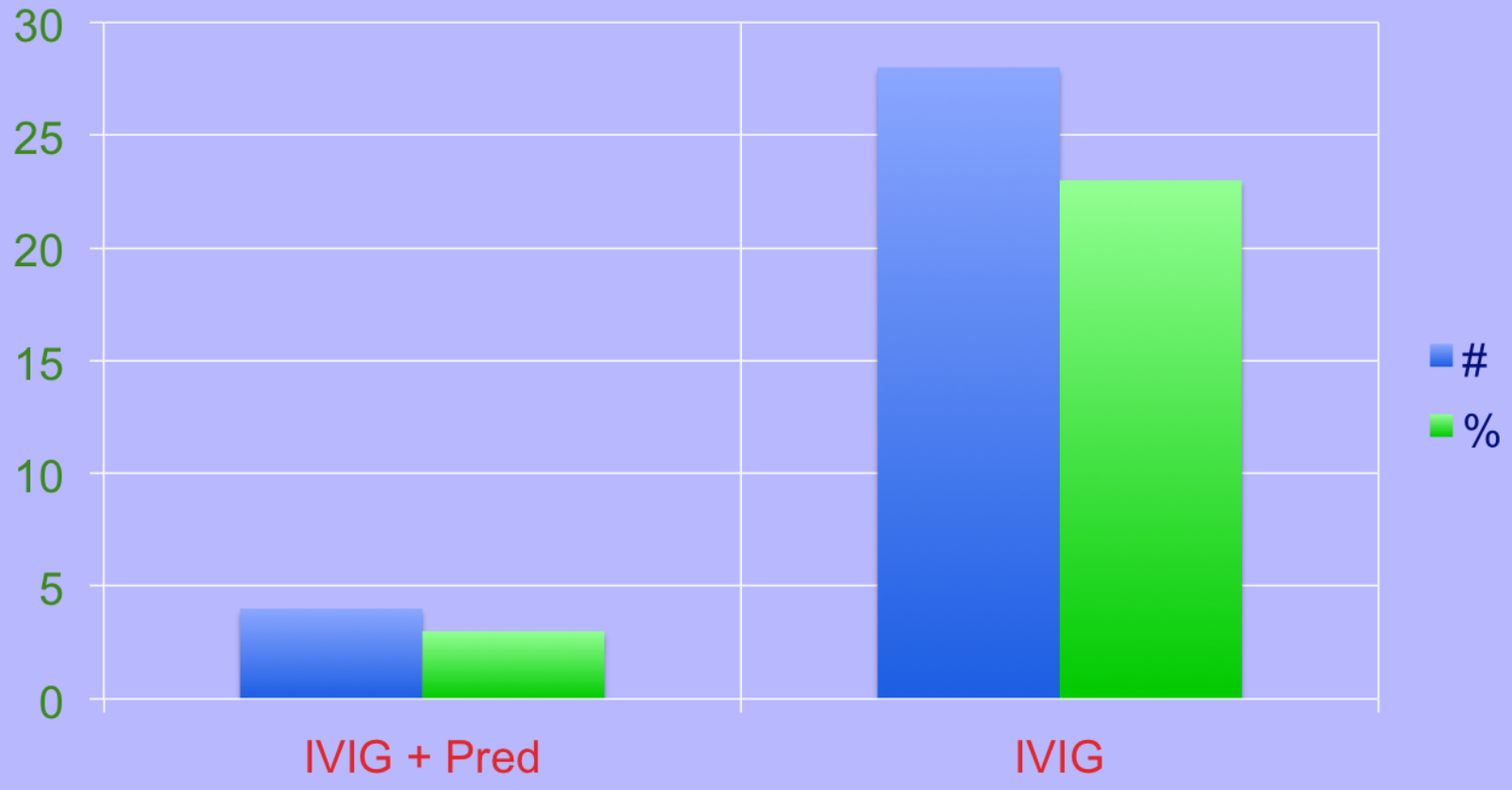
Kobayashi T Circulation 2006; 113: 2606

IVIG (+ aspirin) ± prednisolone in severe KD: randomised, open-label, blinded-endpoints trial

- IVIG 2g/kg + Aspirin (30mg/kg/day)
  - N = 125
- + Methylprednisolone 2mg/kg/day X15 days post normal CRP
  - N = 123
- Risk score ≥5
- Fever ≤9 days
- No CA abnormalities pre enrolment

Raise study: Kobayashi et al Lancet 2012; 379: 1613

CA abnormalities lower in IVIG + pred than IVIG alone



Risk difference 0·20, 95% CI 0·12–0·28, p<0·0001)

Infliximab Plus Plasma Exchange Rescue Therapy in Kawasaki Disease

Kaori Sonoda, MD[1], Masaaki Mori, MD[2], Tatsunori Hokosaki, MD[1], and Shumpei Yokota, MD[1]

Objective To evaluate infliximab (IFX) in patients with Kawasaki disease (KD) that was unresponsive to additional intravenous immunoglobulin (IVIG) therapy and subsequent rescue with supplementary plasma exchange (PE) in patients unresponsive to treatment.

Study design We studied 76 patients with KD who received IVIG therapy twice and were unresponsive to additional IVIG.

Reults Seventy were treated with IFX alone (92.1%). Six patients who were unresponsive IFX (7.9%) were further treated by PE. This resulted in disappearance of fever and other clinical symptoms, and improvement of laboratory data. There was no severe life-threatening adverse events.Twelve of the 76 cases had developed coronary artery dilatation, and 3 had coronary artery aneurysm within 1 month of disease onset. At the end of follow-up, in all cases, coronary artery lesions were suppressed or reversed.

Conclusions Treatment of intractable KD with sequential IVIG, IFX, and PE treatments in a step-wise protocol was effective. *(J Pediatr 2014;164:1128-32).*

Long term issues

- Continued inflammation in CA’s
- Role for statins?

KS in adults

- 57 cases 18 – 30 years of age
- 2 cases & literature review
- Seve et al Sem Arthritis Rheumatol 2005: 34: 785-92

KS & HIV

ELSEVIER

www.elsevierhealth.com/journals/jinf

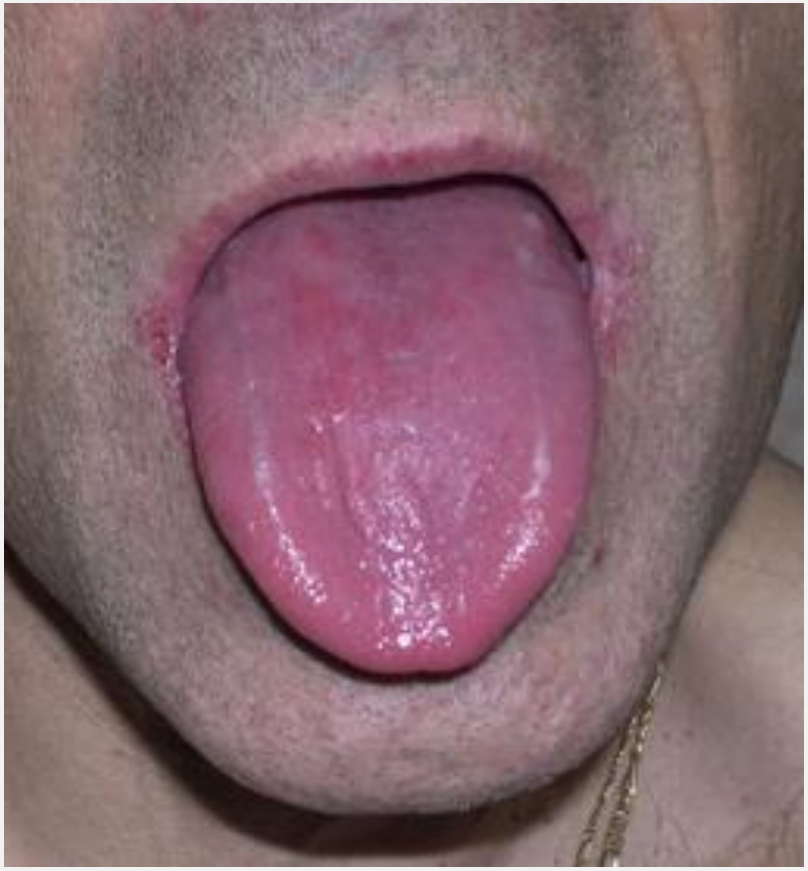
REVIEW

Kawasaki-like syndromes in HIV-infected adults

K. Stankovic [a,*], P. Miailhes [b], D. Bessis [c], T. Ferry [d],
C. Broussolle [a], P. Sève [a]

J Infection 2007; 55: 48

Adult KD



- 20 cases
- High viral loads
- Low CD4
- Hepatitis virus co-infection

Acknowledgements

- Helena Rabie - TCH
- Lisa Frigati – TCH
- Kate Carkeek - TCH