Medium and large vessel vasculitides

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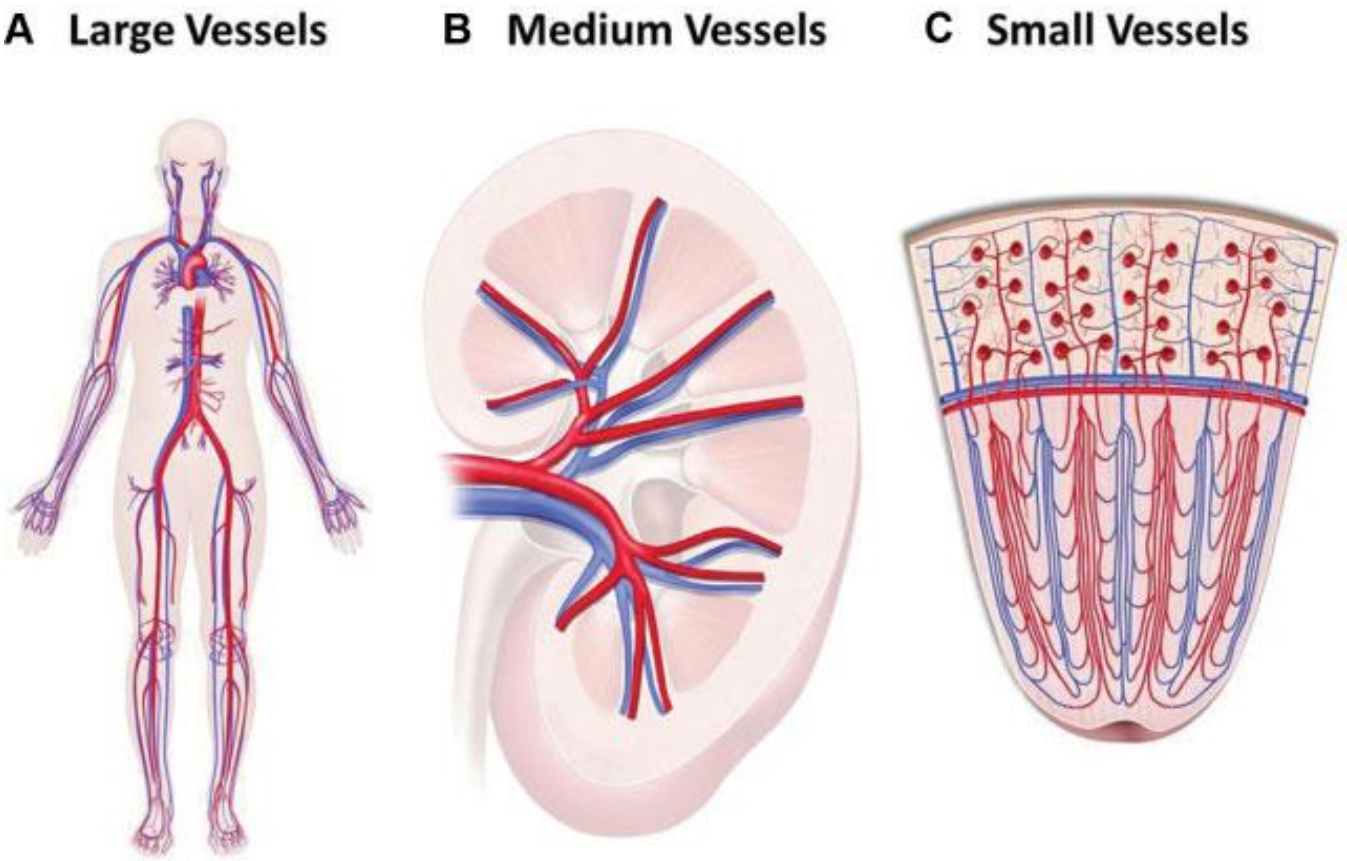
Vessel size



Aorta and branches

- Renal
- Hepatic
- Coronary
- Mesenteric

- Venules
- Capillaries
- Arterioles

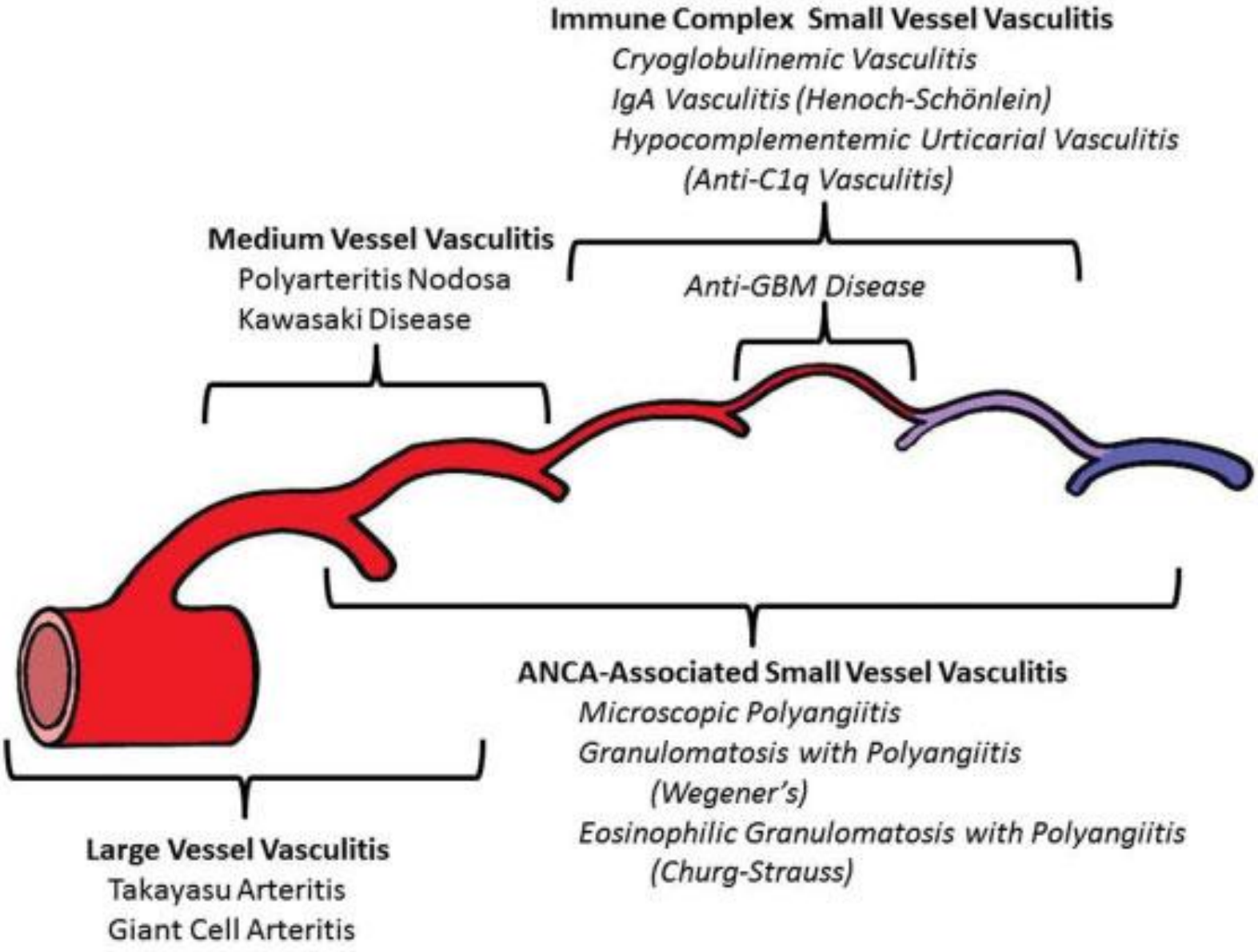

Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis
(Anti-C1q Vasculitis)
Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease
Anti-GBM Disease
ANCA-Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis
(Wegener's)
Eosinophilic Granulomatosis with Polyangiitis
(Churg-Strauss)
Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

Table 2. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides

- **Large vessel vasculitis (LVV)**
  - Takayasu arteritis (TAK)
  - Giant cell arteritis (GCA)
- **Medium vessel vasculitis (MVV)**
  - Polyarteritis nodosa (PAN)
  - Kawasaki disease (KD)
- **Small vessel vasculitis (SVV)**
  - Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
    - Microscopic polyangiitis (MPA)
    - Granulomatosis with polyangiitis (Wegener's) (GPA)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
    - Anti–glomerular basement membrane (anti-GBM) disease
    - Cryoglobulinemic vasculitis (CV)
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
- **Variable vessel vasculitis (VVV)**
  - Behçet's disease (BD)
  - Cogan's syndrome (CS)
- **Single-organ vasculitis (SOV)**
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- **Vasculitis associated with systemic disease**
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- **Vasculitis associated with probable etiology**
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Types of Vasculitides

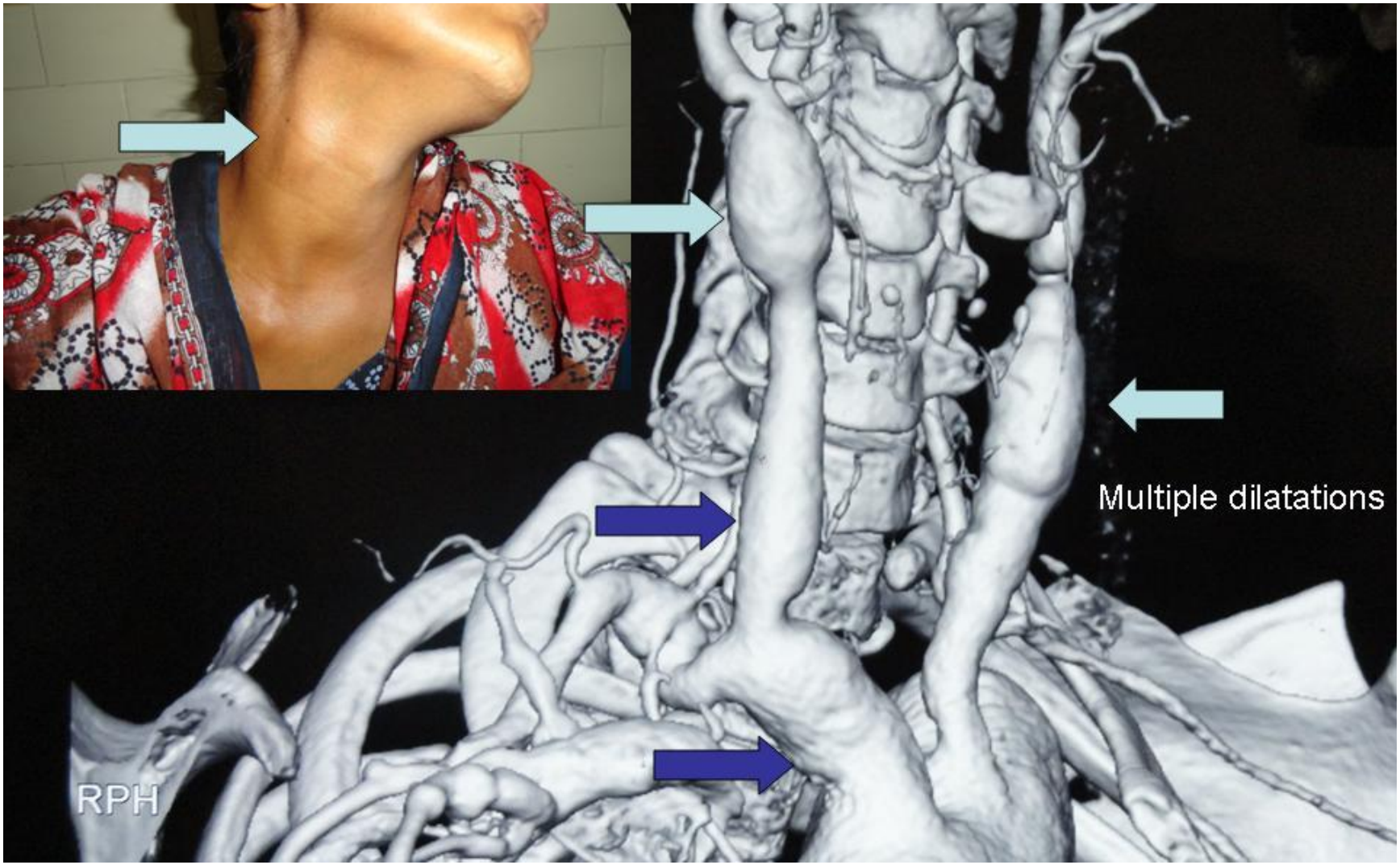
Table 30–2

EULAR/PReS classification of childhood vasculitis

I. Predominantly large vessel vasculitis
   Takayasu arteritis
II. Predominantly medium-sized vessel vasculitis
   Childhood polyarteritis nodosa
   Cutaneous polyarteritis
   Kawasaki disease
III. Predominantly small-sized vessel vasculitis
   A. Granulomatous
      Wegener granulomatosis
      Churg-Strauss syndrome
   B. Nongranulomatous
      Microscopic polyangiitis
      Henoch-Schönlein purpura
      Isolated cutaneous leucocytoclastic vasculitis
      Hypocomplementic urticarial vasculitis
IV. Other vasculitides
   Behçet disease
   Vasculitis secondary to infection (including hepatitis B-associated polyarteritis nodosa), malignancies, and drugs(including hypersensitivity vasculitis)
   Vasculitis associated with connective tissue diseases
   Isolated vasculitis of the central nervous system
   Cogan syndrome
   Unclassified

From Ozen et al.[5]

Takayasu disease



http://apvascular.blogspot.com.br/

Takayasu disease

- Takayasu arteritis (TA) is a rare granulomatous vasculitis involving the aorta and its major branches.
- TA is particularly rare in prepubertal children.
- EULAR/PRINTO/PRES criteria of TA in children:

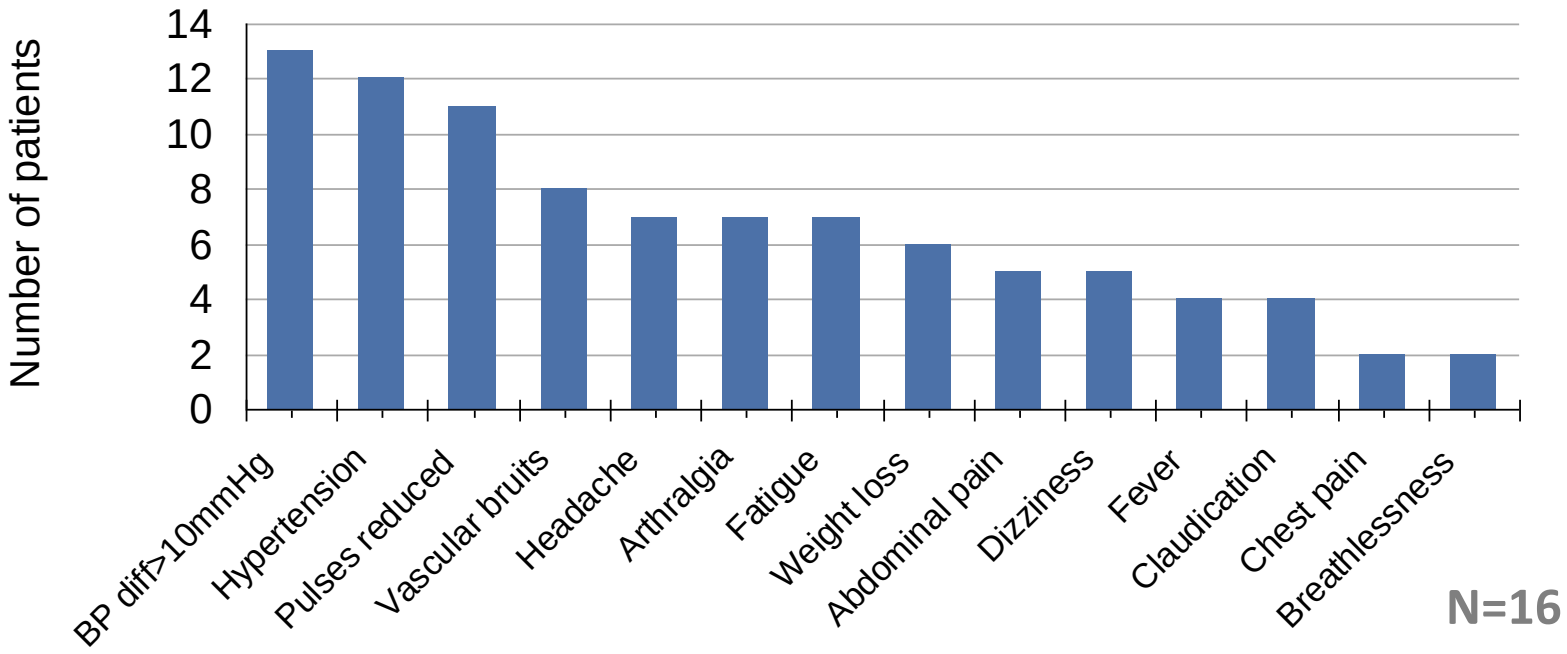
  Angiographic abnormalities of the aorta or its main branches and pulmonary arteries (aneurysm/dilatation, narrowing, occlusion, or arterial wall thickening not due to fibromuscular dysplasia)

  At least one of the following five features:

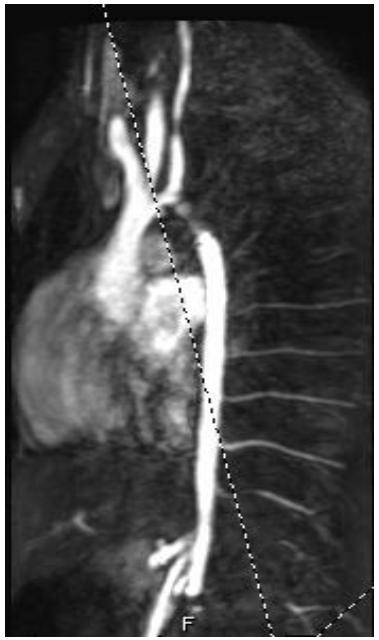
  - Pulse deficit (lost/decreased/unequal peripheral artery pulse[s]) and/or claudication induced by activity
  - Systolic blood pressure difference >10 mmHg between any limb
  - Bruits or thrills over the aorta and/or its major branches
  - Hypertension
  - Elevated acute-phase reactant

Clinical presentation at diagnosis of pediatric TA



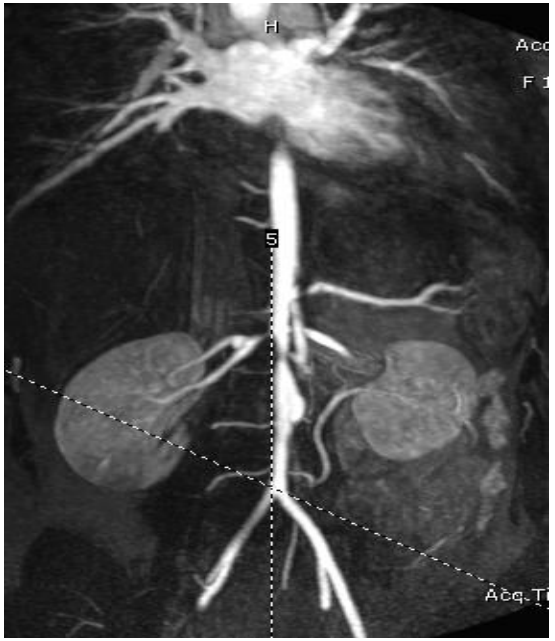
Bocacci S, Borzutzky A, et al. PRES Congress 2010.

Vascular involvement



Stenosis

Stenosis 88%
Dilatation 19%
Occlusion 6%
Aneurysm 6%



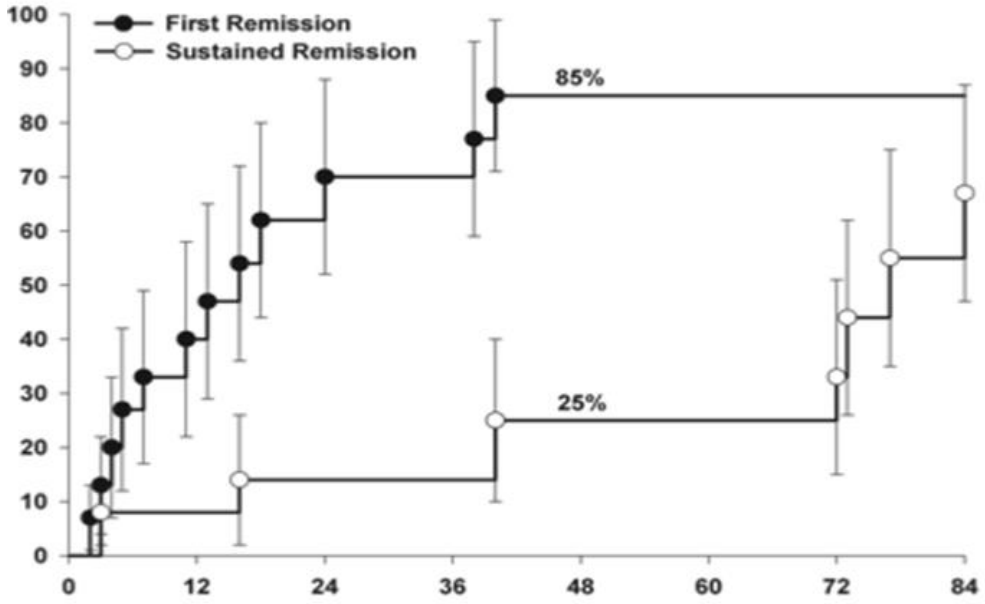
Aneurysm

Renal arteries are the most common site of involvement, followed by subclavian artery, thoracic aorta and abdominal aorta.
No pulmonary or coronary lesions.

Bocacci S, Borzutzky A, et al. PRES Congress 2010.

Treatment of Takayasu's arteritis

- Glucocorticoids
- DMARDS (all of them)
- Biologics: antiTNF + anti IL-6
- Vascular surgery is often needed.



Bocacci S, Borzutzky A, et al. PRES Congress 2010.

Childhood polyarteritis nodosa

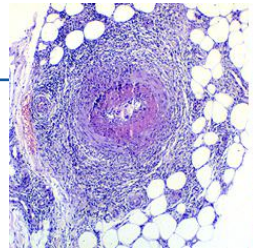
- Systemic necrotising vasculitis with aneurysm formation affecting small- and/or medium-sized arteries.
- Presents with systemic symptoms (eg, fever, malaise, and weight loss) and signs of multisystem involvement.
- Hepatits B is sometimes involved in the etiology of classic PAN

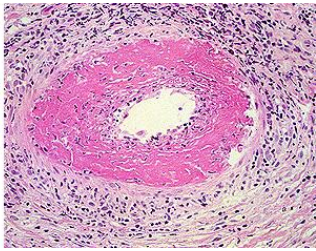
Table I. General characteristics of the presented juvenile PAN patients

Characteristics	Subtypes				Total
	Cutaneous (n = 33)	Classic (n = 5)	Micr. PAN (n = 9)	Systemic (n = 63)	(n: 110)
Age (y), mean ± SD	9.24 ± 3.54	7.45 ± 4.88	10.89 ± 2.76	8.81 ± 3.55	9.05 ± 3.57
Gender (M:F)	15:18	3:2	3:6	33:30	54:56
Time to remission (mo), median (range)	5 (1-84) (n = 19)	6 (3-12) (n = 3)	12 (6-24) (n = 3)	5 (0.5-96) (n = 34)	6 (0.5 – 96) (n: 59)
Follow-up (mo), median, (range)	48 (12-60) (n = 9)	36 (1-96) (n = 5)	60 (3-72) (n = 3)	72 (3-144) (n = 25)	48 (1-144) (n: 42)

Ozen S, et al. J Pediatr 2004

EULAR/PRINTO/PRES classification criteria for childhood polyarteritis nodosa





- Evidence of necrotising vasculitis in medium or small sized arteries

OR

- Angiography showing aneurysm, stenoses or occlusion of a medium or small sized artery, not due to fibromuscular dysplasia, or other non-inflammatory causes. Conventional angiography is the preferred imaging modality.

AND

- At least one of the following five systemic features:
  - Skin involvement (livedo reticularis, tender subcutaneous nodules, superficial or deep skin infarctions)
  - Myalgia or muscle tenderness
  - Hypertension
  - Peripheral neuropathy (sensory peripheral neuropathy or motor mononeuritis multiplex)
  - Renal involvement (proteinuria, hematuria, or red blood cell casts, or glomerular filtration rate of less than 50 percent the normal value for age)

Clinical manifestations

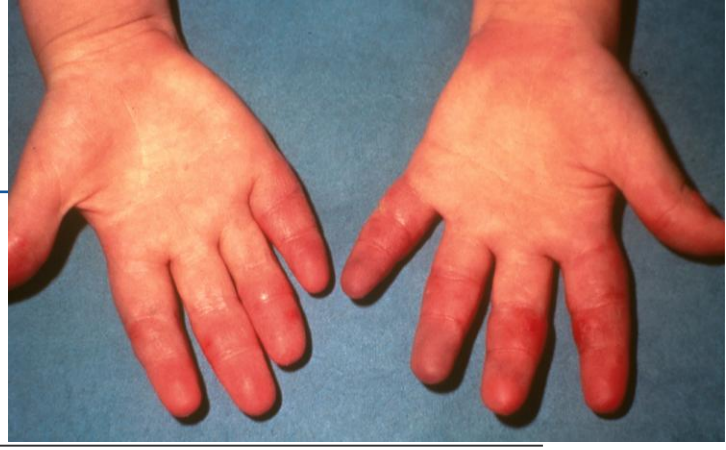


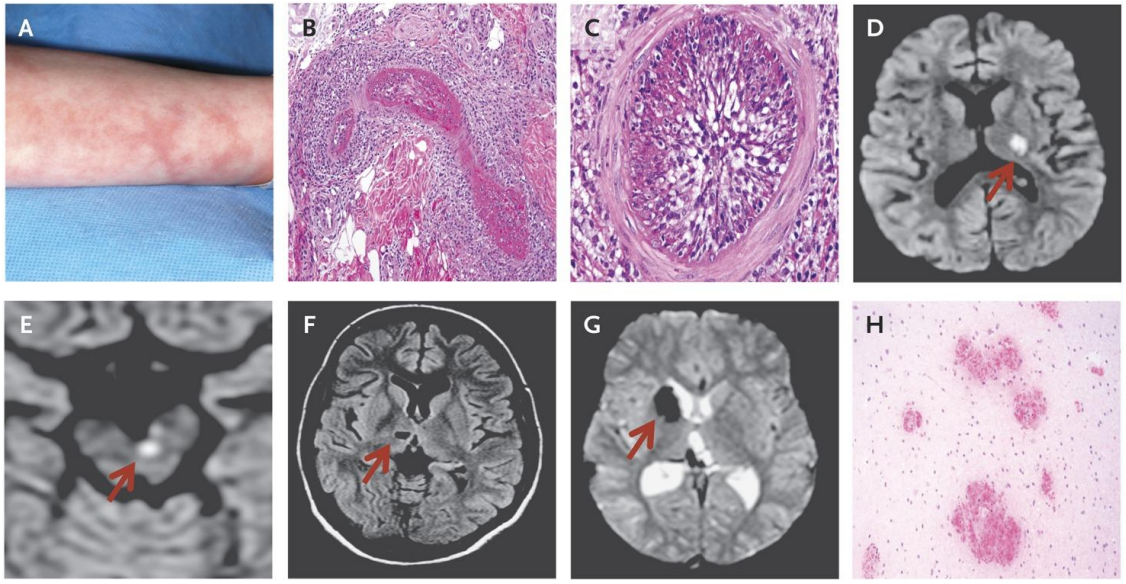
Table II. Presenting features

	Subtypes									
	Cutaneous (n = 33)		Classic (n = 5)		Micr. PAN (n = 9)		Systemic (n = 63)		Total (n = 110)	
Presenting symptoms	**n**	**(%)**	**n**	**(%)**	**n**	**%**	**n**	**(%)**	**n**	**(%)**
Constitutional symptoms	21	(63.6)	5	(100)	9	(100.0)	60	(95.2)	95	(86.4)
Fever	14	(42.4)	2	(40)	4	(44.4)	36	(57.1)	56	(50.9)
Fatigue	3	(9.1)	—	—	1	(11.1)	7	(11.1)	13	(11.8)
Weight loss	5	(15.2)	1	(20	—	—	11	(17.5)	17	(15.4)
Hypertension	—	—	2	(40)	1	(11.1)	13	(20.6)	16	(14.5)
Skin lesions	32	(97.0)	2	(40)	3	(33.3)	45	(71.4)	82	(74.5)
Articular	13	(39.4)	1	(20)	2	(22.2)	25	(39.7)	41	(37.3)
Myalgia	5	(15.2)	2	(40)	1	(11.1)	29	(46.0)	37	(33.6)
Gastrointestinal symptoms	—	—	2	(40)	2	(22.2)	15	(23.8)	19	(17.3)
Pulmonary symptoms	—	—	—	—	5	(55.6)	1	(1.6)	6	(5.5)
Cardiac symptoms	—	—	—	—	—	—	4	(6.3)	4	(3.6)
Renal symptoms	—	—	1	(20)	6	(66.7)	6	(1.6)	13	(11.8)
Nervous system symptoms	1	(3.0)	1	(20)	—	—	14	(22.2)	16	(14.5)
Testicular pain	—	—	—	—	—	—	4	(6.3)	4	(3.6)

Ozen S, et al. J Pediatr 2004

ACR Image Bank

ADA2 deficiency (*CECR1* loss of function mutations)



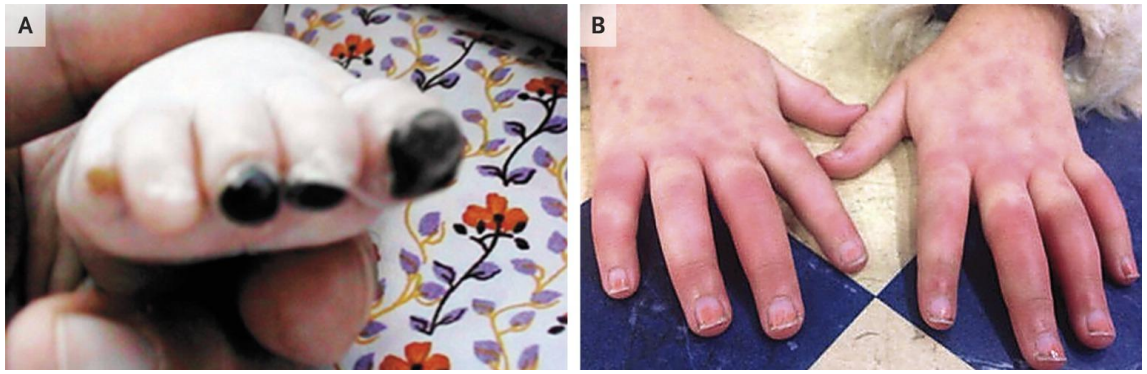


Table 1. Clinical and Laboratory Manifestations in Patients with Deficiency of Adenosine Deaminase 2.

Clinical Manifestation	Patients *no./total no.*
Fever	9/9
Ischemic stroke	8/9
Hemorrhagic stroke	3/9
Ophthalmologic involvement*	5/9
Livedo racemosa	8/9
Hepatosplenomegaly	6/7
Documented vasculitis†	4/9
Polyarteritis nodosa	2/9
Antinuclear antibody	3/9
Antineutrophil cytoplasmic antibody	0/9
Low serum IgM	5/5

* The ophthalmologic manifestations included central retinal artery occlusion in one patient, optic nerve atrophy in one, diplopia with irregular enhancement of the medial rectus muscle (as observed on magnetic resonance imaging) in one, third cranial nerve palsy in one, and strabismus in two. Patients could have more than one ophthalmologic disorder.
† The diagnosis of vasculitis included polyarteritis nodosa.

Zhou Q et al. N Engl J Med 2014
Navon Elkan P et al. N Engl J Med 2014

Cutaneous polyarteritis

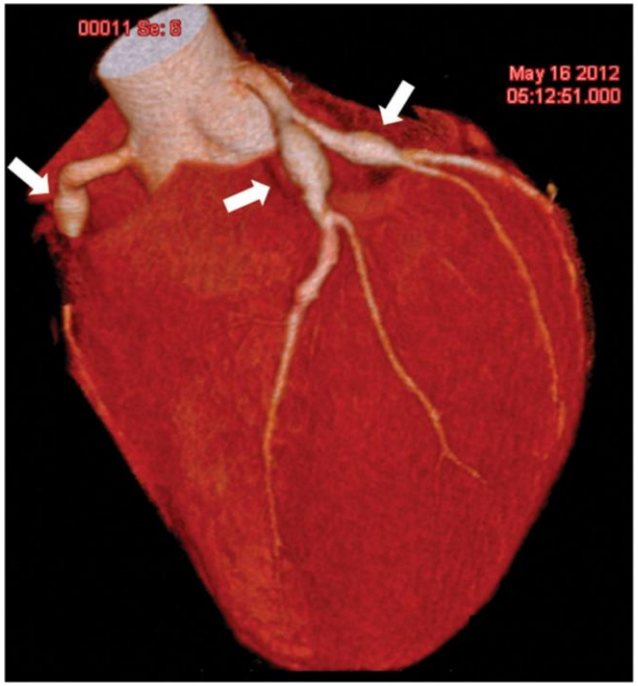
- Cutaneous polyarteritis nodosa is a more limited disorder than systemic polyarteritis nodosa
- It typically affects only the skin and musculoskeletal system.
- Subcutaneous nodular, painful, nonpurpuric lesions with or without livedo reticularis are present without evidence of systemic involvement (except for myalgia, arthralgia, and nonerosive arthritis).
- There is often a history of a preceding streptococcal infection. As a result, there may be serological or microbiological evidence of streptococcal infection.

Treatment of PAN

- Corticosteroids
- Immunosuppression: cyclophosphamide is usually used in systemic PAN
- Hep B antivirals if Hep B is diagnosed.
- Penicillin prophylaxis (and sometimes steroids) in cutaneous PAN.

Kawasaki disease

- KD is the first cause of acquired heart disease in developed countries.
- Acute self-limited febrile disease of unknown etiology.
- Medium vessel vasculitis with predilection for coronary arteries.



The disease begins…

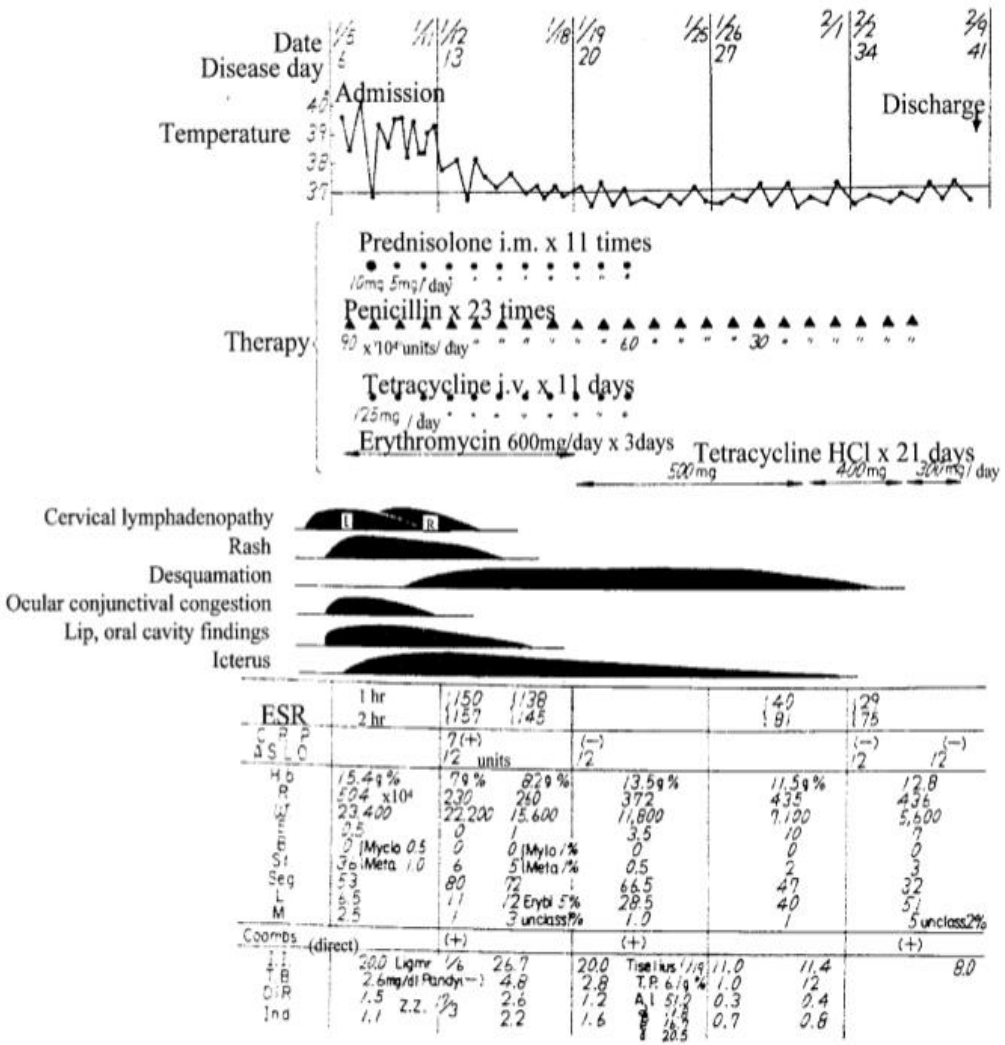
- Dr. Tomisaku Kawasaki saw his first case of KD in 1961 as a pediatrician at the Red Cross Hospital in Tokyo, Japan.
- The patient got better and was discharged with "diagnosis unknown".
- Only after he saw the second case a year later he recognized this could be a new disease.
- He reported the first 7 cases as "non-scarlet fever syndrome with desquamation" at a local pediatric meeting.
- At the urging of his boss he published the first 50 cases in an allergy journal to avoid conflict with the pediatric establishment.

Burns JC, et al. Pediatrics. 2000.

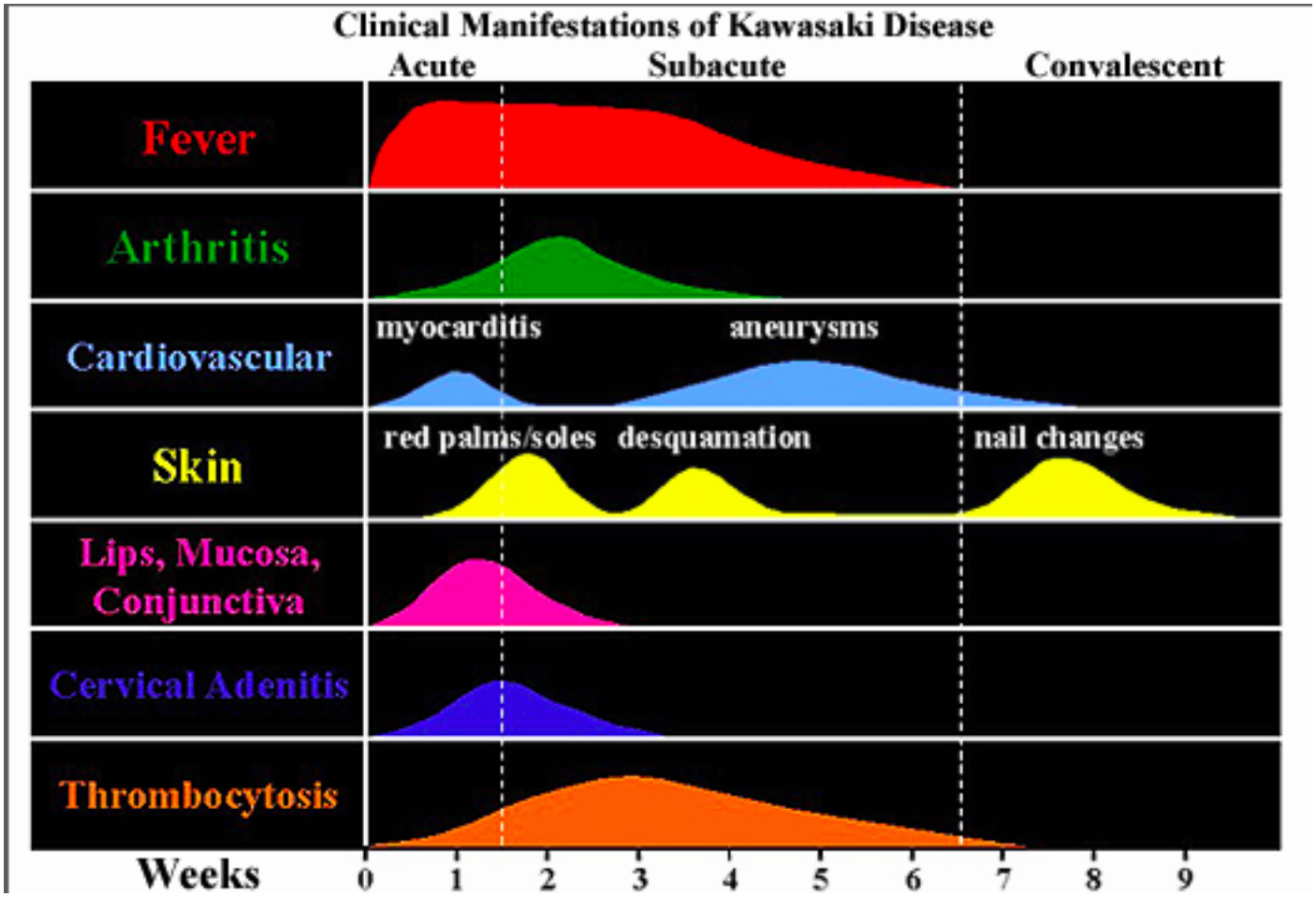
The heart of the story

- In 1965, Dr Noboru Tanaka, Chief of Pathology of the Red Cross Hospital, performed an autopsy of one of the patients of Dr. Kawasaki who died and found thrombosis of a coronary artery.
- Dr. Takajiro Yamamoto, Chief of Pediatrics at St. Luke Hospital in Tokyo was the first to find cardiac complications in live patients with KD.
- In 1968 he reported that 48% of KD patients had abnormalities on EKG.

First case of KD

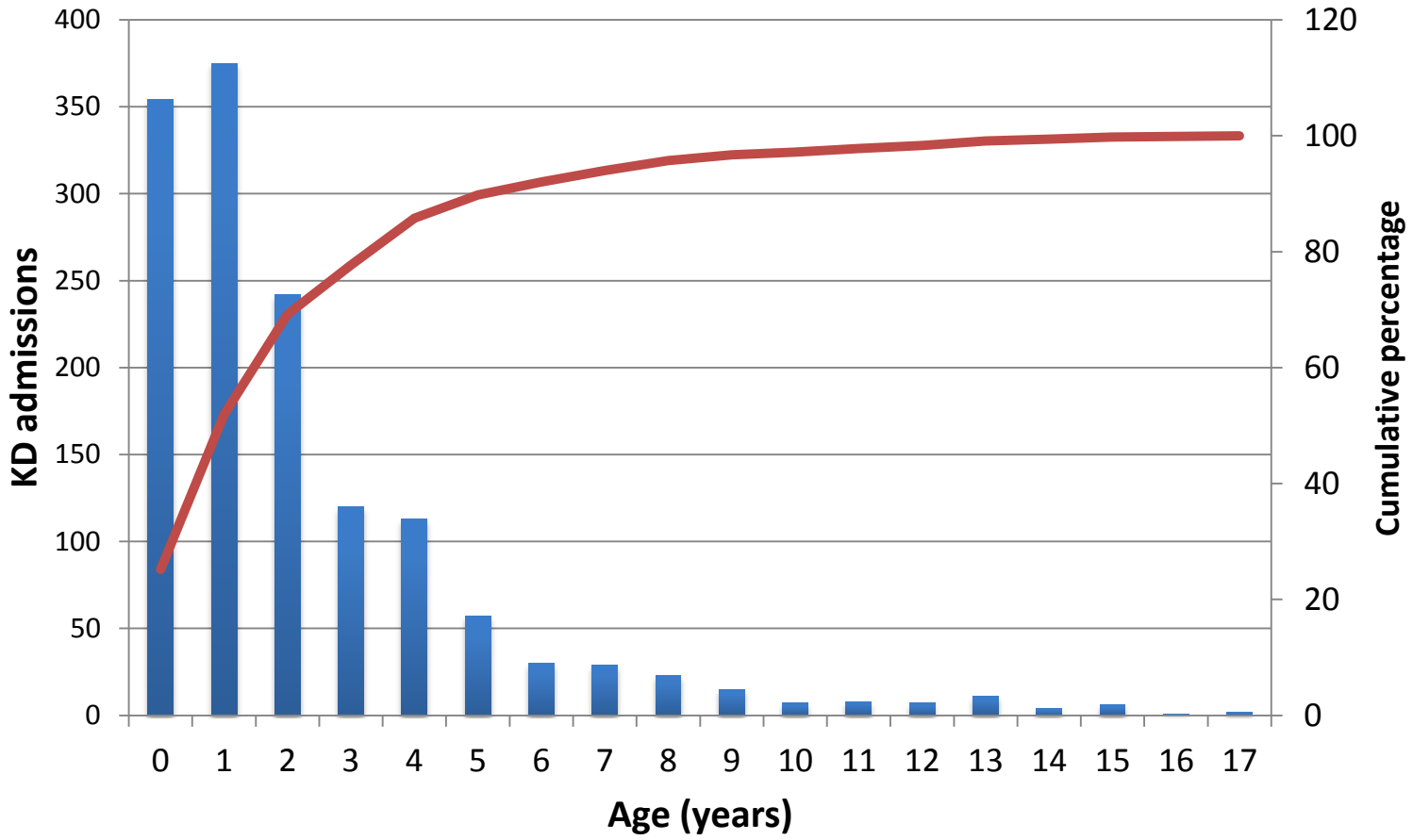


Burns JC, et al. Pediatrics. 2000.

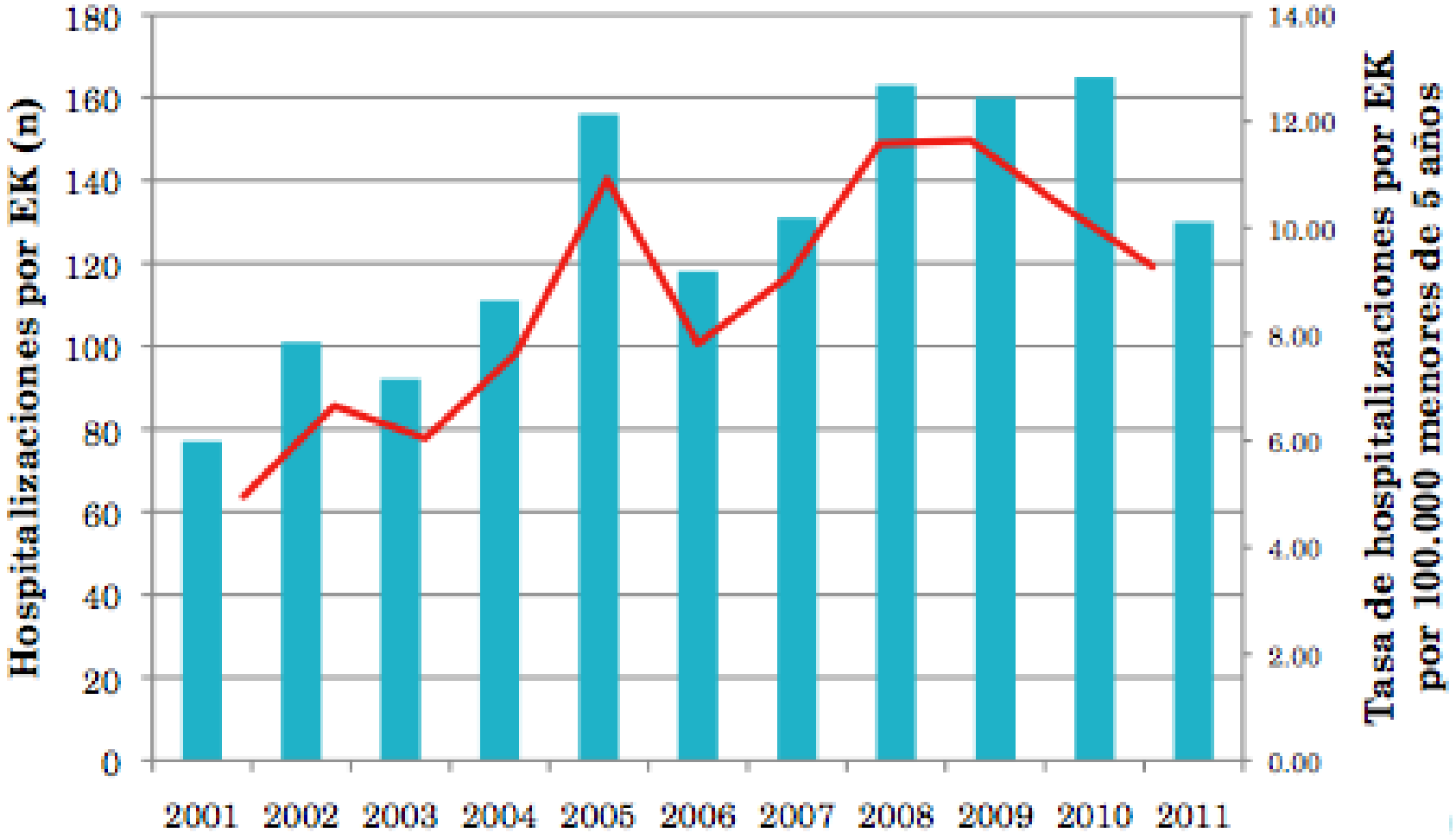

Clinical Manifestations of Kawasaki Disease
Acute
Subacute
Convalescent
Fever
Arthritis
Cardiovascular
myocarditis
aneurysms
Skin
red palms/soles
desquamation
nail changes
Lips, Mucosa, Conjunctiva
Cervical Adenitis
Thrombocytosis
Weeks
0
1
2
3
4
5
6
7
8
9

It spreads to the world...

Age distribution of KD in Chile, 2001-2011



Increasing rates of KD in many countries: increased awareness or true increase in caseloads?



Classical Clinical Manifestations

- The diagnosis of KD is clinical as there is no specific and sensitive lab test.

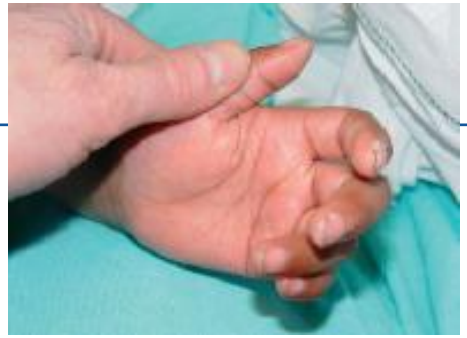
TABLE 1. Clinical and Laboratory Features of Kawasaki Disease

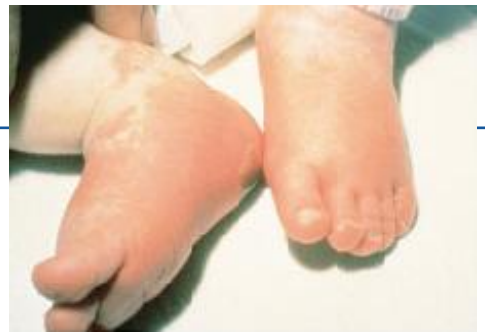
Epidemiological case definition (classic clinical criteria)*
- Fever persisting at least 5 d†
- Presence of at least 4 principal features:
  - Changes in extremities
    - Acute: Erythema of palms, soles; edema of hands, feet
    - Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
  - Polymorphous exanthem
  - Bilateral bulbar conjunctival injection without exudate
  - Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
  - Cervical lymphadenopathy (>1.5-cm diameter), usually unilateral
- Exclusion of other diseases with similar findings‡

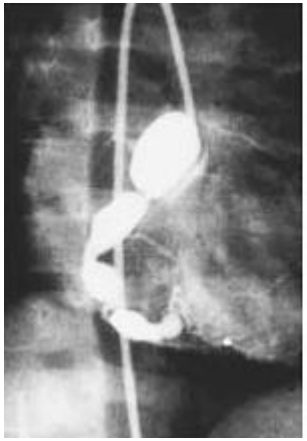
- Other features include arthritis, abdominal pain, diarrhea, BCGitis, irritability.
- All these findings are often not present at the same time, and there is no typical order of appearance.

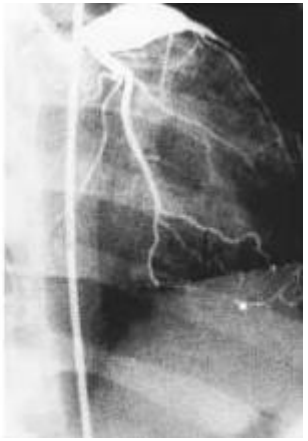
Labs and imaging

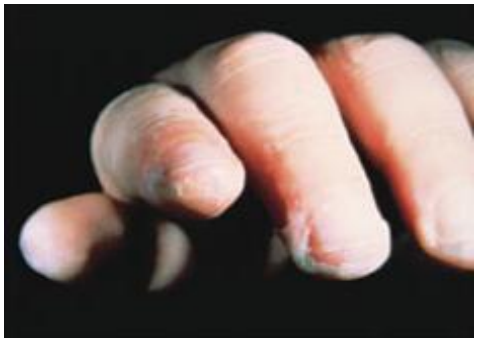
- Systemic inflammation
  - ESR >40 mm/hr
  - CRP>3 mg/dL
- Echocardiogram: up to 30-40% have been reported to have abnormalities in coronary arteries at diagnosis.
  - Hyperrefringency
  - Coronary dilatation
  - Lack of distal tapering
  - Aneurysms
  - Thrombosis

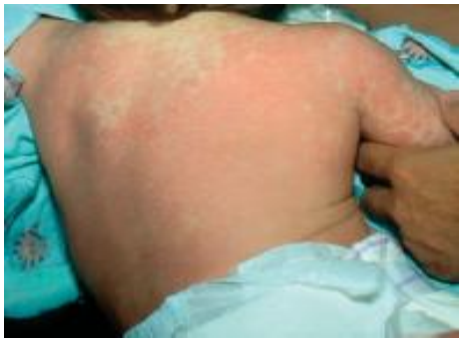












Incomplete KD

- Do not fulfill **classic criteria.**
- Diagnosis is frequently based on an abnormal echo.
- However, a normal echocardiogram does not rule out KD.
- Some series have shown a higher incidence of coronary aneurysms in incomplete vs. Complete KD.
- 40% of patients with coronary aneurysms have incomplete KD.
- Children < 1 year of age frequently have incomplete KD.

◇ Supplemental laboratory criteria include albumin ≤3 g/dL, anemia for age, elevation of alanine aminotransferase, platelets after seven days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine ≥10 white blood cells/high power field.

Treatment of KD

- Kawasaki found out early that antibiotics, steroids and aspirin did not have a dramatic effect on the course of KD.
- In 1981 after IVIG was published to be successful in ITP, 2 Japanese physicians tried it in KD.
- These and other studies demonstrated that IVIG and aspirin reduce the incidence of coronary aneurysms from 20% to 3-5%.
- Standard first-line treatment nowadays is IVIG 2 g/kg (+ aspirin 50-80 mg/kg/day) given in the first 10 days.
- In severe KD or cases predicted to be IVIG resistant some studies suggest corticosteroids be added.

Refractory KD

- 10-20% of KD patients fail initial treatment with one dose of IVIG.
- Failure is defined by persistence or recurrence of fever within 36-48 post IVIG
- IVIG resistance leads to longer hospitalization and higher risk of aneurysms.
- It is hard to study because KD is self-limited and retreats often occurr near date of spontaneous resolution (10-15 days).