ADULT-ONSET STILL'S DISEASE
Diagnosis & Treatment

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Disclosure Facts

ACCME Credit hours	1
Sponsor (Support)	Pearson Frontiers in Rheum
Conflicts Stock/own	0
Investigator	none
Consultant	Abbvie, Amgen, Novartis, BMS, UCB
Coverage RA, SLE, SpA, PsA	Abatacept
TNF inhibitors	Lupus Drugs
IL-6 inhibitors	Rituximab
JAK inhibitors	Drug Safety

This talk represents my views of the above, based on the evidence presented from medical literature and scientific abstracts on Stills Dz Corporate relationships and conflicts should NOT influence lecture content. Send your critique of the fair balance of this presentation/content to jackcush@rheumnow.com

Febrile Syndromes Defined

- Autoinflammatory syndromes: characterized by attacks of inflammation unrelated to infection, autoantibodies or Ag-specific T cells. Typically monogenic disorders seen in infants and children
  - Disorders of innate immunity & inflammasome activity
- Periodic Fevers: subset of autoinflammatory syndromes
  - Hereditary/monogenic or acquired
  - Recurrent fever, inflammatory Sxs, Disease-free intervals
- FUO: fever >101^{o}F for more than 2-3 wks, documented on several occasions after extensive evaluation (hospital x 1 week?)
- Still's disease: AKA systemic JIA, autoinflammatory syndrome affecting children & young adults

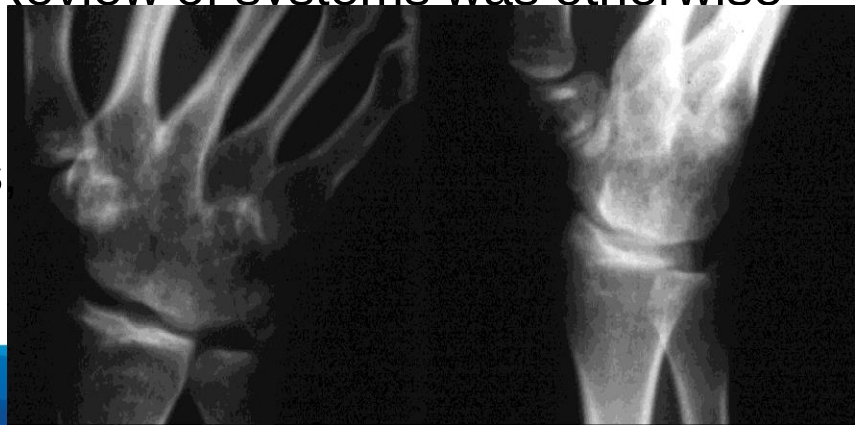
TR, 23 yr. old WF was admitted to the hospital with a 5 day hx of fever, rash, and a sore throat. She c/o daily or twice daily fever up to 104ºF. Fever was always preceded by chills

Erythematous rash over the trunk, neck and extremities. The patient also c/o diffuse myalgias, wrist pain, and 3 days of abdominal pain and diarrhea.

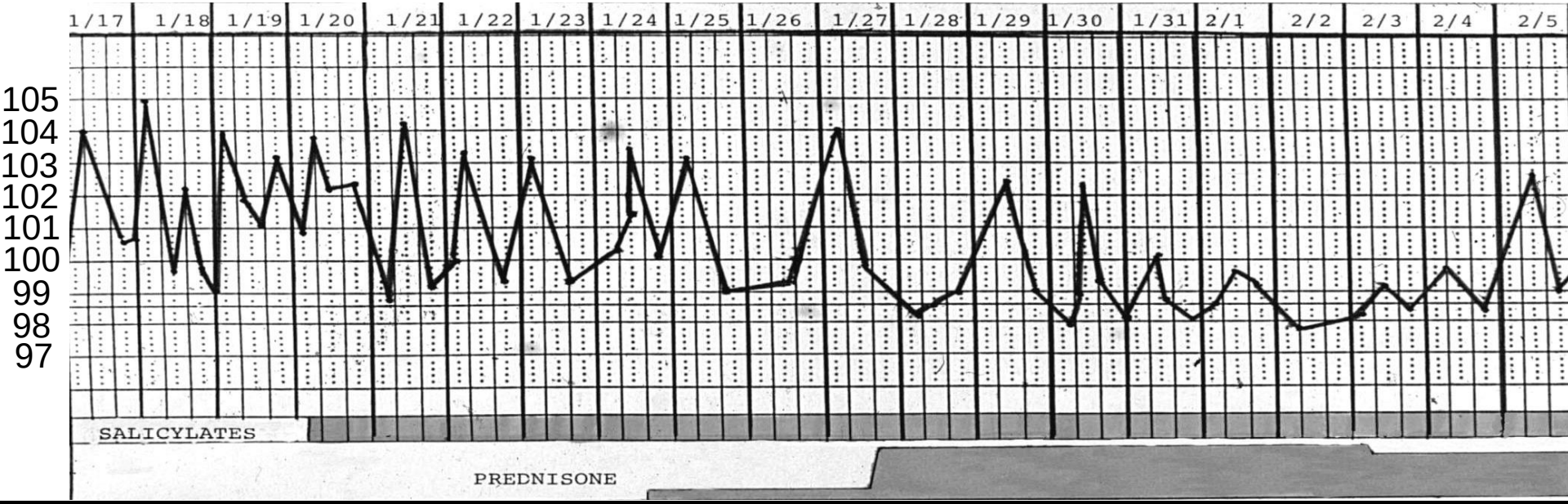
One week earlier she was prescribed penicillin for her sore throat, but developed a rash and discontinued the medication.

PMHx: rheumatic fever at age 9, numerous hospitializations between 9-12 yrs for ARF, arthritis, FUO and hepatitis. Review of systems was otherwise negative.

Hospital course was notable for lymphadenopathy, splenomegaly, pleuritis pericarditis, WBC= 40K, and increased Liver enzymes



Fever Pattern : TR



Rash, myalgia, ST, abd pain			Arthralgia, Spleno-megaly, Vag bleed						Blurred vision			TMJ/neck pain lymphadenopathy			Pleural, pericardial effusions					
ESR	99		90	111				120			89			92		115		65		
Wbc	20	18.6	13.2	19.2				28.0			40.3	23.9		28.3		28		28.6		
Hct	34	36.5	27.4	30.2				33.1			30.9	28		33		30.9		31.5		

Which is true?

- I can diagnose Adult-onset Still's disease based on:
  1. Undiagnosed Fever + Systemic Dz
  2. Serologies
  3. Extreme elevation of WBC + ESR (CRP)
  4. High Ferritin levels
  5. None of the above

Do I Meet Criteria for Still's Disease?

Begin by confirming the diagnosis of Still's disease using our calculator.

Calculate my Risk

Still's Disease Diagnosis Calculator

- [ ] Age less than 16 years
- [ ] Daily or nightly fever (not measured)
- [ ] Daily/nightly fevers always above 102°F (>39°C)
- [ ] Joint pains (arthralgia)
- [ ] Many swollen joints (polyarthritis)
- [ ] Cervical ankyloses (neck fusion)*
- [ ] Rash (any)
- [ ] Intermittent faint red/pink rash (arms, legs, trunk, neck
- [ ] Pleuritis or pleural effusion
- [ ] Generalized lymphadenopathy (many swollen lymph nodes)
- [ ] Hepatomegaly (enlarged liver)
- [ ] Low albumin < 3.0 (hypoalbuminemia)
- [x] Elevated "sed rate" (ESR) > 40 mm/hr
- [x] Elevated WBC with >80% neutrophils (PMNs)
- [x] Age less than 35 years
- [x] Daily/nightly fever (between 100-102°F)
- [ ] Muscle pains (myalgia)
- [x] Swollen painful joints
- [x] Carpal ankyloses (wrist fusion)*
- [ ] Tarsal ankyloses (ankle fusion)*
- [ ] Hives
- [x] Sore throat (preceding fevers, rash)
- [ ] Pericarditis or pericardial effusion
- [x] Splenomegaly (enlarged spleen)
- [ ] Elevated hepatic (liver) enzymes (AST, ALT)
- [x] Negative tests for ANA (lupus) and RF (RA)
- [ ] Elevated WBC > 1[illegible]

Result:

StillsNow

Cush	Yamaguchi	ILAR
Not met	Criteria met	Not met
You do not meet Cush Criteria for the diagnosis of Still's disease	You meet the Yamaguchi Criteria for the diagnosis of Still's disease. This indicates that such a diagnosis is possible; but is not proof of a diagnosis until the diagnosis is confirmed by an expert in the field.	You do not meet ILAR Criteria for the diagnosis of Still's disease.

Adult-Onset Still's Disease

- No diagnostic or serologic tests
- Systemic inflammatory disorder
- Young adults (up to age 35yrs)
- Quotidian fevers, evanescent rashes, POLYarthritis, sore throat, serositis, organomegaly, leukocytosis and a marked acute phase response
- Syndrome = diagnosis of exclusion
- Systemic onset/exacerbations w/ or w/o chronic arthritis, and possibly, disease-free intervals

Cush JJ. Adult onset Still's disease. Bull Rheum Dis 2000; 49(6):1-4

Systemic-Onset JIA vs. AOSD

Feature	Systemic-onset JIA	AOSD
Sex	M=F	M=F
Quotidian fever	99%	94%
Still's rash	90%	87%
Arthritis	95%	93%
Sore Throat	**15%**	**70%**
RES	40-70%	50-70%
Serositis	20-50%	20-40%
Serologies	ANA- RF-	ANA- RF-
Carpal ankylosis	28-50%	45-55%
Erosive Dz	30%	20-25%
HLA	Bw35, DR2, DR4 DR5, Dw7	Bw35, DR4 Dw7

Challenge of AOSD

- Leading autoimmune cause of undiagnosed FUO
- No Diagnostic test (but there are criteria)
- Considerable morbidity (onset: hosp; FUO, MAS, etc)

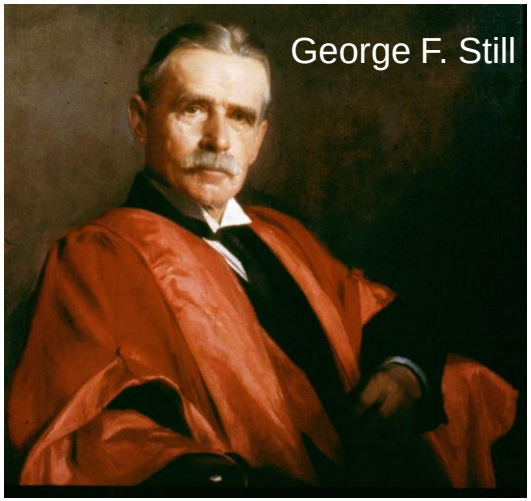
The great thing about Adult Stills Disease is the diagnosis rests solely on clinical findings and a few simple lab tests – no RF or other autoantibody. Usually only a rheumatologist can confirm the diagnosis! - John Esdaile, MD

AOSD Dx is often considered when:

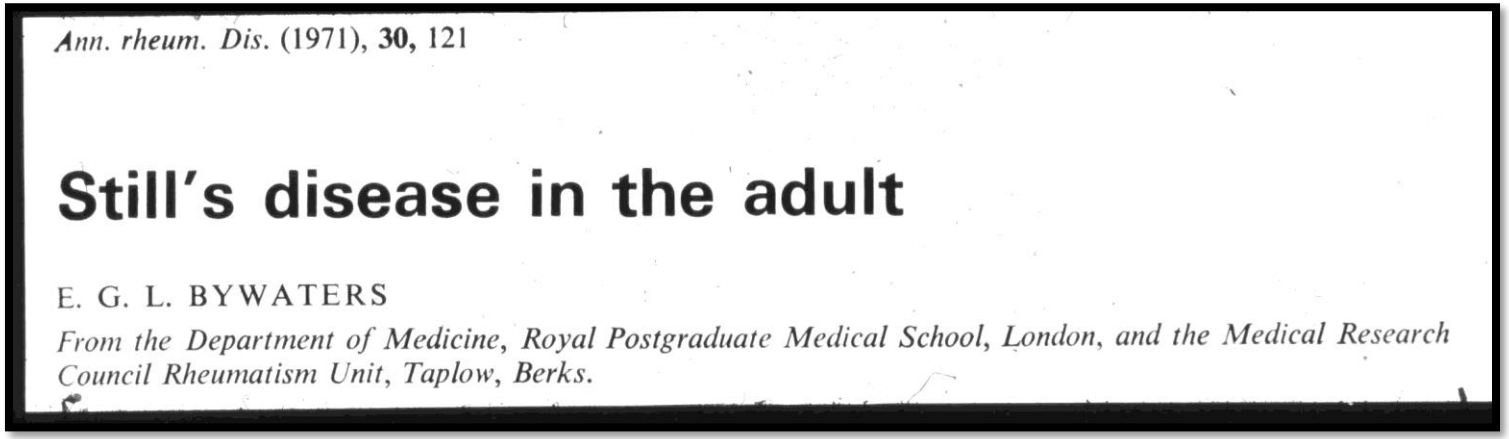
- Pt hospitalized w/ Undiagnosed Fever (± joints, rash, ⇧labs)
- Ferritin > 10,000

History of Still's Disease

1896 Bannatyne and Chauffard
1897 G.F. Still - describes 22 pts. with JA
1933 Boldero - 1st describes "Still's rash"
1933 Moltke - "Still's disease in adults"
1943 Wissler/Fanconi "Subsepsis Hyperallergica"
1971 Bywaters - 14 females with AOSD
1973 Bujak et al - 10 males with AOSD
1976 Medsger and Christy - Carpal ankylosis in AOSD
1980 Goldman et al – 13 pts; 1st Criteria
1980 Esdaile et al – Case series analysis (6+52 pts)



22 children
Deforming arthritis
Lymphadenopathy
Anemia



Ann. rheum. Dis. (1971), **30,** 121

Still's disease in the adult

E. G. L. BYWATERS

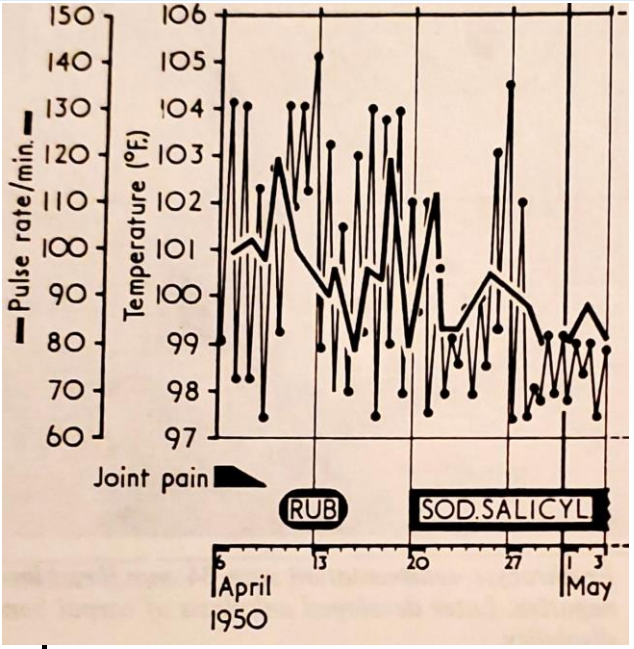
From the Department of Medicine, Royal Postgraduate Medical School, London, and the Medical Research Council Rheumatism Unit, Taplow, Berks.

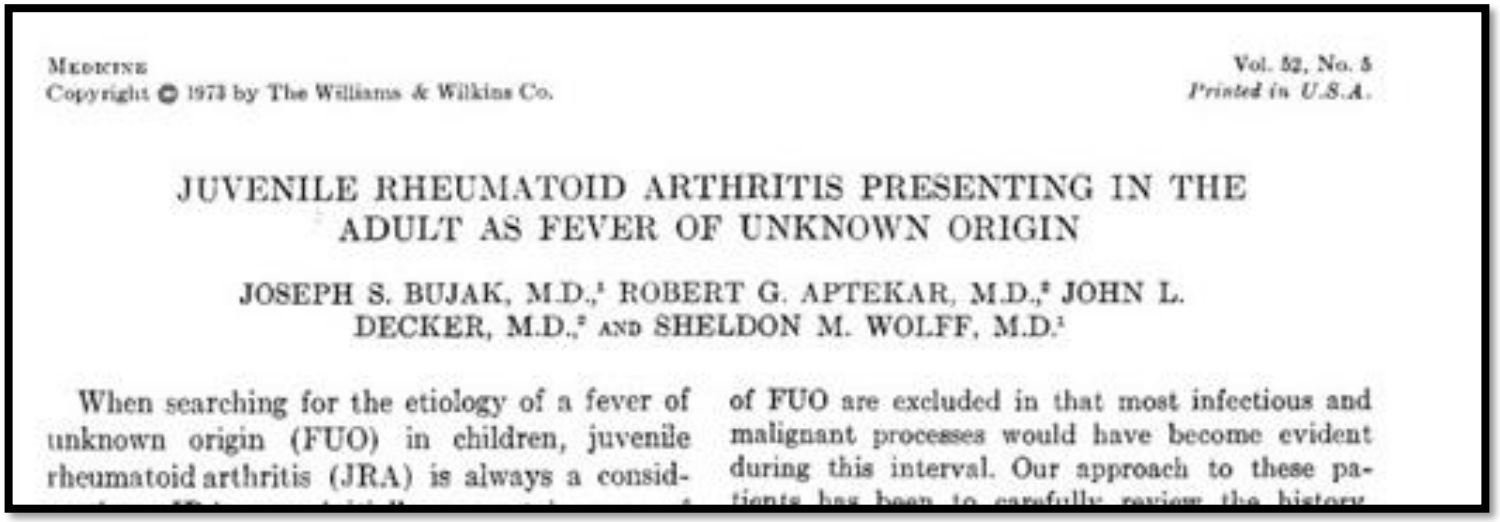
- 1956 Isdale and Bywaters described the evanescent rash of sJIA
- For 20+ years at Taplow they wondered about the hospitalized patients that were not seropositive RA (young, seronegative & milder)
  - Many went on to PsO, UC, CD, Whipples, AS, CTD, etc

- Still's disease does also occur in adults
- 14 patients (all female) from over 20 years (out of 680 pts/ 2 centers)
  - Ten cases followed > 2 years since onset, and four for > 10 years

Bywaters: “Still’s disease in the adult”

- Presentations: onset 17-35 Yrs
- Rash: come/go; w/ fevers ~6pm; along friction lines, rarely itchy; does not spread like Rheum fever, occ chr urticaria
- Fever: dramatic at onset, remittent/quotidian
- Joints: fleeting, occ chronic/erosive, lg & small (hips, DIPs)
  - 3 pts w/ carpal involvement (2 ankylosis), 2 with cervical (no SI)
- 3 hairfall, 4 pericarditis, 2 pleuritis, 2 splenomegaly
- 13/14 RF-





MEDICINE
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JUVENILE RHEUMATOID ARTHRITIS PRESENTING IN THE ADULT AS FEVER OF UNKNOWN ORIGIN

JOSEPH S. BUJAK, M.D.,[1] ROBERT G. APTEKAR, M.D.,[2] JOHN L. DECKER, M.D.,[2] AND SHELDON M. WOLFF, M.D.[1]

When searching for the etiology of a fever of unknown origin (FUO) in children, juvenile rheumatoid arthritis (JRA) is always a consid-

of FUO are excluded in that most infectious and malignant processes would have become evident during this interval. Our approach to these pa-

- Fever was the focus for Dr. Sheldon Wolff at the NIH
  - Collected and carefully examined these patients over many years
  - His group included Bujak, John Decker, Robt Aptekar, Tony Fauci
  - Ultimately this lead to description of many diseases, autoinflammatory conditions, interferonopathies, current NIH research
    - Raphaela Goldbach-Mansky
    - Daniel Kastner

JUVENILE RHEUMATOID ARTHRITIS PRESENTING IN THE ADULT AS FEVER OF UNKNOWN ORIGIN

J S Bujak, R G Aptekar, J L Decker, S M Wolff

Medicine September 1973 - Volume 52 - Issue 5 - p 431-444

- 1973, Over 11 yrs, 10/200 FUO pts followed at NIH unified by having features of systemic JIA ("Still's disease")
- All males
- 5 child onset (6.8)

Asymptomatic Interval(s)*
3 years
3 years
6 years, 10 years
10 years
10 years, 3 years
5 months
2 years
6 years, 4 years, 4 years
11 years, 8 years
0

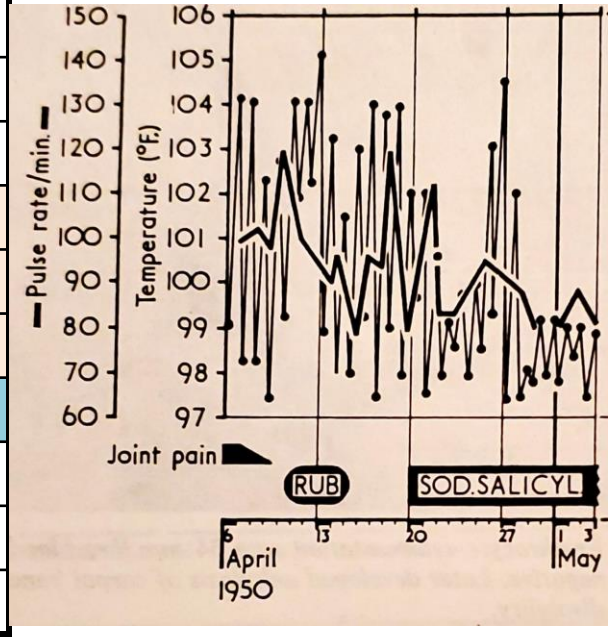
Incidence of Clinical Symptoms in Adult Still's Disease

Patient	Temp. >105°	Rash	Adeno-pathy	Spleno-megaly	Pneu-monitis	Pericar-ditis	Sore Throat	Abdominal Pain	Hepatic Abnor-malities	Arthritis	Poly-arthral-gias and Myalgias
W.R.[1]	+	+	−	−	+	+	+	+	−	+	+
J. Mal.[1]	+	+	+	−	+	+	+	+	+	+	+
B.H.[1]	+	−	+	+	+	−	+	−	−	−	+
W.S.[1]	+	+	+	+	+[4]	−	−	−	−	−	+
J.K.[1]	+	+	+	−	−	−	−	−	−	−	+
J. Maz.	+	−	+	−	−	+	−	−	−	+	+
J.A.	+	+	±[2]	+[3]	+	−	+	+	+	−	+
S.F.	−	+	+	+	+	−	+	−	−	−	+
C.B.	+	+	+	+	−	−	+	−	+	+	+
T.B.	+	−	±[2]	+[3]	−	−	+	−	−	+	+
Totals	9/10	7/10	7/10	6/10	6/10	3/10	7/10	3/10	3/10	5/10	10/10

[1] Patients who were first symptomatic in childhood.
[2] Enlarged mesenteric nodes at laparotomy.
[3] Enlarged at laparotomy, not clinically palpable.
[4] Possibly perisplenitis, see text.

The 1st 24 Cases of AOSD

Features*	Bywaters (n=14)	Bujak (n=10)
Sex	14 F	10 M
Age	17-35	7-29
sJIA Hx	1/14	5/10
Quotidian Fever T>39°C	12/14	10/10
Evanescent rash	14/14	5/10
Polyarthritis	13/14	10/10
Prodromal sore throat	2/14	7/10
Splenomegaly	2/14	6/10
Serositis	4/14	6/10
Seronegative (ANA,RF)	13/14	10/10



*all pts had fever, high ESR, myalgias, arthralgias, leukocytosis

Frequency of AOSD

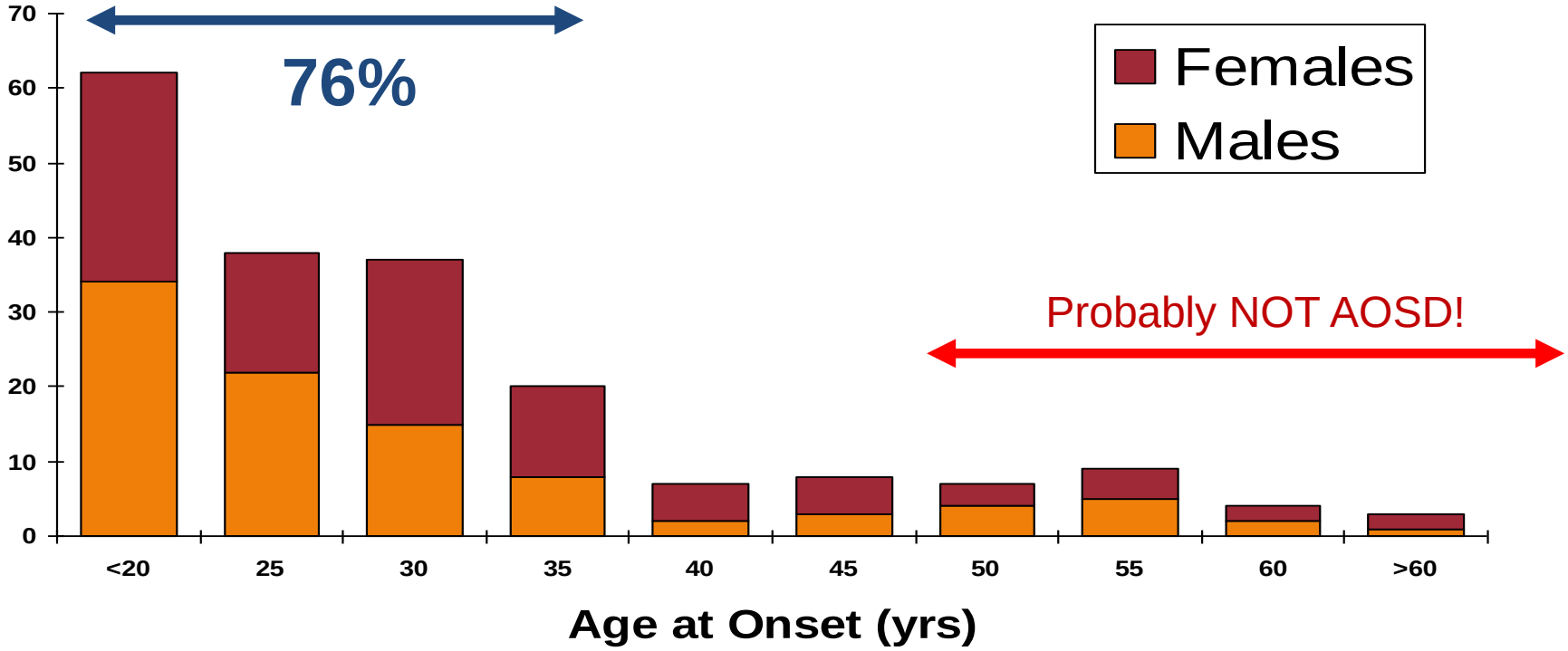
Author/Yr	#AOSD(%)	Time (yrs)	Source	
Bywaters ‘71	14	20	Rheum. Dept	D
Goldman ‘80	13	4	Rheum. Dept	E
Del Paine ‘83	7	9	Rheum. Dept	P
Cush ‘85	21	15	Rheum. Dept	T
Nkoghe ‘02	17	13	Infect. Dz Dept	S
Mert ‘03	20(15%)	17	Infect. Dz. Dept	
Bujak ‘73	10 (5%)	11	200 FUO pts	
Aduan ‘79	21 (6%)	15	347 FUO pts	F
Larson ‘82	5 (5%)	10	109 FUO pts	U
Kazanjian ‘92	5 (6%)	6	86 FUO pts	O
Knockaert ‘92	4 (9%)	9	45 FUO pts	
Tabak ‘03	13 (11%)	17	117 FUO pts	

Incidence Rates of AOSD = 0.16 – 4 cases per 100,000 population per year

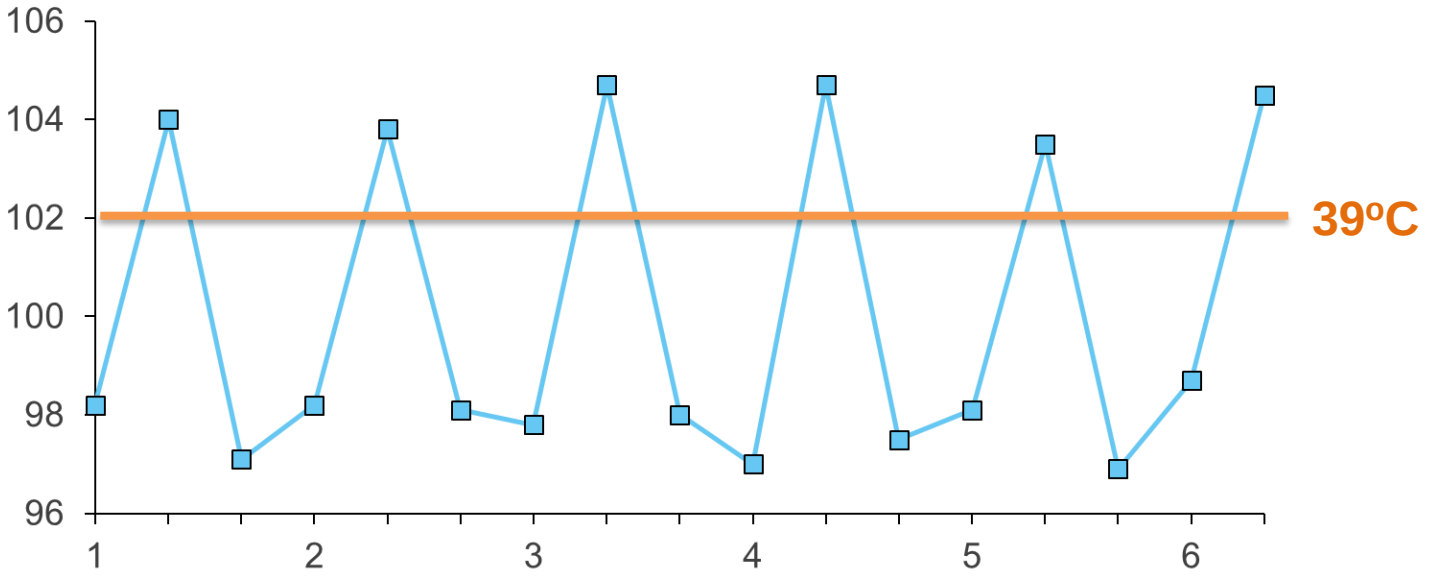
City	Population	New AOSD/yr
Ft. Smith, AR	81,518	1.3
Ft Collins, CO	124,665	2.0
Little Rock, AR	184,055	3
Huntsville, AL	162,536	2
Birmingham, AL	239,416	3.8
Toledo, OH	309,106	5
New Orleans, LA	390,845	6
Denver, CO	560,415	9
Nashville, TN	648,882	10.3
Louisville, KY	698,080	11.2
Dallas, TX	1,211,467	19.4
Los Angeles, CA	3,849,000	61.6
NYC, NY	8,468,000	110

Gerfaud- Valentin et al. Autoimmun Rev. 2014 Jul;13(7):708-22
Evensen KY, et al. Scand J Rheumatol. 2006 Jan-Feb;35(1):48-51.

Sex - Age at Onset



Quotidian (Spiking) Fever



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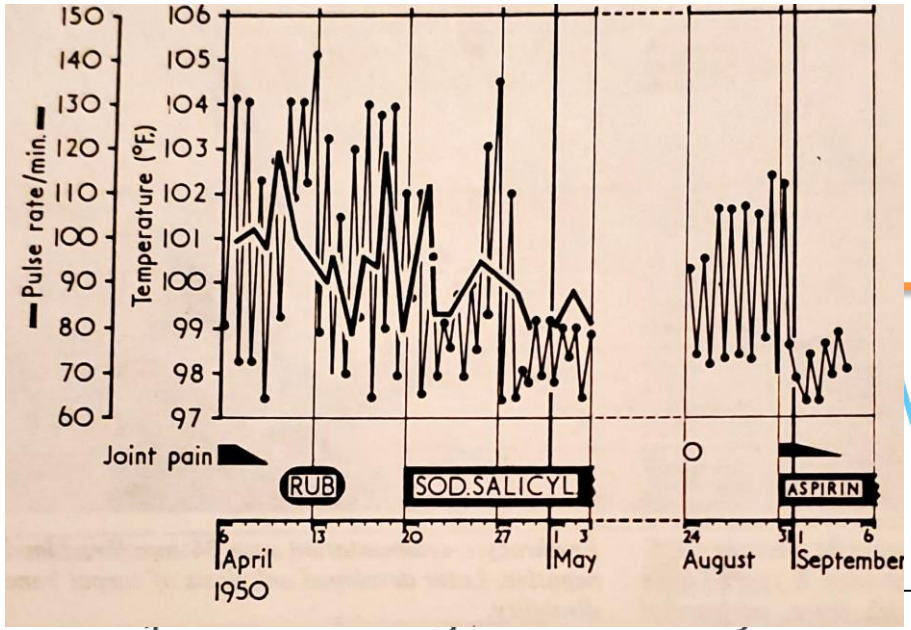
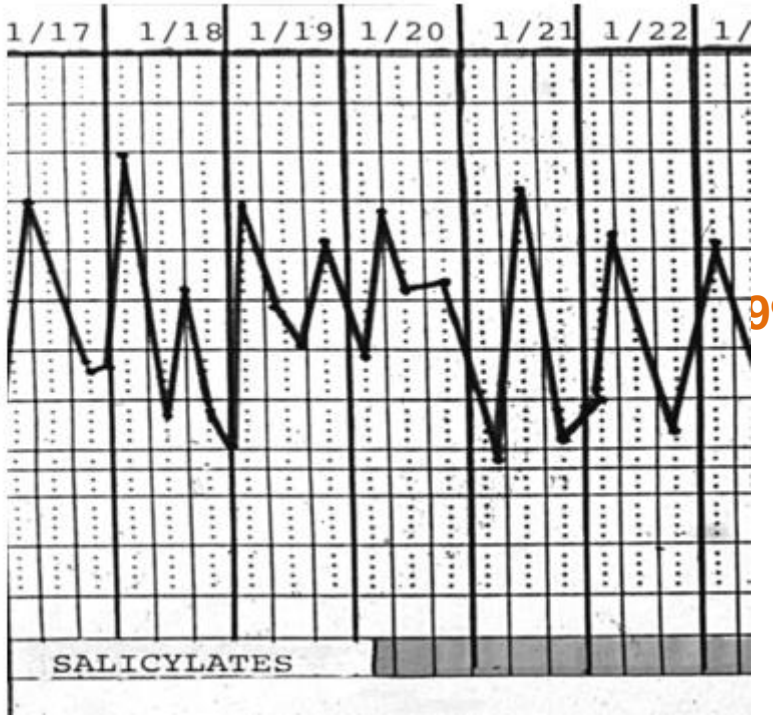
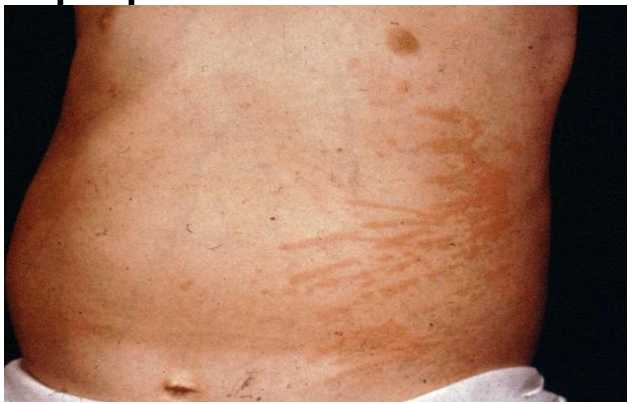


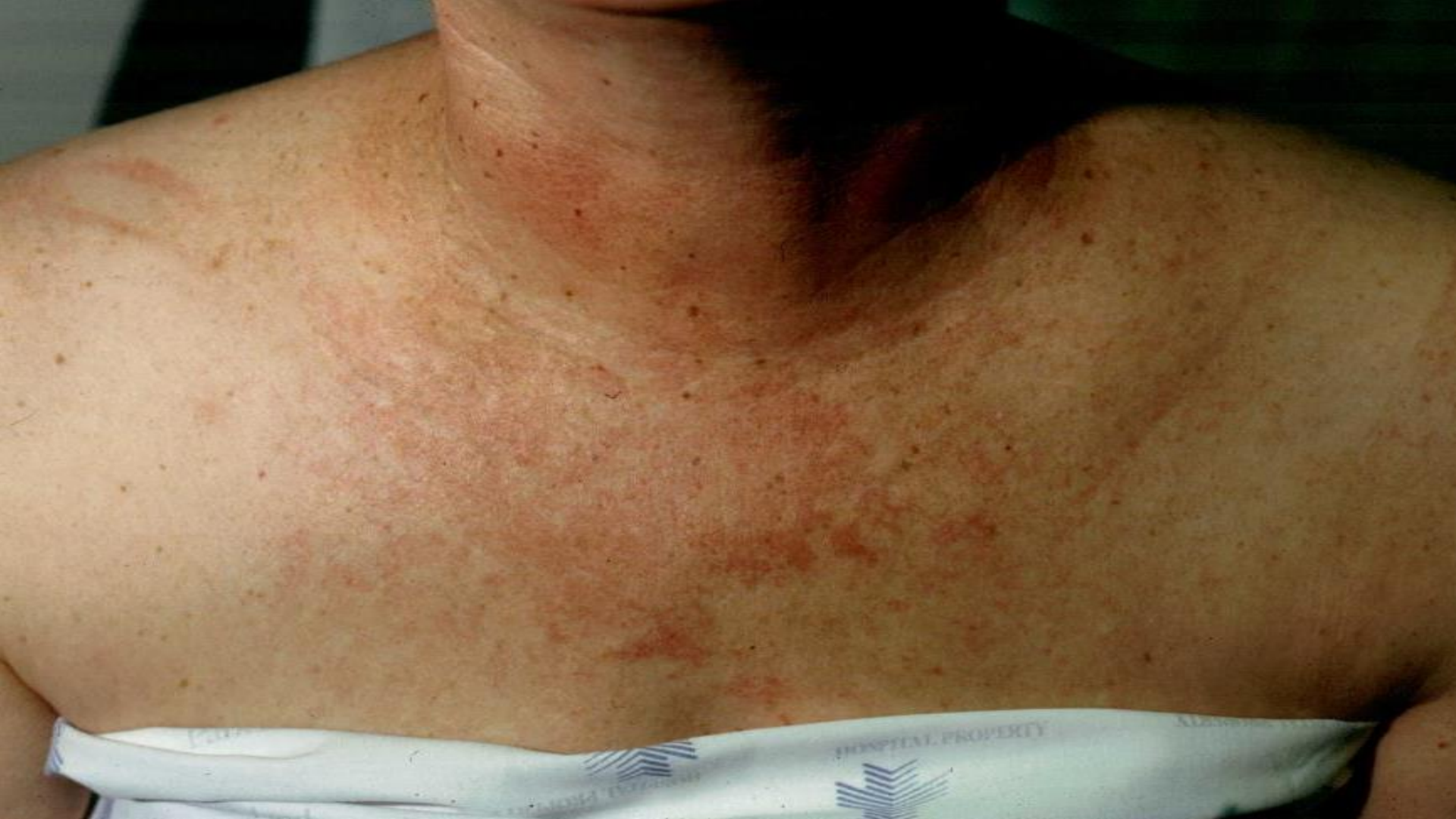


Rheumatoid or “Still’s” Rash

- Characteristically evanescent (esp. with fever)
- Salmon-pink (faint erythema) maculopapular
- Trunk, neck, and extremities
- Dermatographism
- Koebner phenomenon
- Urticaria, pruritus



Uncommon in AOSD: dermal plaques, facial rash, alopecia, erythema nodosum, Raynaud’s phenomena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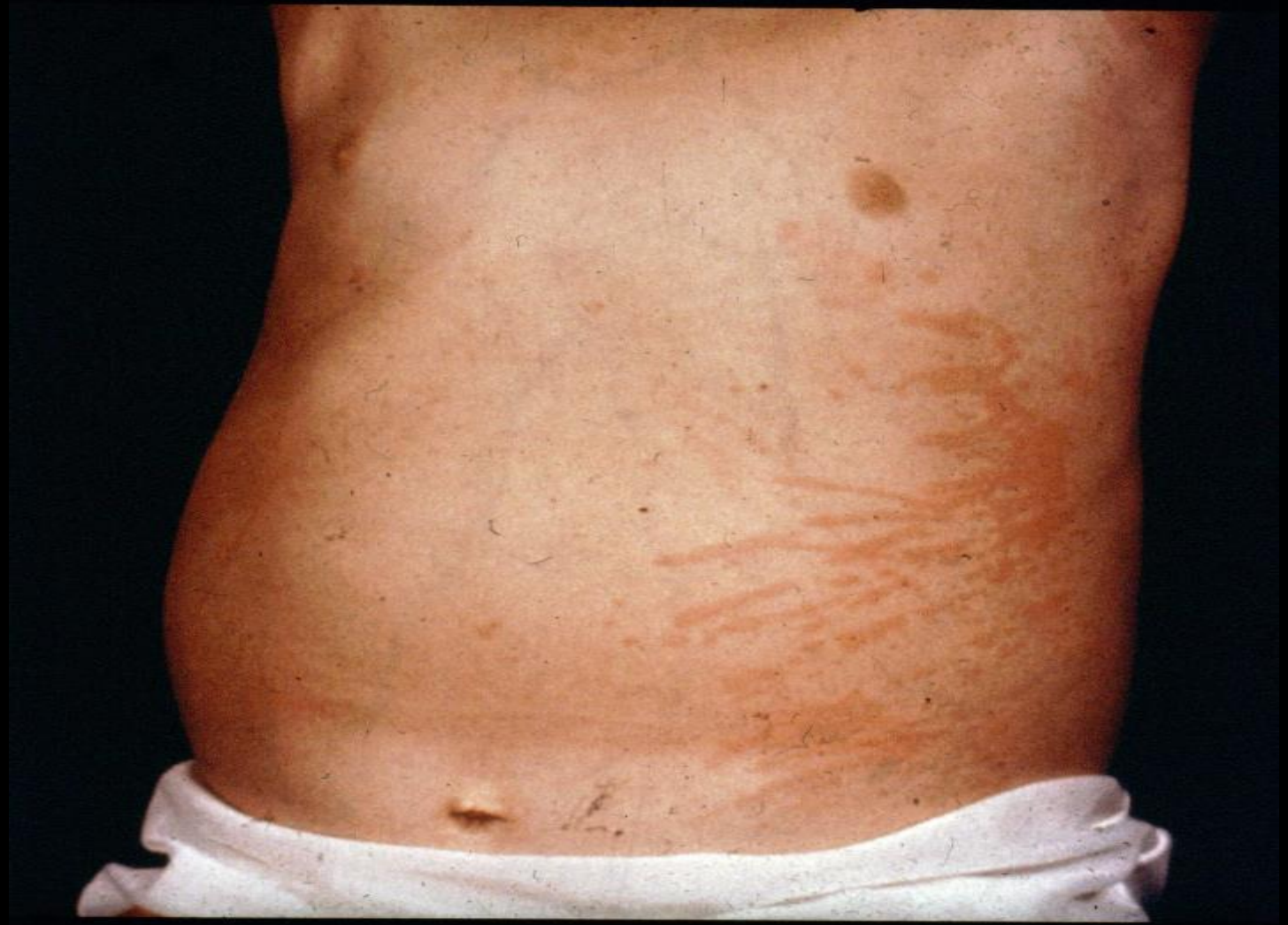
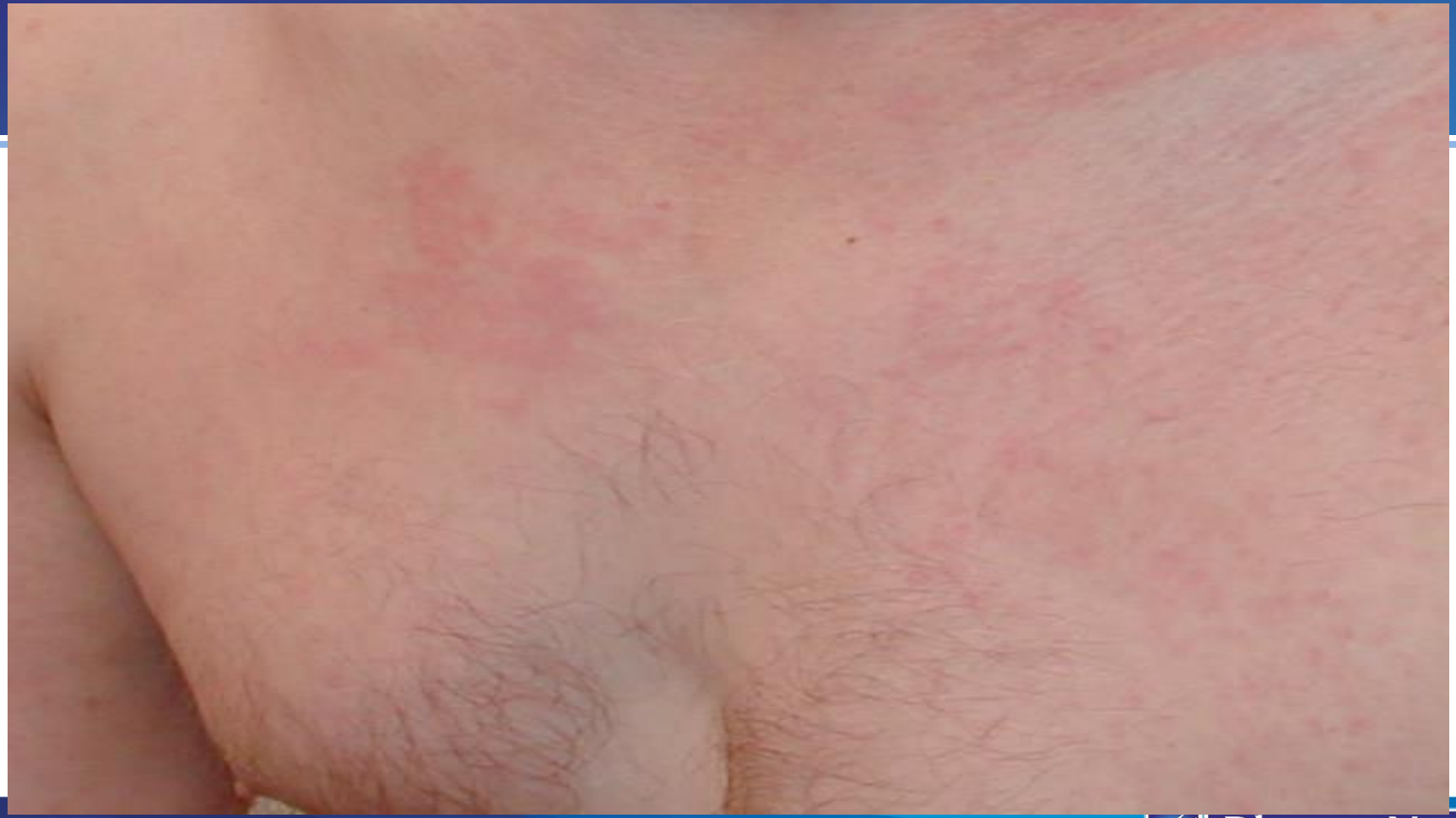
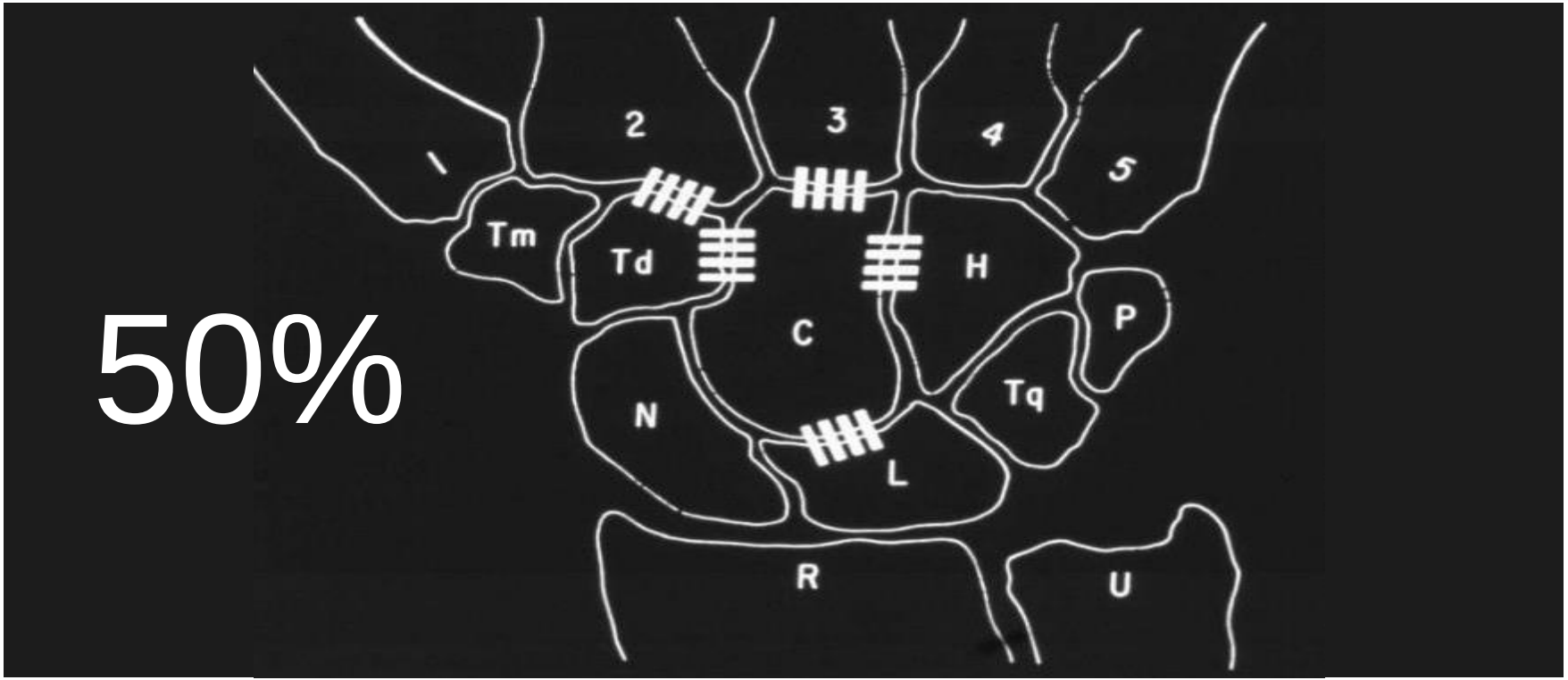




Multiple Choice Question

- The most common/distinctive arthritis of AOSD?
  1. Oligoarthritis
  2. Erosive polyarthritis
  3. Carpal ankylosis
  4. Sacroiliitis
  5. Seropositivity

Intercarpal Ankylosis



Cush JJ, Medsger TA, Christy W, et al. Arthritis Rheum; 30:186-94, 1987
Medsger TA, Christy W. Arthritis Rheum. 1976 Mar-Apr;19(2):232-42.

Musculoskeletal Features

Common

Myalgias

Arthralgias

Fleeting arthritis

Additive polyarthritis

Neck Pain

Syn. WBC=3-40K

Carpal ankylosis

Erosive hip disease

HLA-DR4

Uncommon

Tenosynovitis

Periostitis

Tarsal ankylosis

Cervical ankylosis

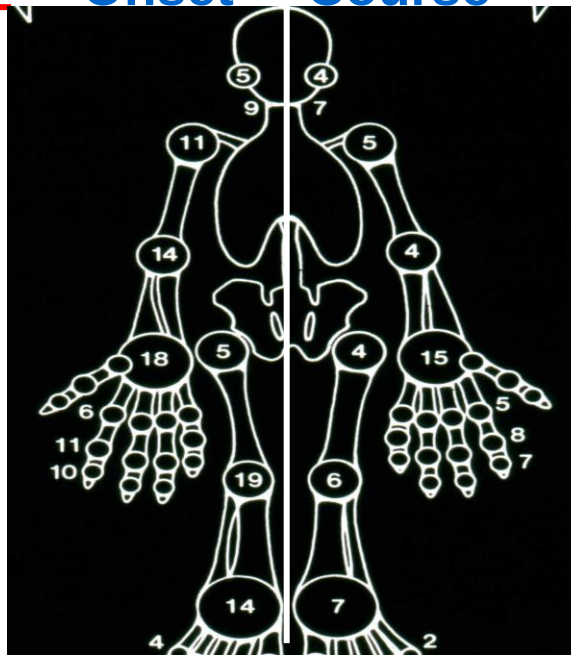
Myositis

Rhabdomyolysis

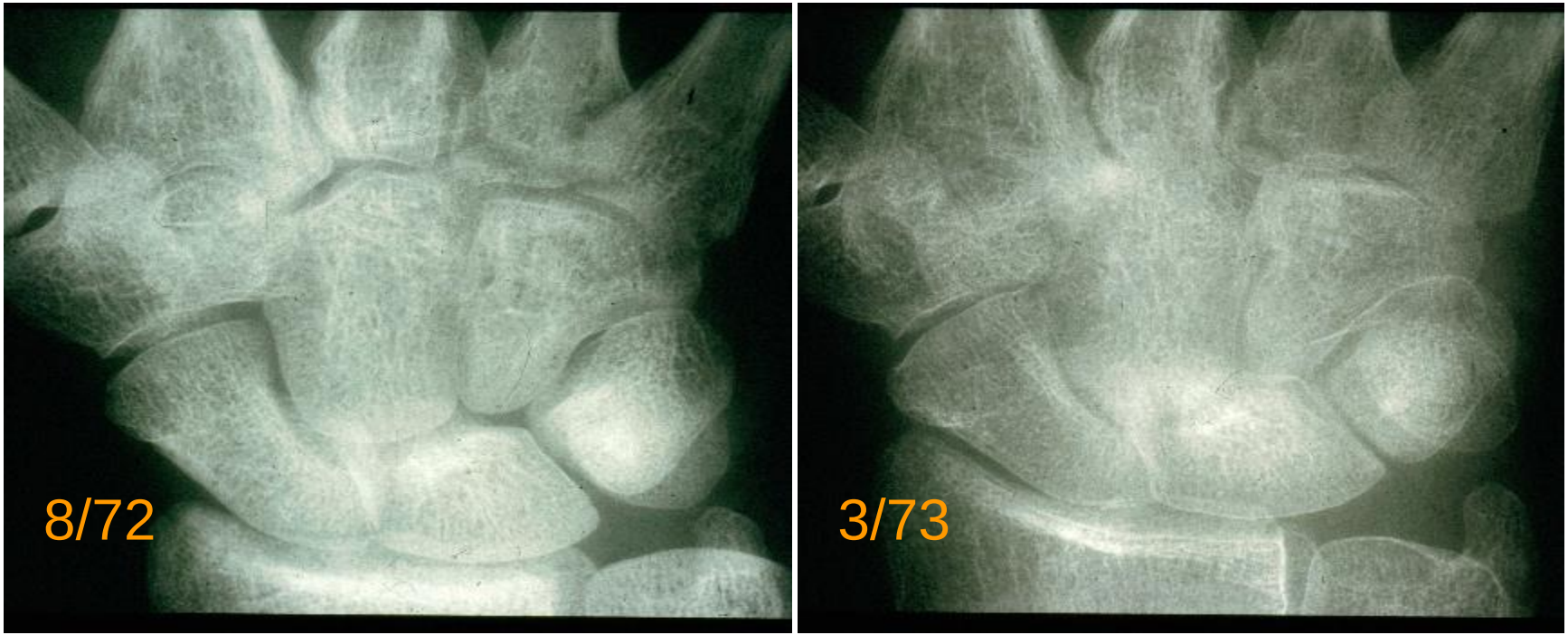
Micrognathia

DIP calcification

Onset Course



LK: Carpal Ankylosis

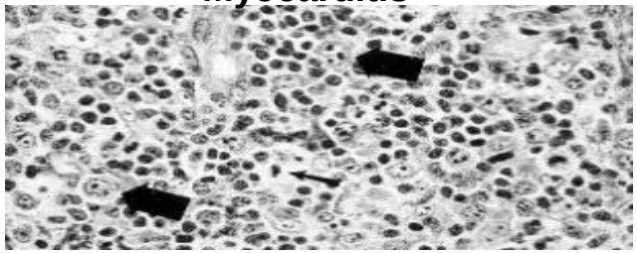


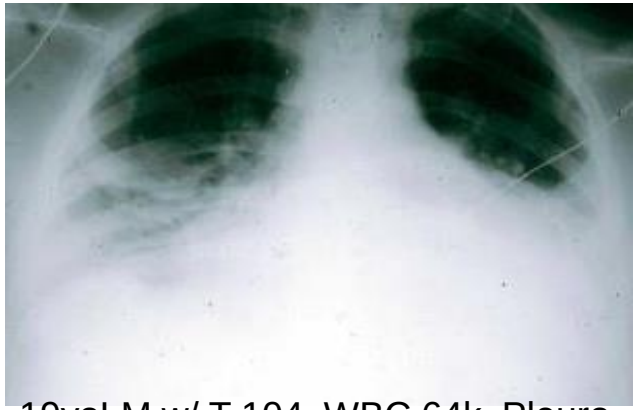
Medsger TA, Christy W. Arthritis Rheum. 1976 Mar-Apr;19(2):232-42.

Common Features

Sore throat	**70%**
Weight loss	**65%**
Myalgias	**75%**
Hepatosplenomegaly	**40%**
Hepatic dysfunction	**70%**
Lymphadenopathy	**65%**
Pleuritis	**40%**
Pericarditis	**30%**
Abdominal Pain	**30%**
Pneumonitis	**20%**
Myocarditis	**rare**

Myocarditis



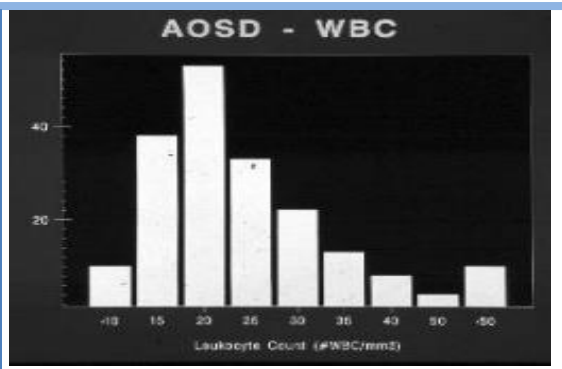


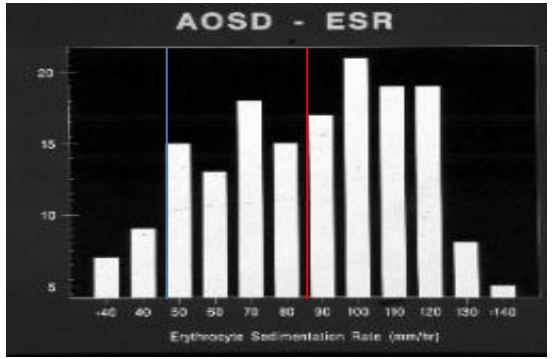
19yoLM w/ T 104, WBC 64k, Pleuro-pericarditis, Myocarditis, Splenomegaly

Cush JJ. Adult onset Still's disease. Bull Rheum Dis 2000; 49(6):1-4

Lab Abnormalities in AOSD

Negative ANA & RF	**95%**
Neutrophilic leukocytosis	**90%**
Anemia chronic disease	**75%**
↑↑ESR, ↑CRP, ↑Platelets	**90%**
Hypoalbuminemia	**75%**
Hyperferritinemia	**50%**



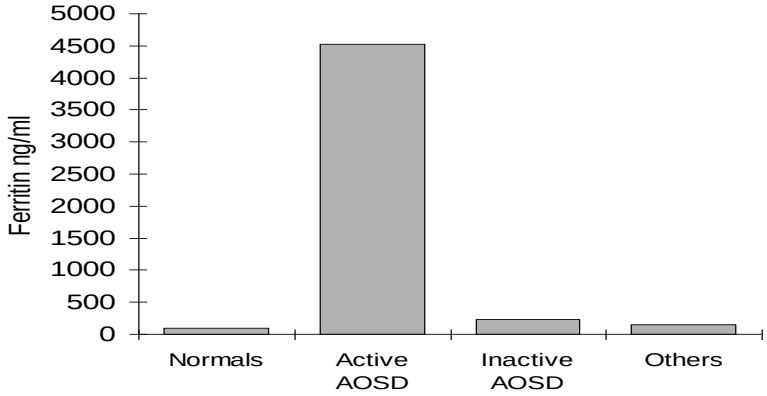


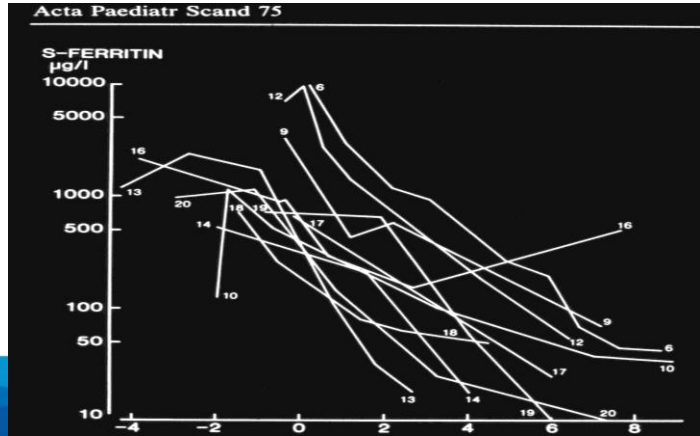
Cush JJ. Adult onset Still's disease. Bull Rheum Dis 2000; 49(6):1-4

Hyperferritinemia

extreme hyperferritnemia defined as ferritin >10,000 µg/L

- Polytransfusion
- Hemochromatosis
- Liver Disease
- Neoplasia
- Sepsis
- Pancreatitis
- **MAS/Hemophagocytic syndrome**
- AOSD/SoJIA

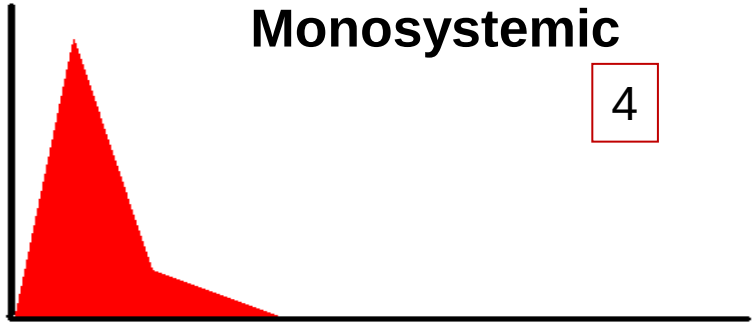


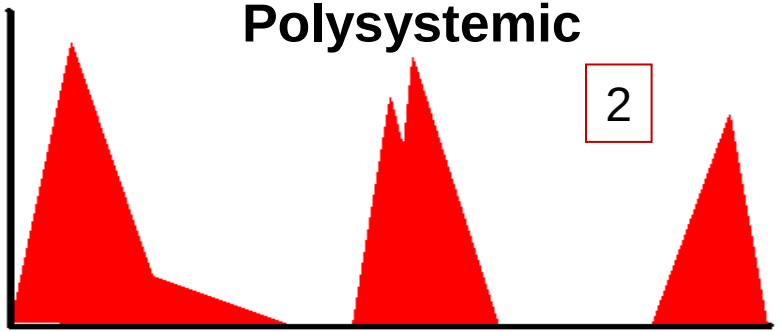


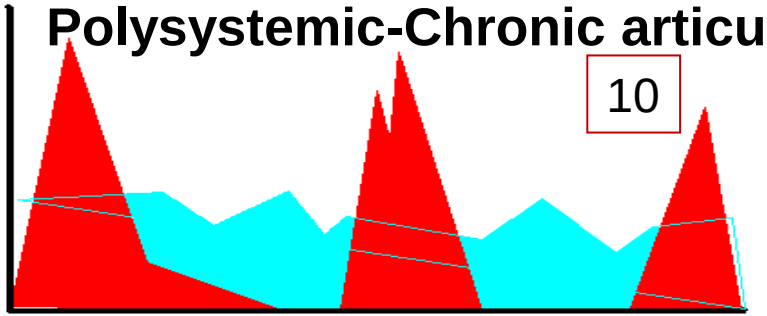
*adapted from van Reeth C, J Rheumatol. 1994 May;21(5):890-5

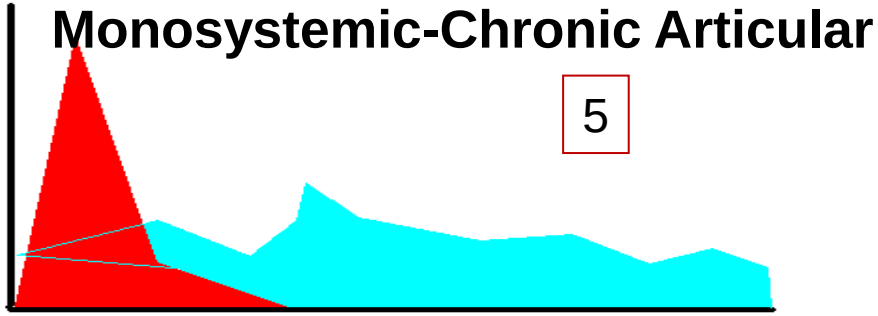
Senjo H, et al. Hematology Hematology Volume 23, 2018

Disease Patterns over Time



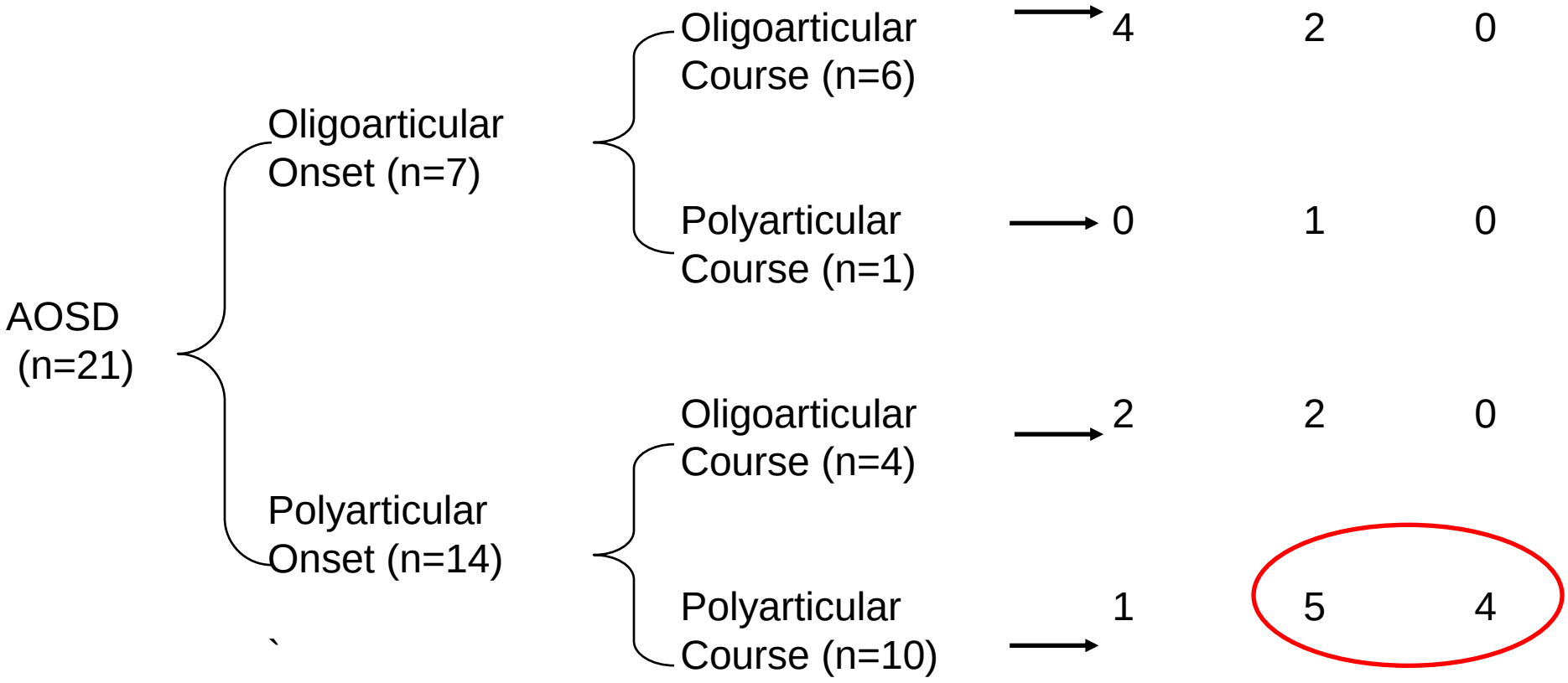






Cush JJ, et al. Arthritis Rheum; 30:186-94, 1987

Influence of Articular Onset & Course on Outcome



Mortality in AOSD

- Morbidity >>> Mortality
- Mortality – from MAS or complications of (steroid) therapy
- Causes: MAS, infection, DIC, lung disease
- 2009-2013 NIS Hospitalizations
  - 5,820 AOSD hospitalized (age 53.6 yrs)
  - MAS (1.7%), DIC-1.1%, TTP 0.4%
    - 154 deaths (2.6%). Higher age, asians (OR 6.3)

Who Diagnoses AOSD with Ease?

- Pediatric Rheumatologists
- Infectious Disease Consultants
- Rheumatologists who know the criteria

Diagnostic Criteria
Cush (1984) 2000

Major (2pts)	Minor (1pt)
Quotidian fever > 39 C	Onset age < 35 yrs.
Still's rash	Arthritis
↑ WBC & ESR	Sore throat
Negative RF & ANA	RES or ↑ LFTs
Carpal Ankylosis	Serositis
	Cervical/tarsal ankylosis

Definite AOSD: 10 points + 6 mos. observation
Probable AOSD: 10 points + 6 weeks observation

Diagnostic Criteria
Yamaguchi 1992

Major	Minor
Fever > 39 C	**Sore throat**
Arthralgia > 2 wks.	**LN or splenomegaly**
Still's rash	**Hepatic dysfunction**
Neutrophilic leukocytosis	**Negative RF & ANA**

AOSD: 5 or more Criteria (including 2 major)
(exclusion of infectious, neoplastic or rheumatic causes)

Do I Meet Criteria for Still's Disease?

Begin by confirming the diagnosis of Still's disease using our calculator.

Calculate my Risk

Still's Disease Diagnosis Calculator

- [ ] Age less than 16 years
- [ ] Daily or nightly fever (not measured)
- [ ] Daily/nightly fevers always above 102°F (>39°C)
- [ ] Joint pains (arthralgia)
- [ ] Many swollen joints (polyarthritis)
- [ ] Cervical ankyloses (neck fusion)*
- [ ] Rash (any)
- [ ] Intermittent faint red/pink rash (arms, legs, trunk, neck
- [ ] Pleuritis or pleural effusion
- [ ] Generalized lymphadenopathy (many swollen lymph nodes)
- [ ] Hepatomegaly (enlarged liver)
- [ ] Low albumin < 3.0 (hypoalbuminemia)
- [x] Elevated "sed rate" (ESR) > 40 mm/hr
- [x] Elevated WBC with >80% neutrophils (PMNs)
- [x] Age less than 35 years
- [x] Daily/nightly fever (between 100-102°F)
- [ ] Muscle pains (myalgia)
- [x] Swollen painful joints
- [x] Carpal ankyloses (wrist fusion)*
- [ ] Tarsal ankyloses (ankle fusion)*
- [ ] Hives
- [x] Sore throat (preceding fevers, rash)
- [ ] Pericarditis or pericardial effusion
- [x] Splenomegaly (enlarged spleen)
- [ ] Elevated hepatic (liver) enzymes (AST, ALT)
- [x] Negative tests for ANA (lupus) and RF (RA)
- [ ] Elevated WBC > 1[illegible]

Result:

StillsNow

Cush	Yamaguchi	ILAR
Not met	Criteria met	Not met
You do not meet Cush Criteria for the diagnosis of Still's disease	You meet the Yamaguchi Criteria for the diagnosis of Still's disease. This indicates that such a diagnosis is possible; but is not proof of a diagnosis until the diagnosis is confirmed by an expert in the field.	You do not meet ILAR Criteria for the diagnosis of Still's disease.

AOSD: Keys to Diagnosis

- Triad = High Fever, evanescent rash, polyarthritis
- **Daily** Fevers ≥ 39°C
- Circadian Fevers: Temps same time EVERY night or later afternoon (not 7AM!)
- “Still’s rash” - evanescent
- Confirm using Cush or Yamaguchi Criteria
- Diagnostic response to IL-1 inhibition?

5 Mistakes in Dx-ing AOSD

1. No Triad present (check criteria)
2. Daily quotidian fever > 102F not seen
3. Intermittent Fever History
4. Dx by Ferritin levels
5. Using TNF inhibitors

When it's not AOSD, could it be an Autoinflammatory Syndrome?

Autosomal recessive

- Familial Mediterranean fever
- HyperIgD (HIDS)
- Deficiency IL-1Ra (DIRA)
- Deficiency IL -36R (DITRA)
- Familial pustular psoriasis
- Majeed syndrome

Autosomal-dominant

- TRAPS
- FCAS
- Muckle-Wells syndrome
- NOMID/CINCA
- PAPA syndrome

Granulomatous

- Blau syndrome
- Early onset sarcoidosis

Other, nongenetic

- Marshall (PFAPA) syndrome
- Systemic JIA / Adult onset Stills'
- Behçet syndrome
- Recurrent pericarditis
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Schnitzler syndrome

Adapted from Haskes P. Pediatr Clin North Am. 2012 Ap`r;59(2):447-70

When to Consider Autoinflammatory Dz

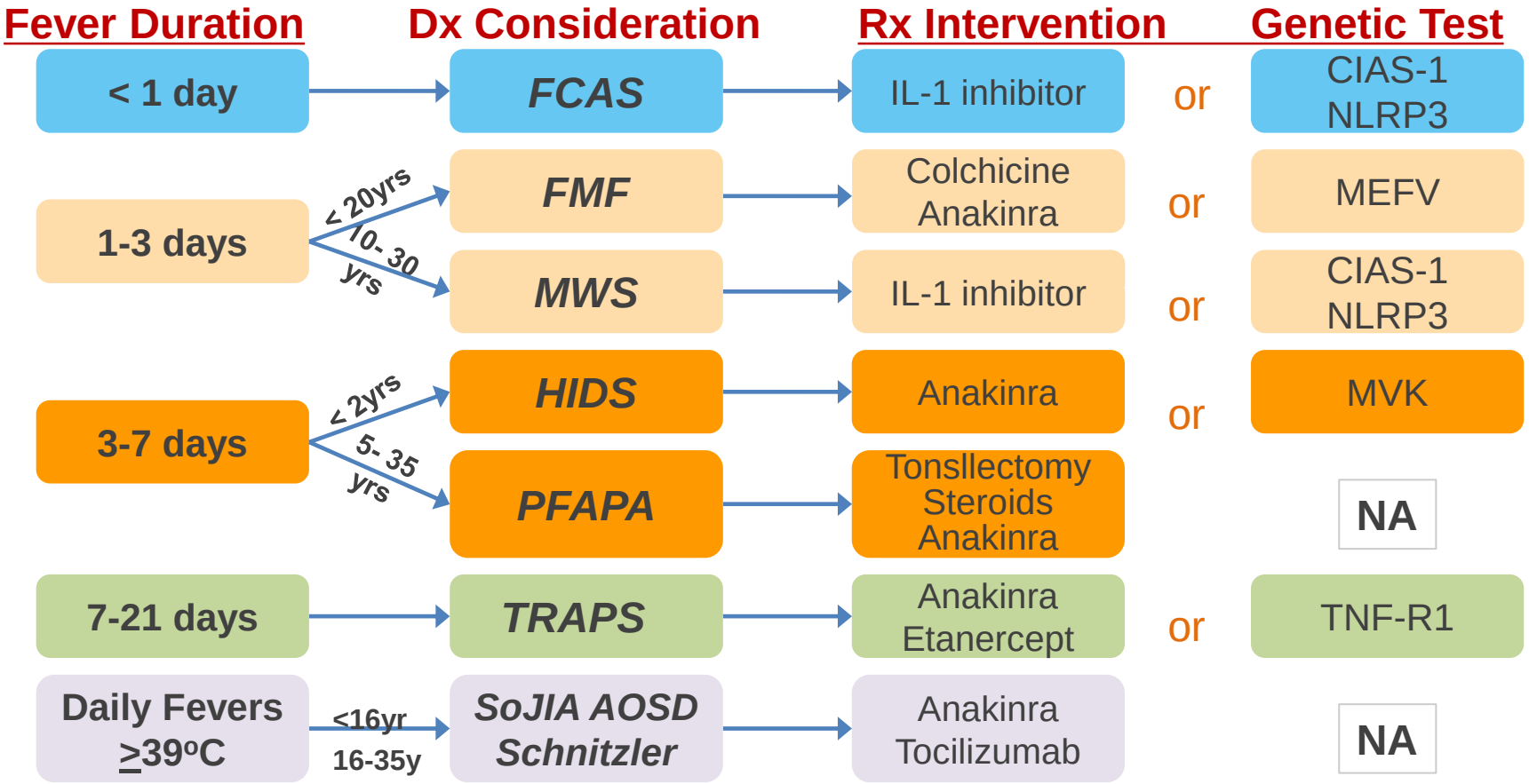
Scenarios

- Not meeting Criteria
  (Yamaguchi, Cush, ILAR)
- Continued, undiagnosed, non-daily (high) fevers
- Nonresponse to standard of care therapies (for sJIA)
- Family Hx of like-Sxs

Symptoms

- MSK complaints
- Atypical rash, oral ulcers, urticaria
- Abdominal pain
- Eye inflammation (conjunctivitis)
- Lymphadenopathy
- Amyloidosis
- Serositis
- CNS, headache, fatigue

Algorithm for Undiagnosed Periodic Fever ≥ 38°C



Comparison of US Labs Offering Genetic Testing for Autoinflammatory Diseases

LABORATORY	MNG Labcorp	Fulgent	Invitae	Invitae	Blueprint Genetics	Prevention Genetics	ARUP Labs
TEST PANEL ORDERING INFO	Fever Syndromes NGS319	Periodic Fever/ Autoinflammatory or PI Panel*	Primary Immuno-deficiency Panel [P1 Panel*] 08100	Autoinflammatory Syndrome Panel 08120	Autoinflammatory Syndrome Panel or PI Panel*	Periodic Fever/ Autoinflammatory or PI Panel*	Periodic Fever Syndromes Panel
BILLING INFO & COST (as of 2/22)	**$ price unlisted** contracts w/institutions. Self-pay option.	**$ price unlisted** Bills insurance. Self pay options & pt. assistance.	**$250** Pt. self-pay. Bills insurance. ≤$100 average copay w/insurance.	**$250** Pt. self-pay. Bills insurance. ≤$100 average copay w/insurance	**$1550 - $1650*** Bills insurance. Financial assist-ance for patients.	**$890 - 13 genes $1490 - PI Panel*** Bills insurance. Payment plans available to pts.	**$ price unlisted** Bills insurance.
GENES TESTED	167	47, 471*	429	18, 156*	47, 336*	13, 586*	10
AUTOINFLAM-MATORY GENES IN THE PANEL: (The number of autoinflamatory genes in the panel is in the red block)	**26:** MEFV, LPIN2, MVK NLRP3, PSTPIP1, NOD2, TNRFSF1A, CARD14, ADA2, NLRP12, PLCG2, PSMB8, IL1RN, IL36RN, TMEM173, 1L10RA & RB, TNFRSF11A, SH3BP2, RBCK1, NLRC4, SLC29A3, TRNT1, ACP5, STX11, XIAP. OTHER: ELANE, +more Missing: LYN, NLRP1, XIAP, OTULIN, RELA, WDR1, POMP, TNFAIP3, RAB27A, COPA, RIPK1, PSENEN, ISG15, IFIH1, ADAM17, RNASEH2(A,B,&C), UNC13D, ADAR, PRF1, SH2D1A, SAMHD1, TREX1, STXBP2, UBA1.	**43 or 50*:** MEFV, LPIN2, MVK, NLRP3, PSTPIP1, ADA2, NOD2, TNFRSF1A, CARD14, AP1S3, COPA, DDX58, LPIN2, ACP5, NLRC4, PLCG2, RIPK1, NLRP12, PSMB8, NLRP1, IL36RN, IL1RN, ADAR, POMP, IL10RA & RB, TNFAIP3, IFIH1, OTULIN, TMEM173, RBCK1, SH3BP2, SLC29A3, PSENEN, SAMHD1, USP18, ADAM17, RNASEH2(A,B,& C), TREX1, TRNT1, TNFRSF11A. OTHER: ELANE. (*50 in 471 PI panel) STX11, STXBP2, SH2D1A, PRF1, UNC13D, WDR1, XIAP. +ALPS, HLH, IBD Missing: LYN, RELA, UBA1.	**56:** MEFV, LPIN2, MVK, NLRP3, PSTPIP1, ADA2, TNFRSF1A, CARD14, AP1S3, NLRC4, NLRP12, NOD2, PSMB8, PLCG2, TRNT1, RBCK1, IL1RN, IL36RN, IL10, IL10RA & RB, SH3BP2, SLC29A3, COPA. + RIPK1, TMEM173, TNFRSF11A, ACP5, TREX1, ADAR, NLRP1, POMP XIAP, SAMHD1, IFIH1, RELA, RNASEH2(A,B,& C), OTULIN, PRF1, STX11, STXBP2, WDR1, RAB27A, UNC13D, LYN, SH2D1A, SH3BP2, TNFAIP3, PSENEN, ADAM17, PSMG2, PSMA3, PSMB4, SAMD9L, RBCK1, DNASE1L3, DNASE2 OTHER: ELANE. Missing: UBA1	**15, 46*:** MEFV, NLRP3, PSTPIP1, ADA2, TNFRSF1A, PSMB8, TRNT1, NLRC4, MVK NLRP12, LPIN2, POMP, PSMB4 PSMA3, PSMG2. OTHER: ELANE. + these in 156 gene panel: IL1RN, CARD14, PLCG2, TREX1, RBCK1, XIAP, IL36RN IL10RA & RB, ACP5, SAMHD1 SH3BP2, SLC29A3, COPA, ADAM17, ADAR, NOD2, LYN RNASEH2(A,B,&C), SH2D1A STXBP2, TMEM173, IL1H1, STX11, UNC13D, RIPK1, TNFAIP3, TNFRSF11A, NLRP1, OTULIN, DNASE1L3, DNASE2 Missing: RELA, WDR1, UBA1 Can order extra neuro panel for VEXAS (UBA1) w/Invitae	**37 or 48*:** MEFV, LPIN2, NLRP3, PSTPIP1, NOD2, TNFRSF1A, CARD14, MVK, NLRP12, PLCG2, PSMB8, IL1RN, IL36RN, ACP5, ADA2 TMEM173, TREX1, ADAR, RNASEH2(A,B , PSENEN, SAMHD1, IFIH1, OTULIN, TNFAIP3, NLRC4, TRNT1 NLRP1, SLC29A3, COPA, WDR1, IL10RA& RB, POMP, UBA1, PSMB4, DNASE1L3, OTHER: LANE. + these in 336 PI panel: RAB27A, STX11, STXBP2, PRF1, UNC13D, SH2D1A, RELA, DDX58, XIAP, ISG15. Missing: TNFRSF11A, LYN. Panels with VEXAS (UBA1)	**12 or 59*:** MEFV, LPIN2, MVK, NLRP3, PSTPIP1, NOD2, TNFRSF1A, CARD14, NLRP12, PSMB8, IL36RN, TNFAIP3. OTHER: ELANE. + these in 586 gene panel: ACP5, ADA2, RBCK1, ADAM17, ADAR, AP1S3, COPA, DDX58, IFIH1, IL1R, NLRC4, NLRP1, IL10RA & RB, RELA, OTULIN, PLCG2, POMP, RIPK1, PSMB8, PSENEN, SAMHD1,SH3BP2, RNASEH2(A,B,&C), SLC29A3, STX11, STXBP2, PRF1, UNC13D, SH2D1A, TMEM173, TNFRSF11A, TREX1, TRNT1, LYN, WDR1, XIAP, PSMA3, PSMB4, PSMG2, DNASE1L3, DNASE2, SAMD9L, RBCK1, RNF31. Missing: UBA1	**9:** MEFV, LPIN2, MVK, NLRP3, NLRP12, NOD2, PSTPIP1, TNFRSF1A, TNFAIP3. OTHER: ELANE. Missing: CARD14, ADA2, NLRP12, PLCG2,PSMB8, IL1RN, IL36RN, IL10, IL10RA & RB, TMEM173, TNFRSF11A, SLC29A3, NLRP1, ACP5, LYN, XIAP, TMEM173, TREX1, ADAR, NLRC4, SAMHD1, IFIH1, RNASEH2(A,B,& C), OTULIN, COPA, WDR1, XIAP, POMP, RELA, RIPK1, UBA1 & more.
OTHER GENES IN THE PANEL (starts w/ELANE)							

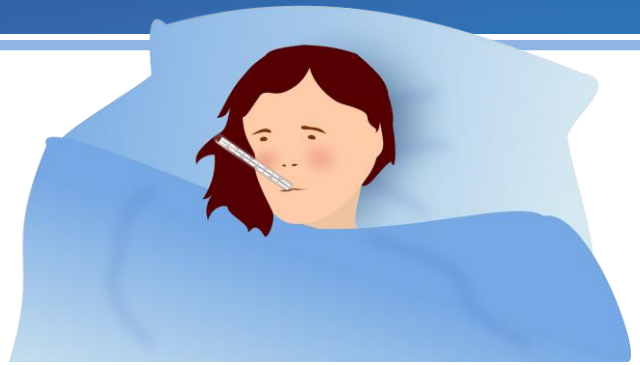
This table was updated in FEBRUARY 2022: This chart is updated often, and is available on the Autoinflammatory Alliance blog at http://saidsupport.org/diagnosis-genetics-periodic-fever-syndromes/

Invitae.com

- Autoinflammatory Syndromes Panel
- Cash $100 – $250

Primary Panel:

ACP5	ADA	ADA2	ADAM17	ADAR	AICDA	BTK
CARD14	CD3G	CD40LG	COPA	CTLA4	CYBA	CYBB
DCLRE1C	DKC1	DOCK8	ELANE	FOXP3	G6PC3	ICOS
IFIH1	IL10	IL10RA	IL10RB	IL1RN	IL21	IL2RA
IL2RG	IL36RN	ITGB2	LIG4	LPIN2	LRBA	MEFV
MVK	NCF2	NCF4	NFAT5	NLRC4	NLRP12	NLRP3
NOD2	PIK3CD	PIK3R1	PLCG2	PSMB8	PSTPIP1	RAG1
RAG2	RBCK1	RNASEH2A	RNASEH2B	RNASEH2C	RTEL1	SAMHD1
SH2D1A	SH3BP2	SLC29A3	SLC37A4	STAT1	STAT3	STIM1
STXBP2	TMEM173	TNFRSF1A	TREX1	TRNT1	TTC7A	WAS
XIAP	ZAP70					



Periodic Fever Syndromes Panel

✓ Primary panel

18 genes selected

✓ ADA2	✓ ASAH1	✓ ELANE	✓ LPIN2
✓ MEFV	✓ MVK	✓ NLRC4	✓ NLRP12
✓ NLRP3	✓ POMP	✓ PSMA3	✓ PSMB4
✓ PSMB8	✓ PSMG2		

https://www.invitae.com/en/physician/category/CAT000075/#catrontent-CAT000219

Autoinflammatory Summary

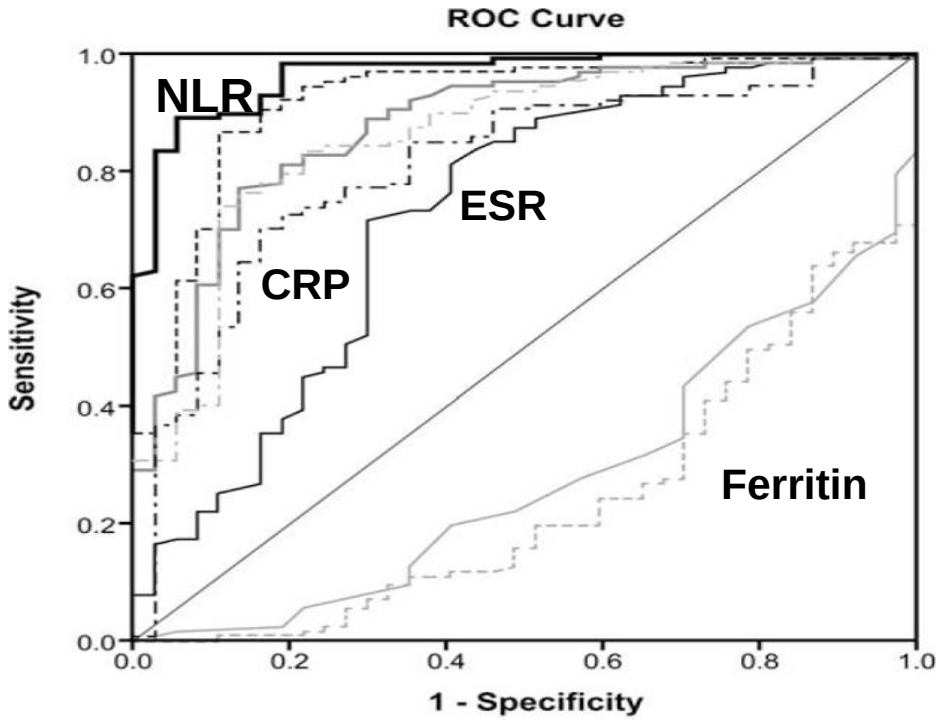
Jonathan Hausmann MD @hausmannMD · Nov 11, 2019

60%

The percentage of patients at @NIH's autoinflammatory disease cohort that are undifferentiated and do not have a specific disease diagnosis -Dr. Amanda Ombrello. #ACR19 @rheumnow

Assessing Activity

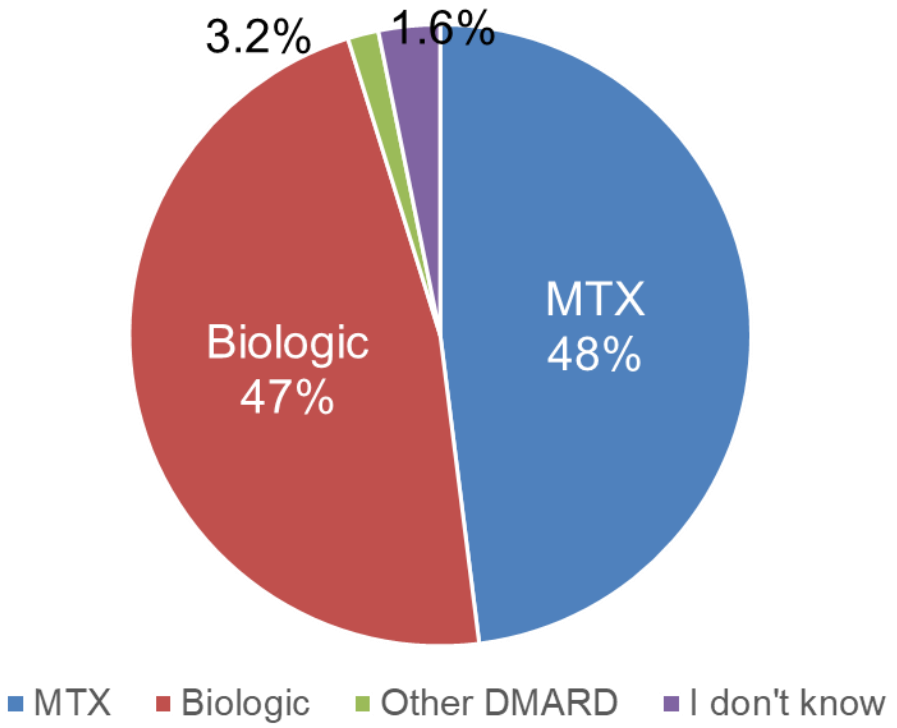
- Articular disease
  - Synovitis, ESR, CRP, CBC
- Systemic disease
  - Fever, rash, ST, HSM, Serositis, LN
  - **ESR, CRP** >> Ferritin (specific)
  - NLR (PMN to-lymph)ratio >3 (>5.86 MAS)
  - **Aldolase** – biomarker
  - IL-18, S100, IL-37
  - **Myeloid-related protein 8/14 (MRP8/14)**
- Inflammasome activity
  - Microarrays – fade with improvement disappear w/ true remission



*Seo Jy, et al. Medicine 2017 Jul;96(29):e7546 Izuka S, et l. Clin Exp Rheumatol. 2020 Feb 11 Rheumatology. 2022 Jul 6;61(7):3082-3092.

What Do you use after steroids

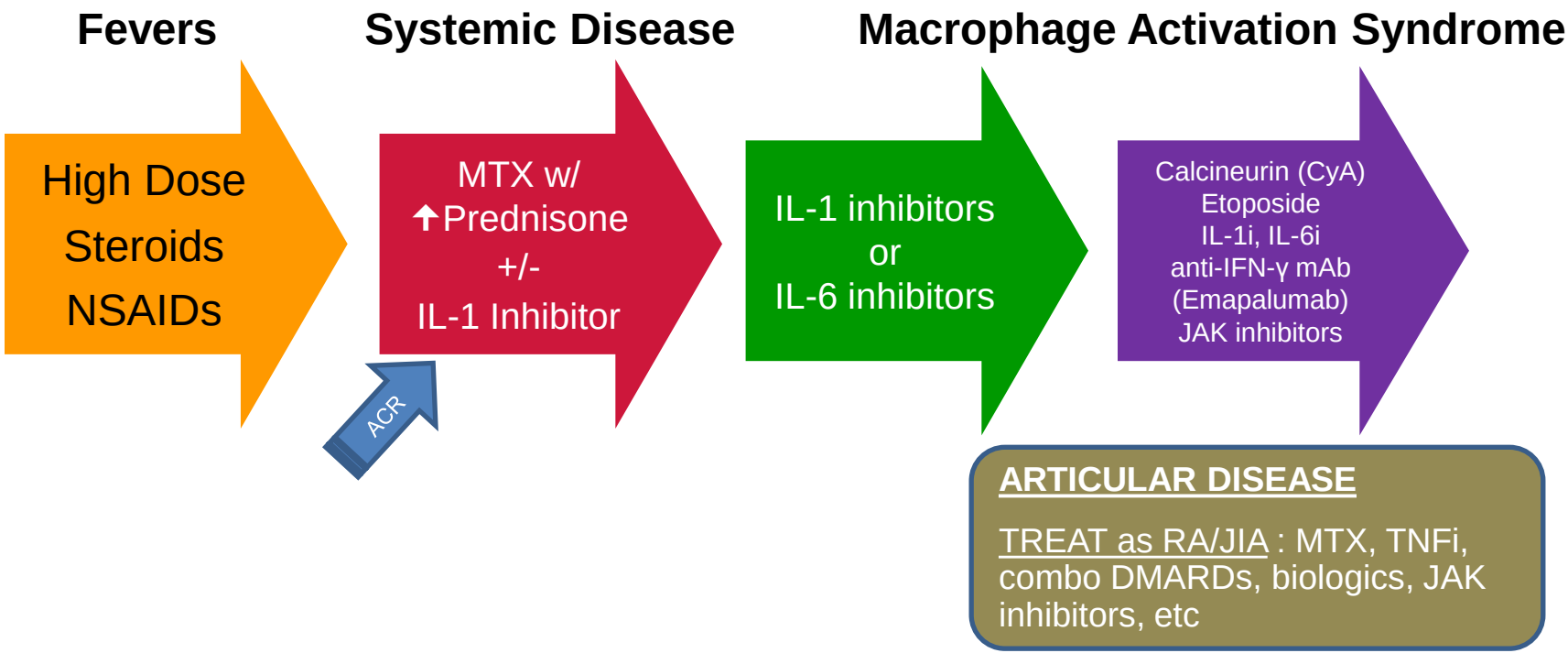
After steroids, what is your choice of therapy for active Still's disease?



RheumNow "Live Vote" survey July 2018, N = 257 Rheums

RheumNow

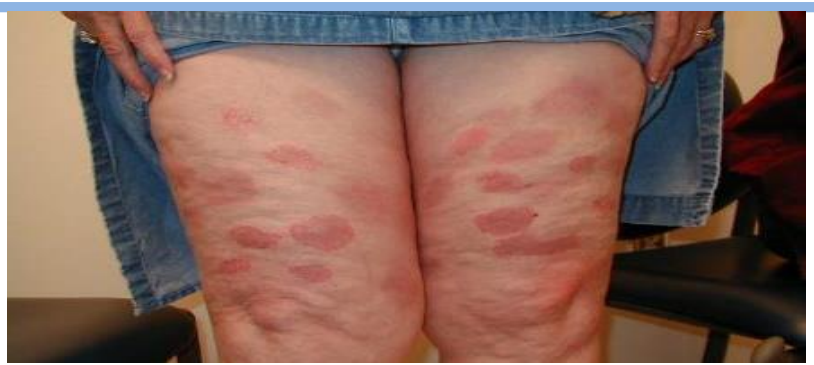
AOSDTreatment Paradigm

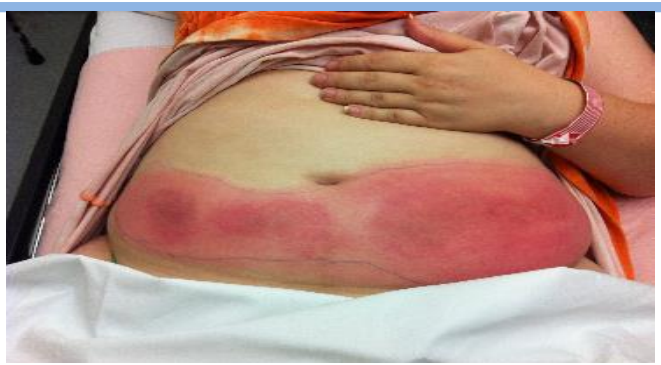


FDA Approved Therapies

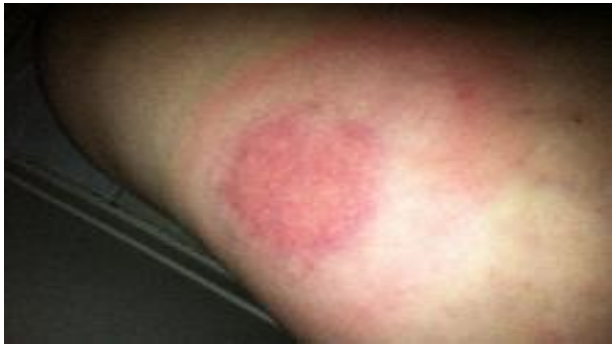
- AOSD
  - Canakinumab
- Systemic JIA
  - Canakinumab
  - Tocilizumab

Injection Site Reactions





- Anakinra ISR may occur in 1st 28 days
- Frequency of ISR
  - Anakinra 71% (RA)
  - Canakinumab 9 -12% (CAPS;sJIA)
  - Rilonacept 48% (CAPS)



Photos courtesy J. Cush, MD
Data from Package inserts: anakinra, canakinumab, rilonacept

Caveats on Management

SYSTEMIC DISEASE

Steroids – NOT low doses in AOSD

DMARDs – inferior to IL-1/IL-6 inhibitor

Cytokine inhibitors: rapid responses; Higher doses?

- Anakinra – give qhs 100-200 mg
- Canakinumab – 4mg/kg q 4wk (150,300)
- Tocilizumab – 4-12 mg/kg q 2 weeks till better, settle on 8mg q4wk

ARTICULAR DISEASE

Same as RA

MTX, TNFi, IL-6 inhib, combo DMARDs, JAK inhibitors, etc.

MAS

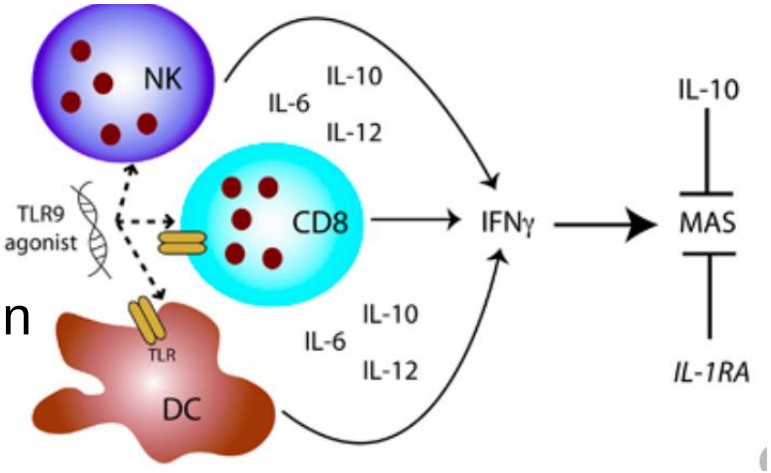
IL-6 or IL-1 inhibitors, Emapalumab, Cyclosporin or Etoposide (JAK inhibitor)

AOSD Complications

- MAS – occurs in 10%
- DIC
- Severe RA-like Polyarthritis (~25%)
- Carpal ankylosis (50%)
- Lung disease (rare, but high morbidity/mortality)
  - DRESS? Pulm HTN, Alveolar proteinosis, ILD

Cytokine Storm Syndrome | Macrophage Activation Syndrome | Hemophagocytic LymphoHistiocytosis

- High Fever, hypotension, CNS/AMS
- Hyperferritinemia > 10,000, ↑ ↑ ↑ LFTs
  - Leukopenia, lymphopenia ,thrombocytopenia
  - ↑LDH, ↑CD25, ↑IL-6,↑C-reactive protein
- Coagulopathy, ↑D-dimers, ↑PTT, ↓fibrinogen
- (BM hematophagocytosis)
- 10% of systemic JIA
- **High Mortality – <20% sJIA; <40% AOSD**
- Rx:Inhibitors of IL-1 or IL-6, Cyclosporine or Etoposide, Emapalumab



Ravelli A, Grom A, Behrens E, Cron R. Genes Immunity; 2012;13: 289 -- 298;

Randy Q. Cron, MD, PhD, & W. Winn Chatham – The Rheumatologist March 16, 2020
https://www.the-rheumatologist.org/article/dont-forget-the-host-covid-19-cytokine-storm/

Anti-IFN-γ (emapalumab) in MAS complicating systemic JIA

- Efficacy, safety and timing of response of emapalumab
- Pilot open-label single-arm, in 9 patients with MAS from sJIA and high-dose GC-IR
- Emapalumab (first dose: 6 mg/kg; subsequent doses: 3 mg/kg twice weekly) for ≤4 weeks on achieving
- All patients had a complete response
- Neutralization of IFNg evidenced by ↓ CXCL9
- Progressive improvement in laboratory parameters
- All decrease steroids to < 0.8 mg/kg qd
- Emapalumab was well tolerated
- All patients achieved CR.
- FDA approved as **Gamifant** for Primary HLH

	Baseline	Day 1	Day 2	Day3	Day 5	Day 7
Pt 1	3 413.7	2 909.2	1 302.3	997.5	538.4	407.8
Pt 2	13 259.4	16 298.7	21 962.0	20 266.3	1 656.1	461.8
Pt 3	1 518.2	2 672.3	774.0	405.1	228.0	192.2
Pt 4	98 120.5	43 211.9	11 132.4	NA	1 681.6	767.8
Pt 5	18 011.4	4 204.0	1 910.2	920.7	513.7	468.6
Pt 6	3 752.9	2 024.1	1 124.1	1 307.5	854.0	624.0
Median (Range)	8 506.1 (1 518.2-98 120.5)	3557.11 (2 024.1-43 211)	1 606.3 (774.0-21 962.0)	997.5 (405.1-20 266.3)	696.2 (228.0-1 681.6)	465.2 (192.2-767.8)

Serum CXCL9 levels at baseline and during the first 7 days of treatments with emapalumab

Works Fast, Very Expensive – but will it replace either Cyclosporine or Etoposide?

Summary

- SoJIA and AOSD are the same disorder
  - Pediatric and Adult Rheumatologists need to be aligned
- Still's disease – Diagnosis
  - Triad: Quotidian Fever >39^{o}C + JRA rash + polyarthritis
  - Criteria – Cush or Yamaguchi
- R/O infection, leukemia, lymphoma
  - Other autoinflammatory conditions? (atypical; fail criteria)
- AOSD at high risk of MAS – monitor CBC, LFTs, Ferritin
- IL-1 or IL-6 inhibition has been a major advance
- Remission occurs in 8 months to 8 years