Musculoskeletal disorders in childhood

Pavla Doležalová

Centre for Paediatric Rheumatology and Autoinflammatory Diseases

General University Hospital in Prague and 1st Faculty of Mdicine

Charles Unversity, Prague, Czech Republic

Outline

- Terms and definitions
- Musculoskeletal examination and history
- Non-inflammatory arthropathies
  - Hypermobility disorders
  - Developmental conditions
  - Metabolic and related diseases
  - Pain amplification syndromes
- Inflammatory arthropaties
  - Acute arthritis – reactive, septic
  - Secondary arthritis
  - JIA

„Joint Swelling“

- Intraarticular accumulation of fluid and/or synovial tissue
  - Inflammatory: arthritis / synovitis
  - Mechanical: synovial irritation, bleeding
- Extraarticular swelling
  - Subcutaneous soft tissues
  - „Periarthritis“
- Bone / cartilage overgrowth

„Joint / Musculoskeletal (MSK) Pain“

- Joint pain = arthralgia
  - !! Not equal to arthritis

  - Very subjective, very common in childhood
  - Multiple variables
    - Age, genetic makeup, family pain behaviors, socioeconomic factors
  - Wide differential diagnosis
  - Difficult history-taking

MSK Pain History

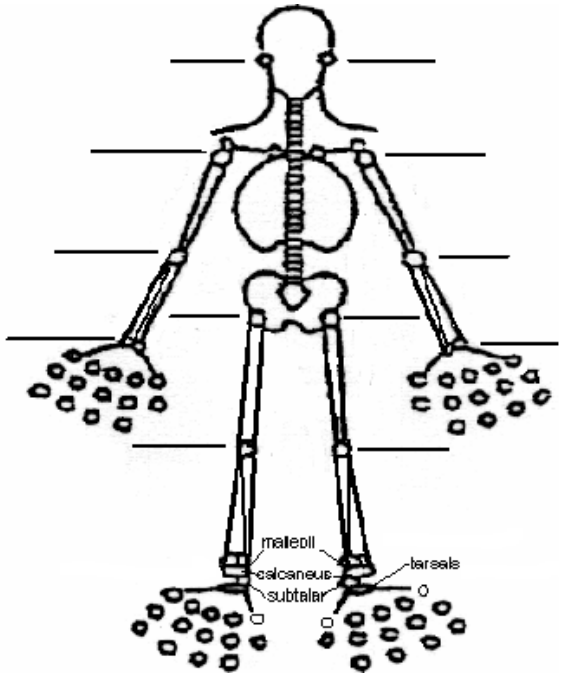
- Pain characteristics
  - Type of pain (dull, sharp, colicky…)
  - Intensity, duration, localisation, radiance
  - Predisposing and relieving factors (relation to activity)
  - Timing (morning, evening, night)
- Stiffness
- Dysfunction
- Age-appropriate activities
- Visible changes

MSK Pain: History-based differential

Aetiology	*Relationships*	*Site*	*Specific features*
Mechanical	After activity Older children	Weight-bearing joints	Blockade, instability, sharp pain relieved with rest
Inflammatory	After rest	Any joint	Early morning stiffness, intermittent pain, not relieved with rest, synovitis
Idiopathic	Stress and/or trauma	Extremity all body	Excrutiating pain, dysfunction, non-restorative sleep, missing school

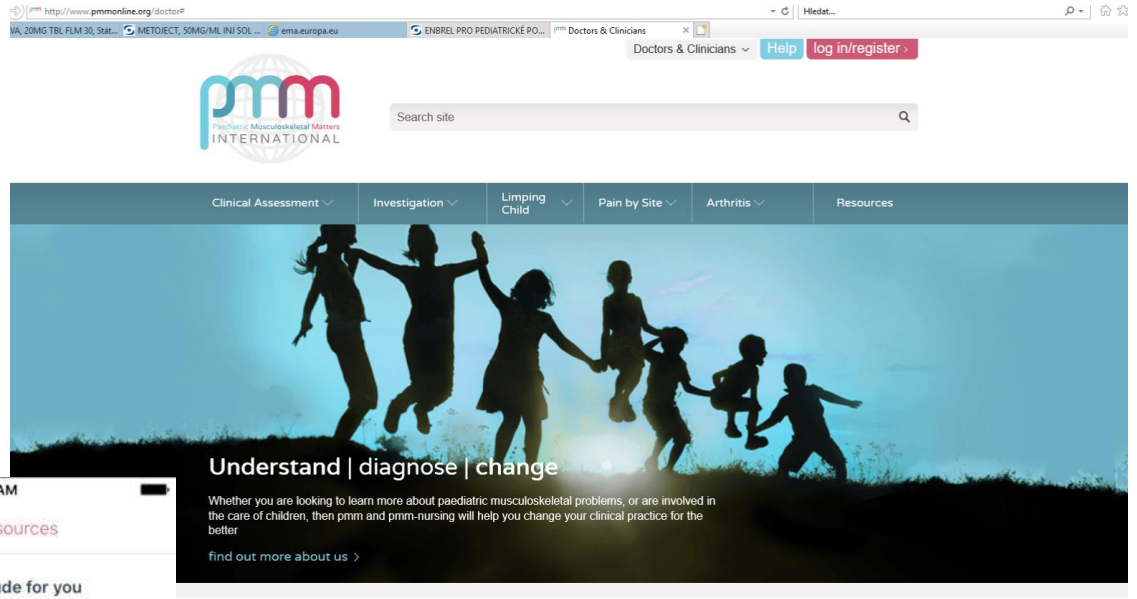
Rheumatology physical exam

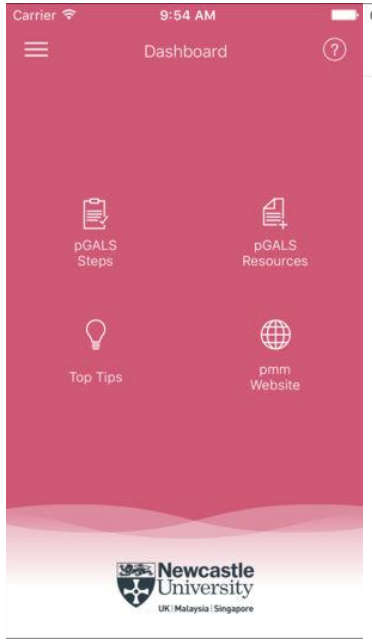
- Observation
  - Skin colour
  - Bone prominences
  - Muscle bulk
  - Side discrepancy (width, length)
  - Posture
  - Appearance of painful site
- Palpation
  - Skin temperature
  - Swelling
    - Soft tissues, effusion, bone overgrowth
  - Location of max pain
- Range of motion
  - Passive, active
  - Compensatory movements
  - Pain

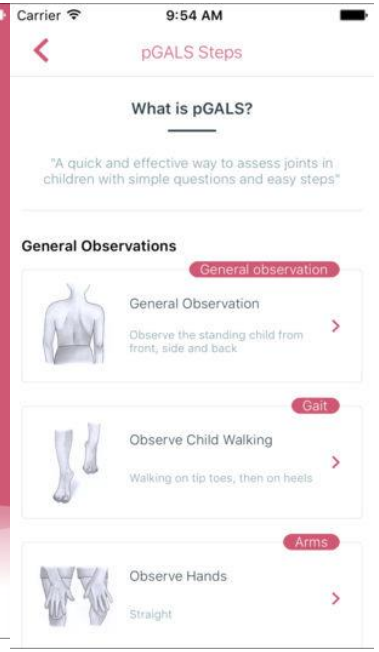


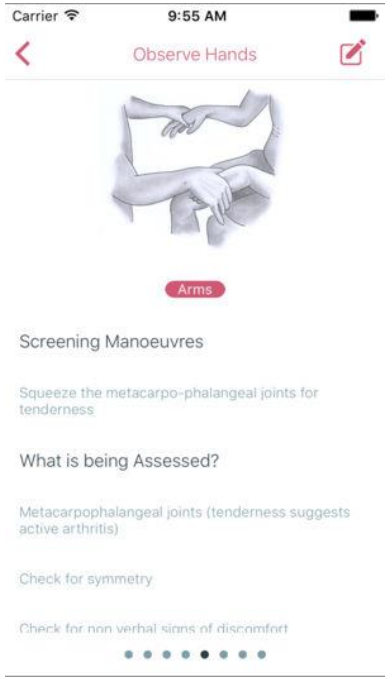
MSK system – clinical assessment

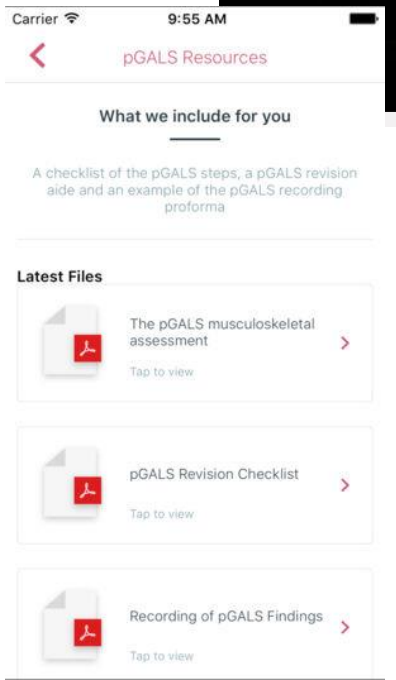
- **Paediatrician:**
  - Observation
  - pGALS: Paediatric Gait Arms Legs Spine
  - http://www.pmmonline.org/





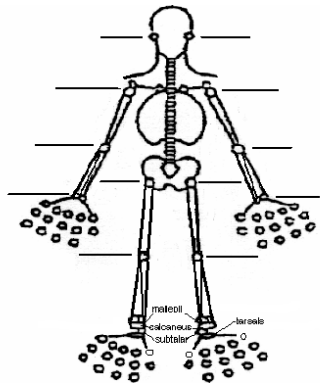




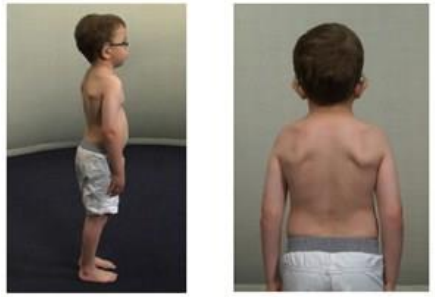


Rheumatologist:

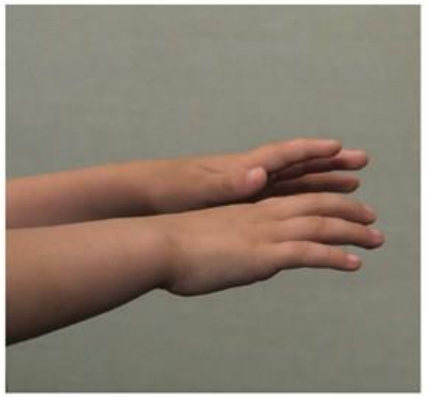
- 75 joints
- active and limited joint counts

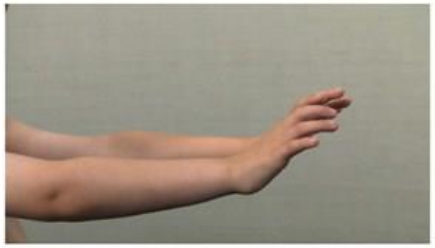
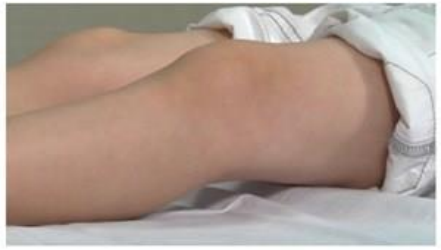


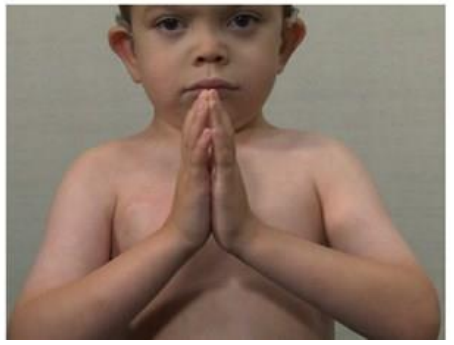
MSK system assessment



pGALS in MPS I

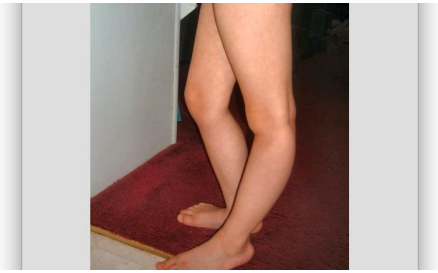




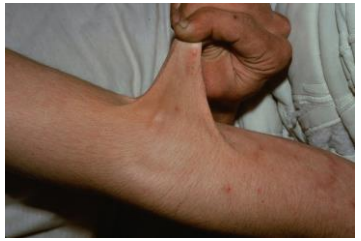


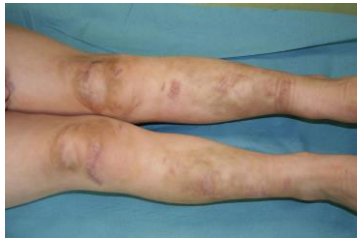
Non-nflammatory / mechanical arthropathies

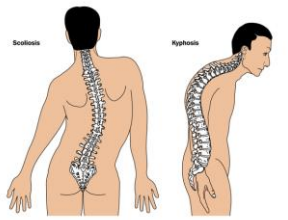
Non-inflammatory arthropathies: Hypermobility

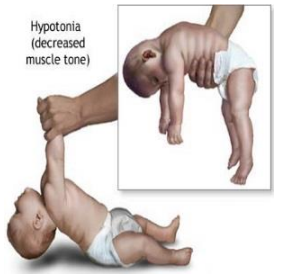
- **Physiological**
  - Typical evolutionary feature, no complaints
- **Joint „overuse“ – benign hypermobility syndrome**
  - Mechanical pain, synovial irritation
  - ↓ endurance, irritable bowel, autonomic dysfunction, fatigue
- **Ehlers-Danlos syndrome**
  - Variably severe phenotype
- **Marfan syndrome**
  - Fibrilin 1 expressed in connective tissue of many organs

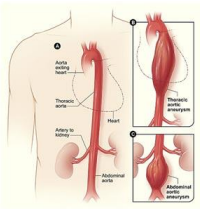


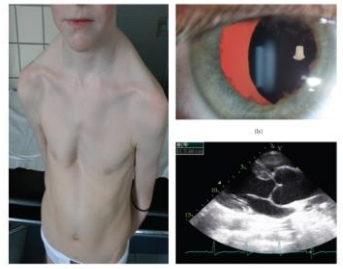


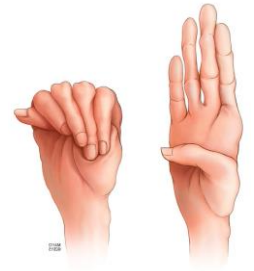








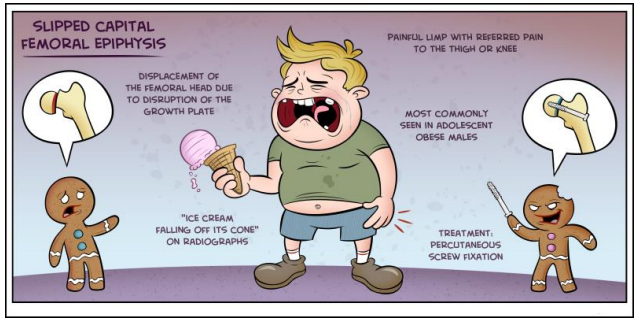


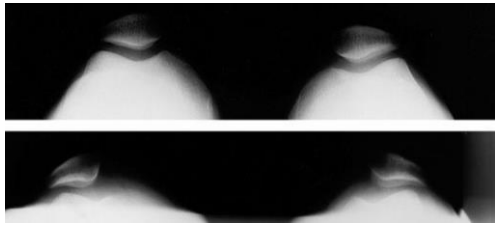


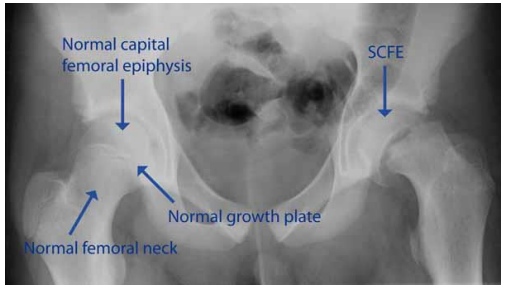
Sobey G. Arch Dis Child 2015;100:57–61. doi:10.1136/archdischild-2013-304822
Mueller GC, Stark V, Steiner K et al. Acta Pediatr 2013, 102:e84-9

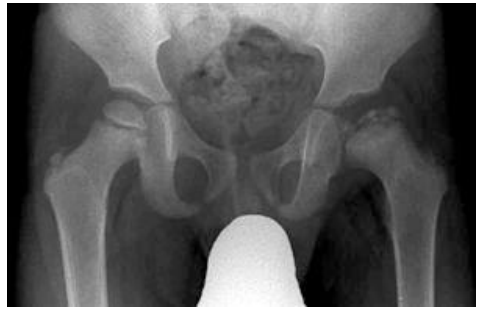
Non-inflammatory arthropathies

- **Anterior knee pain syndrome** (patelofemoral)
  - Patelar dysplasia and/od hypermobility common
- **Slipped upper femoral epiphysis**
  - Boys 8-15 yrs, often obese
- **Osteochodroses**
  - Idiopathic disorders of growing skeleton
  - „Avascular“ necrosis
    - Femoral head – Legg-Calve-Perthes disease
    - Tibial tuberosity – Osgood-Schlatter







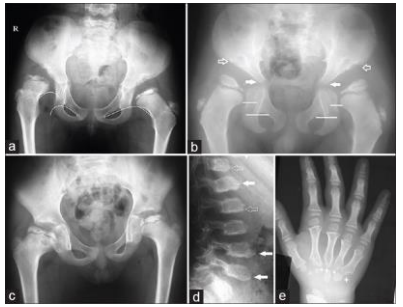


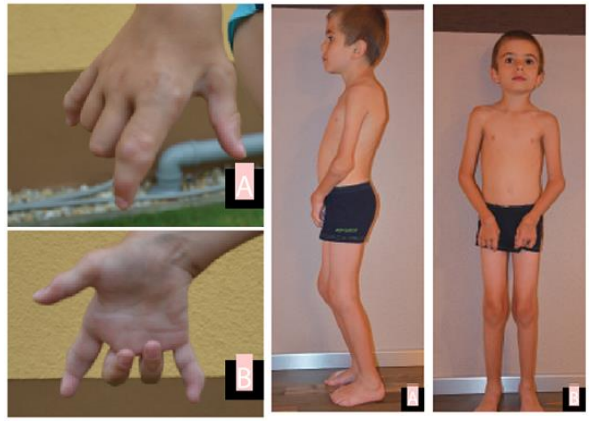
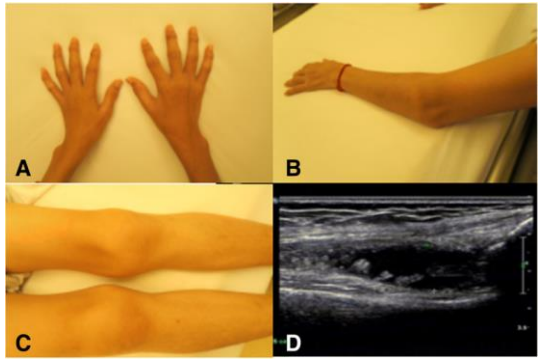
Rathleff M, Skuldbol S, Rash M et al. BMC Musculoskelet. Disord. 2013, 14:225

Non-inflammatory arthropathies

- **Lysosomal storage diseases - Mucopolysacharidoses**
  - MPS I Scheie may mimic polyarticular JIA
  - MPS IVA, IVB, C may start with knee swelling
- **Lipogranulomatosis – Farber disease**
  - Ceramide accumulation – pro-inflammatory effect
  - Phenotype spectrum from MSK only to multi-organ involvement
- **CACP syndrome**
- **Bone dysplasias**
  - Childhood progressive pseudorheumatoid arthropathy – WISP3 gene mutation



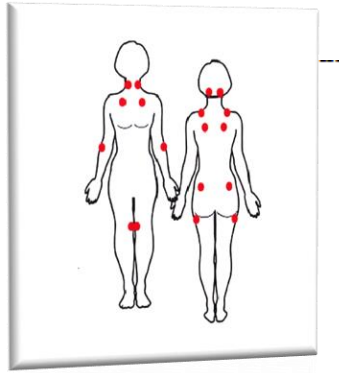



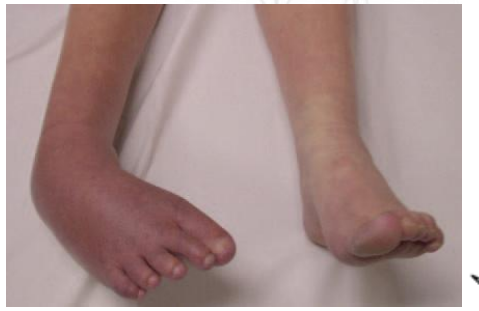



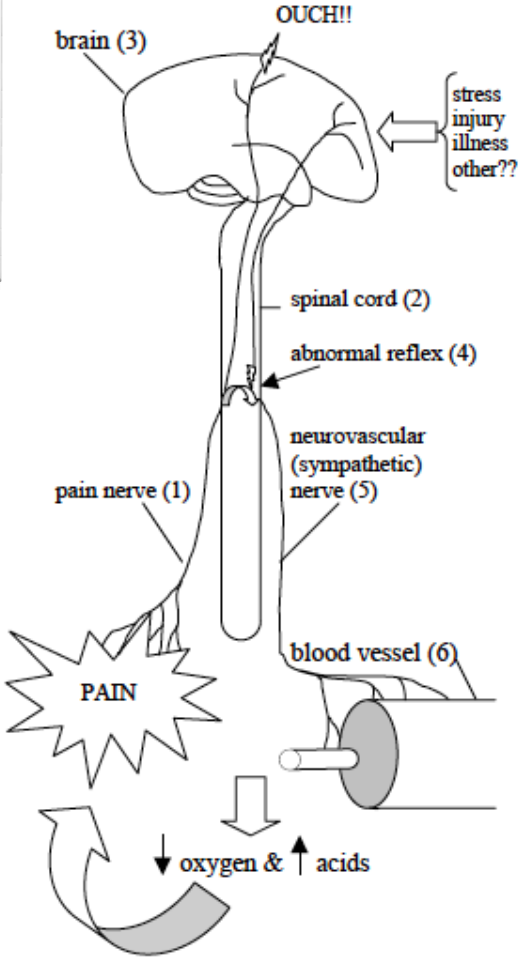
Cimaz R, Coppa GV, Koné-Paut I et al. Pediatr Rheumatol Online J 2009,7:18
Aldenhoven M, Sakkers RJ, Bolenes J et al. Ann Rheum Dis 2009,68:1659-65
Garcia-Segarra N, Mittaz L, Campos-Xavier AB et al. Am J Med Genet A 2012, 160C:217-29

Idiopathic pain /Pain amplification syndromes

- **Localised idiopathic pain (LIPS)**
  - Complex regional pain syndrome (algodystrophy)
  - Growing pains
- **Generalised / diffuse idiopathic pain (DIPS)**
  - Fibromyalgia
- **Undetermined, mixed pattern**
  - MSK pain for over 1 month (LIPS), over 3 months (DIPS)
  - without organic origin
- **„Growing“ pains**
  - Recurrent night pain with no day problems and normal findings during the day
  - Usually at age 3-10





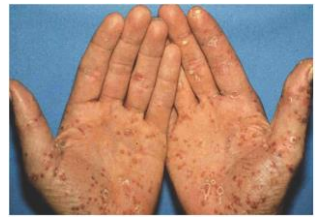


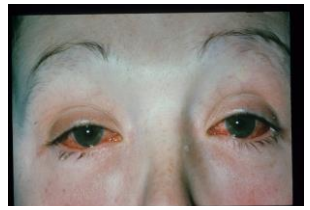
Inflammatory arthropathies

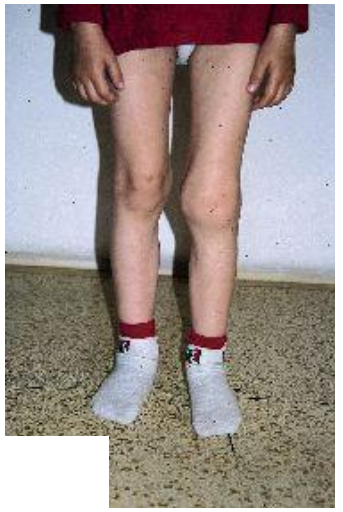
Acute arthritis: Reactive

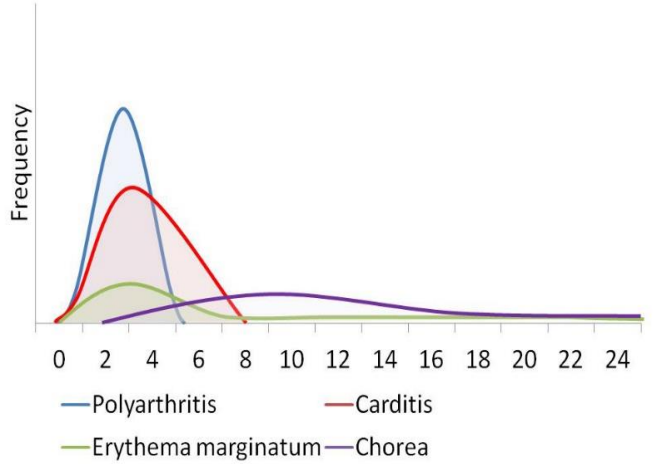
- Acute, self-limited sterile arthritides related to previous extraarticular infection
- Subgroups:
  - **post-enteritic**
  - Post-viral, viral arthritides
- Acute onset 1-4 wks post GI or genitourinary infection
  - Constitutional and extraarticular symptoms
- Evolution
  - Weeks (months) duration, self-limited, good response to NSAID
  - Up to 30% evolve into chronic arthritis

- **Acute rheumatic fever**
  - Preceding GAS pharyngitis 10-31 days
  - Revised Jones criteria









Burgos Vargas 2011, Gupta 2007 Denardo et al 1994, Bowyer et al 1996, Symmons et al 1996, Malleson et al 1996 Riise et al 2008 Gewitz MH et al. Circulati

ARF

Springer Link

Acute rheumatic fever outbreak in southern central European country

European Journal of Pediatrics
pp 1–7

Authors Authors and affiliations AuthorsAuthors

Urška Kočevar , Nataša Toplak, Blaž Kosmač, Luka Kopač, Samo Vesel, Natalija Krajnc, Matjaž Homan, Rina Rus, Tadej Avčin

Original Article
First Online: 04 November 2016
DOI (Digital Object Identifier): 10.1007/s00431-016-2801-z

Definition and epidemiology

- Complication of group A streptococcal (GAS) pharyngitis in predisposed individual
- Sharp reduction of incidence in past decades
- Remains a medical and public health problem
  - Rheumatic heart disease=leading cause of acquired heart disease in children in developing countries
  - Overall prevalence 15 million, 282 000 new cases/year, 233 000 deaths every year Carapetis et al 2005
- Incidence of 1st attack 5-51 cases / 100 000 children Tibazarwa et al 2008
  - Geographic differences
  - Recent outbreaks in Western countries
  - Increased prevalence due to immigration Remenyi B et al 2013
- Age of onset between 5-14 yrs, males and females equal

Pathogenesis

- GAS = the only Strep serogroup causing ARF
  - Skin infection does not cause ARF
  - Latency of 2-3 wks
- 15% school-aged children will get GAS pharyngitis
  - <3% develop ARF
- Genetic predisposition is likely (class II HLA)
- Serotypes 3 and 18 most common Johnson et al 1992, Smoot et al 2002
  - M-protein = type-specific Ag of pathogenic importance
  - Several epitopes cross-reactive with human tissues Ayoub and Kaplan 1991
  - Potential superantigen role Tomai t al 1990
  - Ab against some GAS epitopes cross-react with laminin and cardiac myosin Galvin et al 2000
  - Serum of chorea patients cros-reacts with GAS carbohydrate epitope Kirvan et al 2003
  - Anti.collagen Ab theory – sub-endothelial collagen as a target Tandon et al 2013

Clinical presentation

- 10-31 days from GAS pharyngitis
  - Neurological manifestations 4-6 wks
  - 30% patients do not recall pharyngitis history Mandell et al 2009
- Main manifestations described by Jones (1944)
  - Major
    - Arthritis, carditis, Sydenham chorea, erythema marginatum, subcutaneous nodules
  - Minor
    - Arthralgia, fever
    - ↑ acute phase reactants, prolonged PR interval

MSK

- Acute arthritis
  - 70% patients
  - Polyarthritis is typical, monoarthritis counts in high prevalence populations Gewitz et al 2015
  - Migratory, but joints overlap, few days duration
  - Redness of the skin may be present
  - Preferentially large joints Burke and Chang 2014
  - Excellent response to NSAID

Carditis

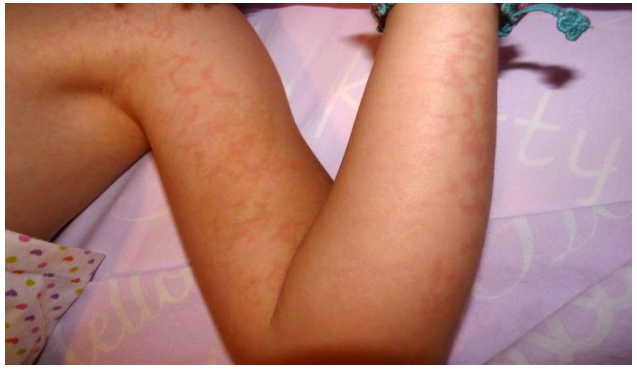
- Affects 30-80% patients during 1st episode
- The only acute manifestation that may cause damage Roberts et al 2013
- Usually together with arthritis
- Wide clinical spectrum
  - Pancarditis with heart failure to clinically silent disease detected only by ECHO
  - Tachycardia, new murmur
  - Usually myocardium and endocardium, mitral (aortic) valve – typical pansystolic mitral regurgitation murmur

Chorea

- Sydenham's chorea, San Vitus dance, chorea minor
- Involvement of basal ganglia and caudate nucleus
- Affects 5-36% of ARF patients
- Longer latency from infection
- Typically emotional lability, loss of physical coordination, weakness
  - Eratic involuntary movements, dysarthria, affected handwriting, tongue fasciculations
  - Sometimes unilateral, not present in sleep
  - Self-limited, resolves within weeks

Skin manifestations

- Erythema marginatum
  - uncommon, 6% patients, at early stage
  - Evanescent pink rash with pale centers, vertiginous margins, non-pruritic, blanching



- Subcutaneous nodules
  - In less than 4% cases Seckler and Hoke 2011
  - Nodules up to 2 cm in diameter over joints, scalp, spinal processi

2015 revision of Jones criteria

- Recognizes disproportionate distribution of ARF
  - low.-risk population:
    - ARF incidence <2 per 100 000 school children
  - All-age prevalence of RHD ≤1/1 million population
- Definitions of individual criteria fitted to the risk level
  - Monoarthritis, subclinical carditis
- Definitions of echocardiographic findings to fulfill the carditis criterion
- Definitions of the preceding GAS infection

Gewitz MH et al. Circulation 2015;131:1806-18

Diagnosis of ARF

- Evidence of GAS infection
  - Elevated or rising ASO titer
  - Positive throat culture
  - Positive rapid Ag test
  - History of recent scarlet fever
- Non-specific inflammation
  - ESR, CRP
- Echocardiography

ASO

Age group	Upper limits of normal Todd units
5 years	160
6-9 years	240
10-12 years	320

	Antistreptolysin O	Antideoxyribonuclease B
Begins to rise	1 week	2 weeks
Peaks	3-5 weeks	6-8 weeks
Begins to decline	6-8 weeks	3 months

Primary Prevention

- Adequate treatment of GAS pharyngitis
  - Penicillin preferred

Drug	Route of administration	Treatment duration
Penicillin V (phenoxymethyl penicillin)	Oral	10 days
Amoxicillin	Oral	10 days
Benzathine penicillin G	Intramuscular	One single dose
For patients allergic to penicillin		
Narrow-spectrum cephalosporins	Oral	10 days
Clindamycin	Oral	10 days

Therapy

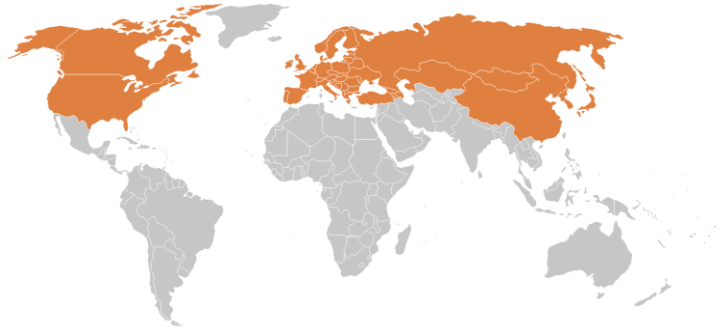
- Bed rest, GAS eradication, aspirin, corticosteroids
- Arthritis: NSAID
  - Salicylates 50-75 mg/kg/day
  - Other NSAIDs (naproxen)
- Carditis
  - Salicylates 100 mg/kg/day with levels monitored for toxicity, 4-8 weeks then gradual taper over 4 weeks
  - Corticosteroids for severe carditis. Prednisone 1-2 mg/kg/day, 2-3 weeks then gradual taper

Secondary prophylaxis

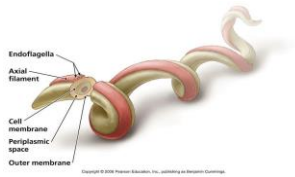
Antibiotic	Mode of administration	Dose
Benzathine benzylpenicillin	Single intramuscular injection every 3–4 weeks.	For adults and children ≥30kg in weight: 1200000 units. For children <30kg in weight: 600000 units.
Penicillin V.	Oral.	250mg twice daily.
Sulfonamide (e.g. sulfadiazine, sulfadoxine, sulfisoxazole).	Oral.	For adults and children ≥30kg in weight: 1 gram daily. For children <30kg in weight: 500mg daily.
Erythromycin.	Oral.	250mg twice daily.

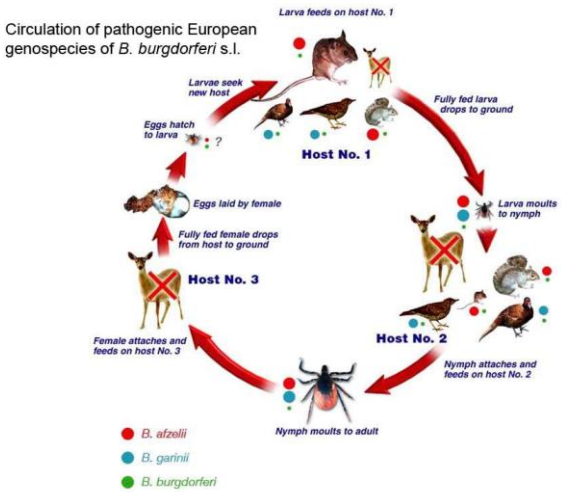
Category of risk	Duration After Last Attack
Rheumatic fever without carditis	5 years or until 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual heart disease (no valvular disease)	10 years or until 21 years of age (whichever is longer)
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis

Acute arthritis: Infectious



- **Lyme disease**
  - Europe: from Scandinavia to northern Southern Europe
  - >300 cases / 100 000 inhabitants
  - Bimodal age distribution
    - School age, after 5th decade





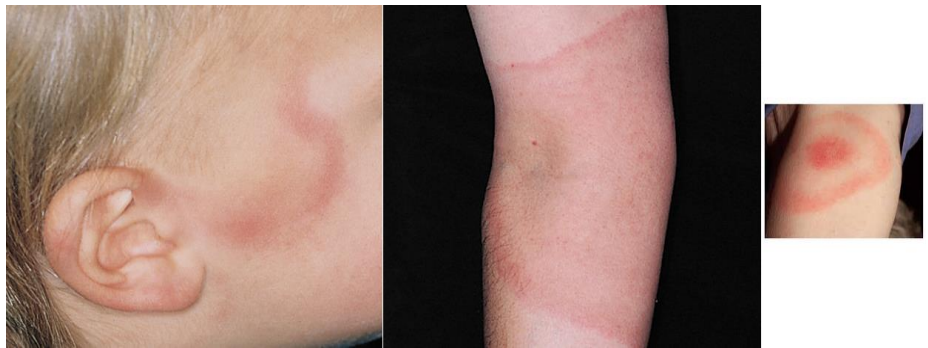
Stanek G et al. Lancet 2012;379:461-73 Esposito S,et al.. Int J Infect Dis 2013;17:e153-e158
Frank G, Mahoney HM, and Eppes SC, *Pediatr.Clin.North Am.*, 2005,52, 1083-106. Gillespie WJ, *Infect.Dis.Clin.North Am.*, 1990,4, 361-376

Clinical presentation

- **Early infection**
  - Stage 1 – localised to the skin
  - Stage 2- early dissemination (days to weeks)
- **Persistent infection**
  - Stage 3 (months to years)
- Incubation of 3-32 days from the bite
  - EM (70-80% cases) =stage 1 localised
- Secondary lesions, acute meningitis, cranial neuropathy, radiculoneuritis, A-V block, arthralgia = Early dissemination
- Intermittent arthritis (60% untreated cases), acrodermatitis, neurologic abnormalities=stage 3

Clinical presentation: Skin

- Incubation of 3-32 days from the bite
  - EM (70-80% cases) =stage 1 localised
- Secondary lesions, lymphocytoma – dissemination
- Often flu-like symptoms
- Resolves spontaneously in 3-4 wks regardless therapy
- Antibodies not yet produced



Neuroborreliosis

- Lymphocytic meningitis and facial palsy
  - Most common early manifestations of disseminated disease
  - Constitutional symptoms possible
  - Weeks-months after bite
  - Neck stiffness often mild or absent
  - Other cranial nerves may be affected

  - Meningoradiculoneuritis rare in children
  - Other rare: myoclonus, ataxia, acute transverse myelitis, idiopathic IH

Arthritis

- Late manifestation
- Months to years after infection
- More common in children than adults
- Knees most commonly affected
  - Predictors of septic aetiology:
    - ANC>10 000 cells/mm^3
    - ESR ≥ 40mm/h
- Borrelia in SF
  - Not detected, PCR may be positive
  - Dx confirmed by serology
- Outcome
  - 39% peristence of synovitis >6 months
  - 13% >12 months

Brescia AC, Rose CD, Fawcett PT. Clin Rheumatol 2009;28:591-3

Other manifestations

- Transient A/V block in 4-10% adults
- Children with early disseminated disease
  - 15.9% had carditis
  - Resolved with ATB
- Ocular involvement
  - Conjunctivitis, keratitis, iridocyclitis, intermediate uveitis, choroiditis, optic neuritis

Diagnosis

- Clinical history
- Serology
  - Not required for EM
  - Ab production in disseminated disease detectable in blood
  - CSF and SF positivity – later
  - Both IgM and IgG remain elevated for years, cannot serve for F/U
  - 2-tier testing recommended
    - Total Ab plus immunoblot confirmation

Manifestations and Ab profile

Involved organs	Early manifestations	Serological results	Late manifestations	Serological results
Skin	Erythema migrans, Lymphocytoma	None	Acrodermatitis chronica atrophicans	IgG EIA+ IgG IB+
Central nervous system	Lymphocytic meningitis, facial palsy	Lymphocytic pleocytosis, IgM+ and early IgG response	Radiculoneuritis, encephalomyelitis	Intrathecal antibody production, IgG EIA+ IgG IB+
Heart	Myopericarditis AV-block	IgM+ and early IgG response	Cardiomyopathy	IgG EIA+ IgG IB+
Eye	Conjunctivitis	IgM+ and early IgG response	Uveitis, keratitis	IgG EIA+ IgG IB+
Musculoskeletal system	“Summer flu”, myalgias, arthralgias	None	Episodic arthritis, chronic arthritis	IgG EIA+ IgG IB+

Clinical diagnostic score

- Presence of Lyme arthritis
  - Values ≥6 v
  - Values ≤2.5 exclude the diagnosis

Criterion	Score
Episodic arthritis	+ 4
Arthralgia before onset of arthritis	- 3
Age at onset of arthritis	+ 0.3 x age (yrs)
Initial arthritis in knee joint	+ 2
History of tick bite	+ 2
Number of joints involved	- 0.4 x number of large joints affected

Huppertz HI et al. Eur J Pediatr 1998;157:304

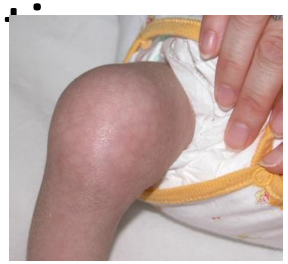
Therapy

- According to the stage and type of involvement and patient age

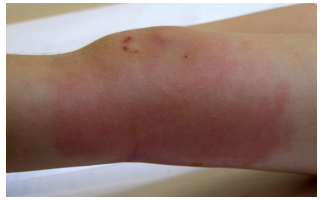
Manifestation	Drug	Dosage for children	Duration
Erythema migrans	Amoxicillin	50 mg/kg/day in 3 divided oral doses (max.500 mg/dose)	10-21 days‡
	Doxycycline*	200 mg/day in 1-2 oral doses	10-21 days‡
Neuroborreliosis and Lyme carditis	Ceftriaxone	50 - 100 mg/kg/day in 1 i.v. dose	2 – 4 weeks
	Cefotaxime	150 mg/kg/day in 3 i.v. doses	2 – 4 weeks
Lyme arthritis	Amoxicillin	50 mg/kg/day in 3 divided oral doses (max.500 mg/dose)	4 weeks
	Doxycycline*	200 mg/day in 1-2 oral doses	4 weeks
	Ceftriaxone	50 - 100 mg/kg/day in 1 i.v. dose	2 - 4 weeks
	Cefuroxime	30 mg/kg/day in 2 doses	4 weeks

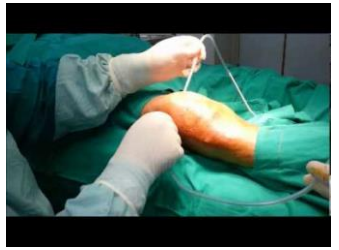
Septic arthritis

- **Septic arthritis**
  - 5.5 – 12 cases / 100 000 children
  - Most common <3 yrs
- Hematogeneous spread
  - Most frequent
  - Focal infection
- Direct extension from bone or soft ti
- Penetrating trauma
- Post-surgery complication



Age	Microorganisms
Neonate	Group B streptococcus
	Staphylococcus aureus
	Gram-negative bacillis
Infant	Staphylococcus aureus
	Streptococcus spp
	Kingella kingae
	Haemophilus influenzae
Child	Staphylococcus aureus
	Kingella kingae
	Streptococcus pneumoniae
	Streptococcus pyogenes
Adolescent	Staphylococcus aureus
	Streptococcus pneumoniae
	Streptococcus pyogenes
	Neisseria gonorrhoeae





Stanek G et al. Lancet 2012;379:461-73 Esposito S,et al.. Int J Infect Dis 2013;17:e153-e158
Frank G, Mahoney HM, and Eppes SC, *Pediatr.Clin.North Am.*, 2005,52, 1083-106. Gillespie WJ, *Infect.Dis.Clin.North Am.*, 1990,4, 361-376

Causative agents

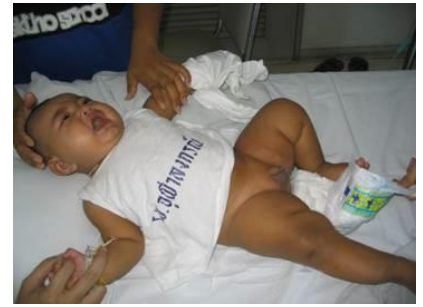
- Differ according to the age group
- Staph = most common (>2 yrs)
- HIB ↓ Kingella ↑
- Salmonella
  - Sickle cell disease, ID

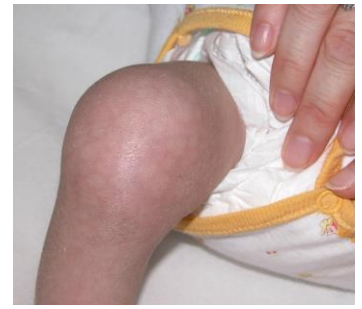
Age	Microorganisms
Neonate	Group B streptococcus
	Staphylococcus aureus
	Gram-negative bacillis
Infant	Staphylococcus aureus
	Streptococcus spp
	Kingella kingae
	Haemophilus influenzae
Child	Staphylococcus aureus
	Kingella kingae
	Streptococcus pneumoniae
	Streptococcus pyogenes
Adolescent	Staphylococcus aureus
	Streptococcus pneumoniae
	Streptococcus pyogenes
	Neisseria gonorrhoeae

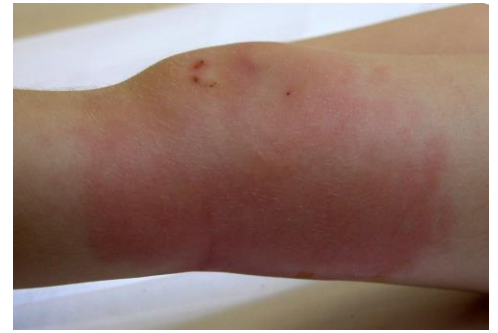
Cassidy JT, Petty RE, Ronald Laxer L, and Lindsley C, 2011, *Textbook of Pediatric Rheumatology, 6th Ed*
Arnold SR et al, *J.Pediatr.Orthop. 2006*, **26**, 703-708.
Yagupsky P, *Adv.Exp.Med.Biol. 2006*, **582**, 179-190

Clinical picture

- Fever, constitutional symptoms
- Severe pain, loss of function
- Usually monoarthritis
  - Multiple joints in immunocompromised
- Lower limb joints more commonly affected



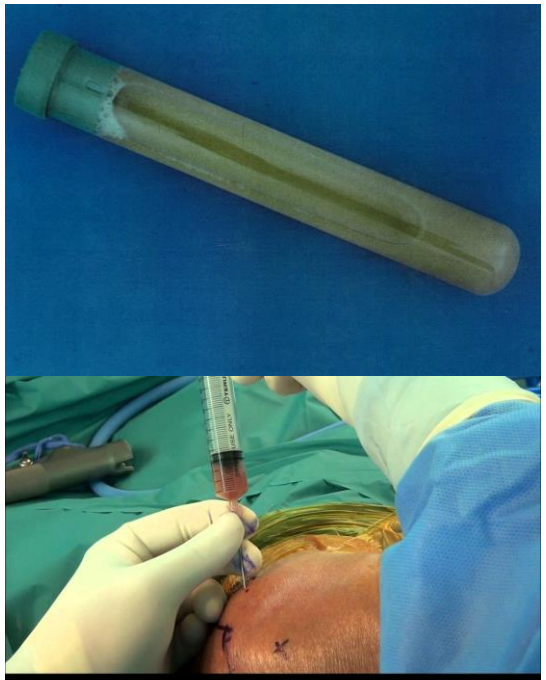




Goergens ED et al, *J.Paediatr.Child Health* 2005, **41**, 59-62.
Peltola H et al, *Clin.Infect.Dis.*, 2009, **48**, 1201-1210.

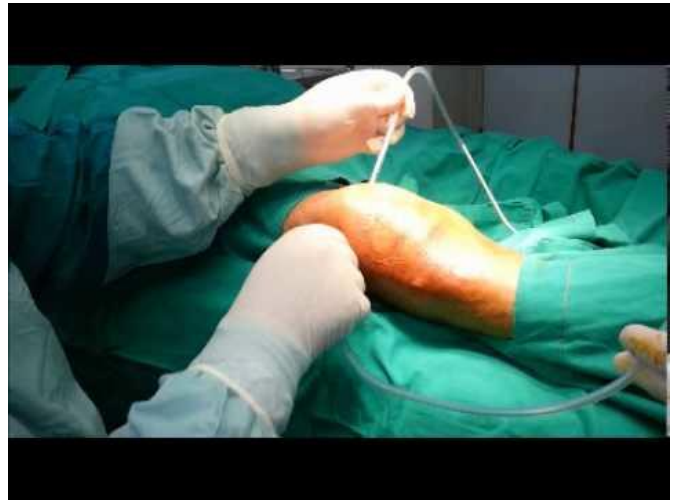
Diagnosis

- High level of suspicion in monoarthritis with constitutional symptoms
- PED RHEUM EMERGENCY
  - Immediate joint aspiration
  - SF for microscopy, culture, cell count
    - Appearance
    - WBC >50.000 cells/µL, ↓glu, ↑protein
      - NOT pathognomonic
    - 30% sterile
      - Bacteriostatic activity of SF
    - Blood cultures simultaneously
  - Imaging for differential Dx
    - XR, US, MRI, CT, bone scan



Management I

- Multidisciplinary
  - Orthopedic surgeon
    - Arthrotomy for pressure relief
    - Joint lavage (?)
  - Infectionist
    - Antimicrobial agent choice



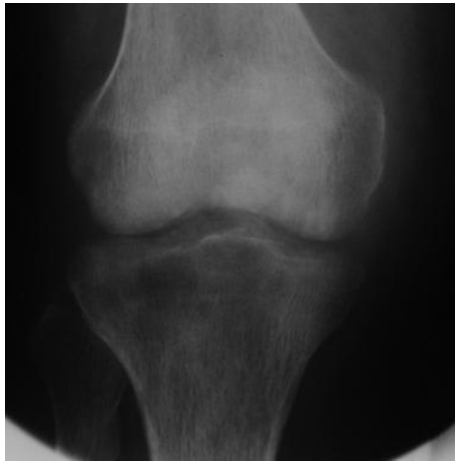
Management II

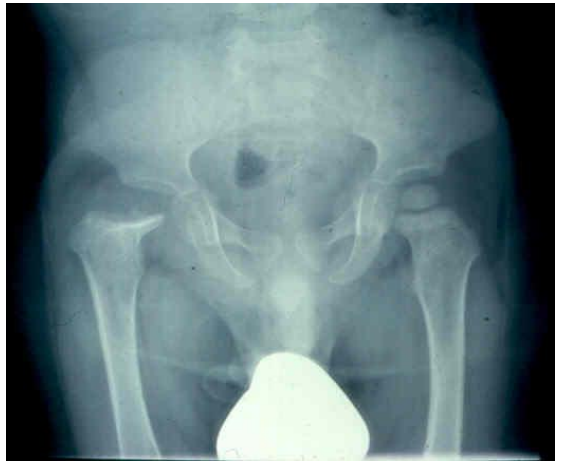
- Antibiotics i.v. ASAP
  - Start with empirical, then fine-tune
  - Anti-staph penicillins
    - cloxacillin, clindamycin, 2st and 2nd generation cephalosporins
  - In case MRSA is >10% of staph strains in the area
    - Vancomycin, clindamycin (large dose ≥40 mg/kg/day)
  - If HIB suspected
    - Cefotaxime, cefuroxime
  - Kingella kingae
    - β-lactams
  - Gonococcal
    - Ceftriaxone, cefotaxime
- Duration
  - Minimum 3 wks in uncomplicated cases, 1 week i.v. at least
  - Previously healthy, 1 joint only, good initial response

Paakkonen M, and Peltola H, *Pediatr.Infect.Dis.J.*, 2013,**32**, 684-685.

Outcome

- Risk of permanent damage
  - Hip in neonates
- Residual dysfunction in 10-25% of children





Cassidy JT, Petty RE, Ronald Laxer L, and Lindsley C, 2011, *Textbook of Pediatric Rheumatology, 6th Ed*

„Secondary“ arthritis

- Arthritis in acute paedatric vasculitis
  - IgAV (HSP), KD
- Arthritis of other systemic diseases
  - IBD, SLE, JDM, Scleroderma
  - Neoplasia (bone pain), Paraneoplastic arthritis, Bleeding disorders
    - **ALL, lymphoma, neuroblastoma**, bone and soft tissue tumours
    - Pain inappropriate to objective MSK findings, constitutional symptoms
  - Autoinflammatory disease of joints and bones
    - Arthritis/arthropathy of periodic fever syndromes
    - Sterile pyogenic arthritis of PAPA syndrome
    - CRMO/SAPHO