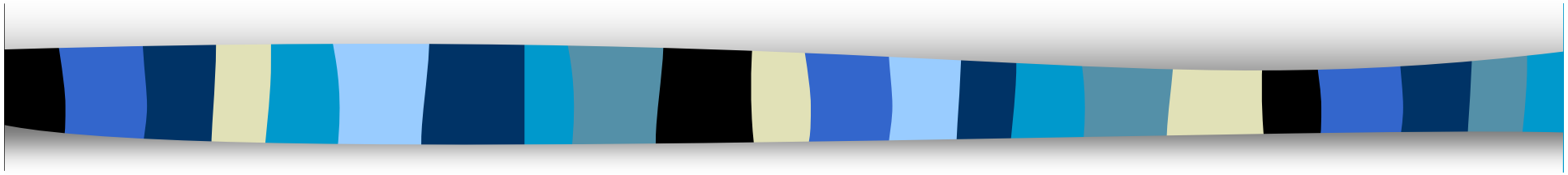
Bone and Joint Infection
The medical view…



Dr Julia Clark

Consultant Paediatric
Infectious Disease

Definitions

- Osteomyelitis (OM) is inflammation of the bone accompanied by bone destruction, usually due to bacterial infection.
- Septic arthritis (SA) is acute infection of synovial joints, usually secondary to bacteraemia.
  - Affects synovial membrane and the joint space.
  - In younger children, the capsule of the joint often extends to the metaphysis, which when the cortex is damaged can lead to septic arthritis secondary to osteomyelitis and vice versa.
  - The epiphyseal growth plate can also be affected, causing growth discrepancies and long term disability.

Classification by onset

- Acute – Symptoms for < 14 days
- Sub-Acute – > 2 weeks of symptoms
- Chronic
  - Alternating periods of quiescence & recurrent
  - pain, swelling and sinus tract development
  - Often with a sequestrum (necrotic bone)

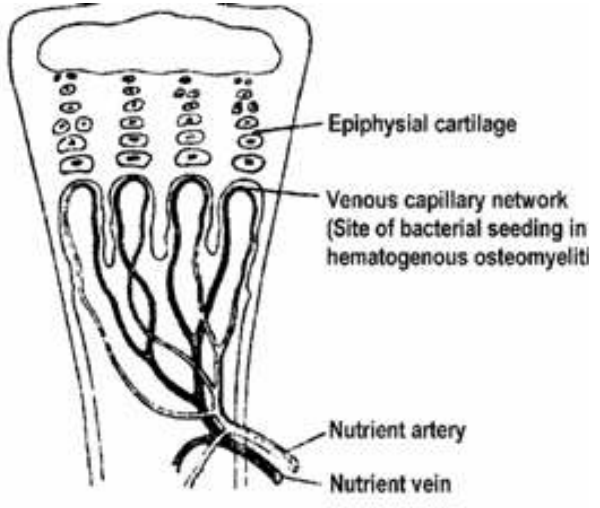
Classification by pathogenesis

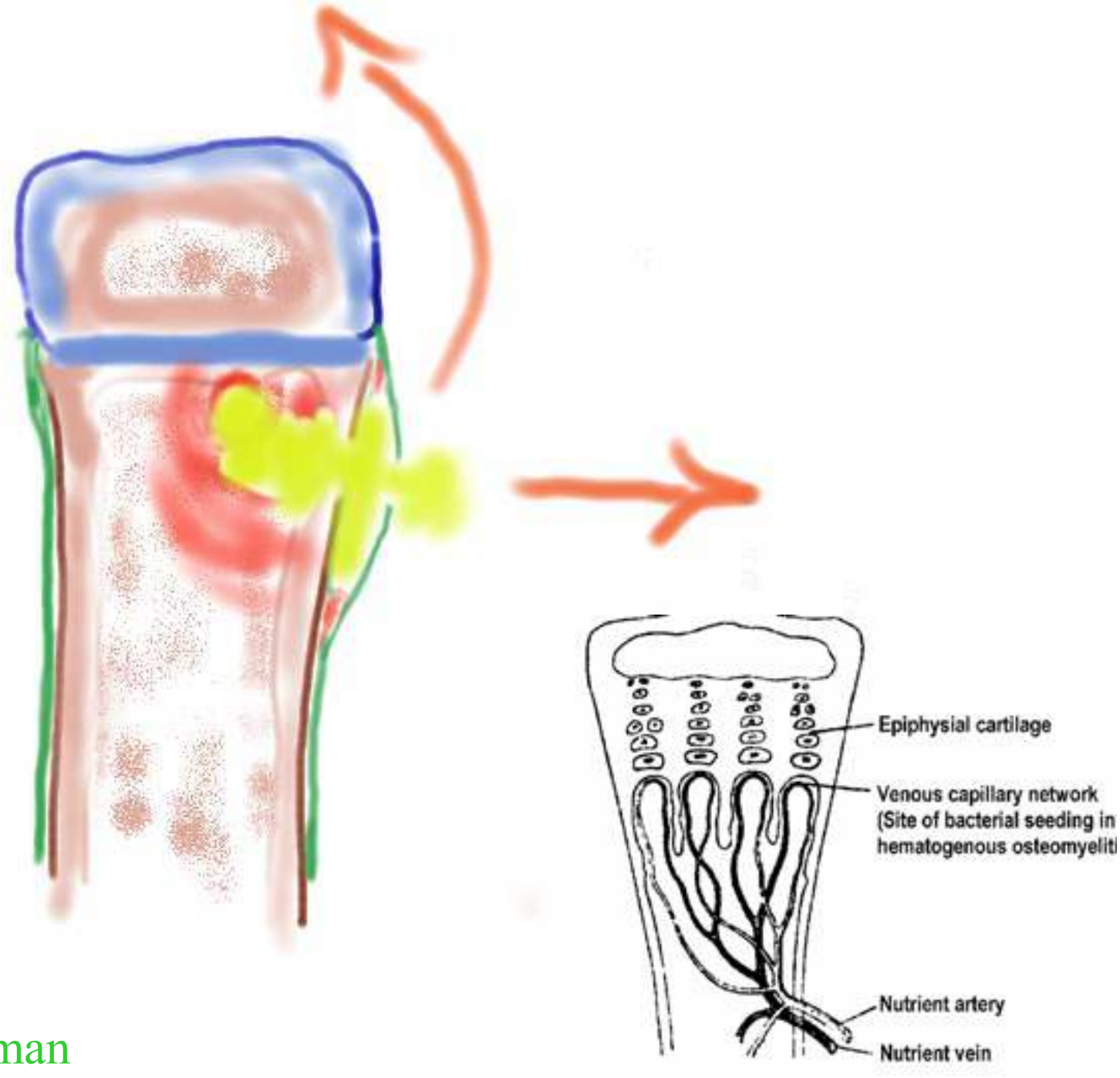
- Hematogenous Osteomyelitis
  - Arising from occult bacteraemia with secondary seeding of the bone or joint
  - Most common
- Direct inoculation
  - Post surgical
  - Post traumatic (eg. open fracture)

Pathophysiology

Bacterial deposition

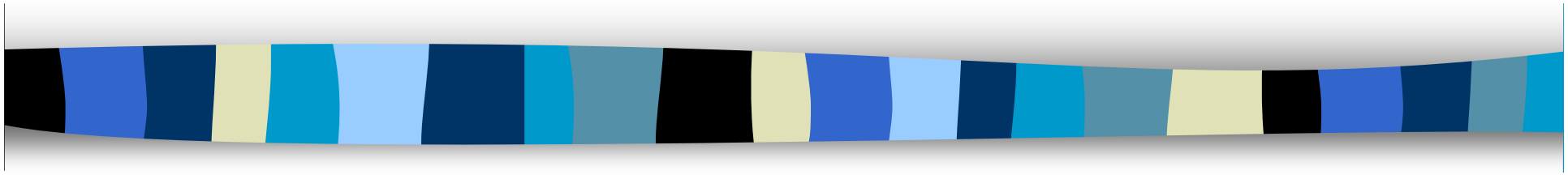
- Trauma or emboli lead to occlusion of slowflowing sinusoidal vessels
- Bacteria enter via the metaphyseal branches of the nutrient artery causing infection of metaphysis adjacent to the epiphyseal growth plate
- Rich metaphyseal vascular supply
- Growth plate is nourished by diffusion of nutrients

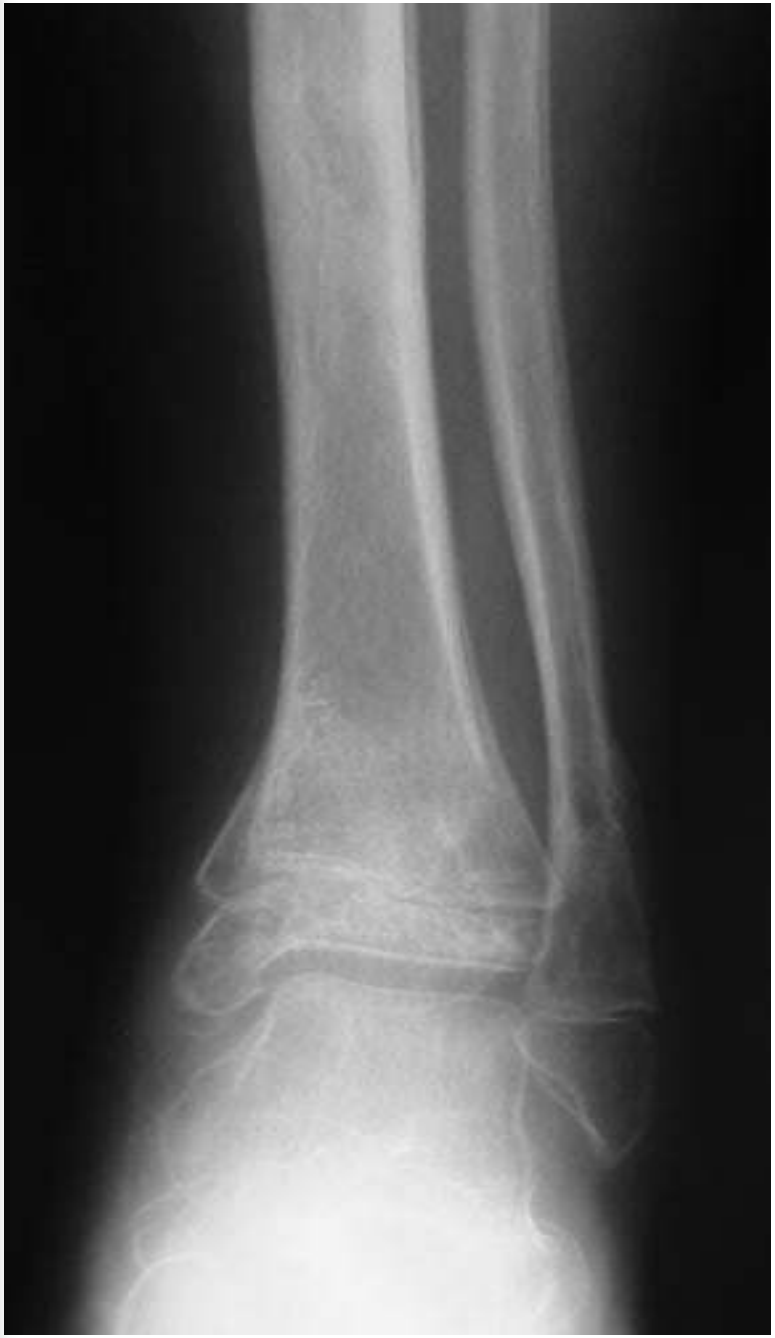


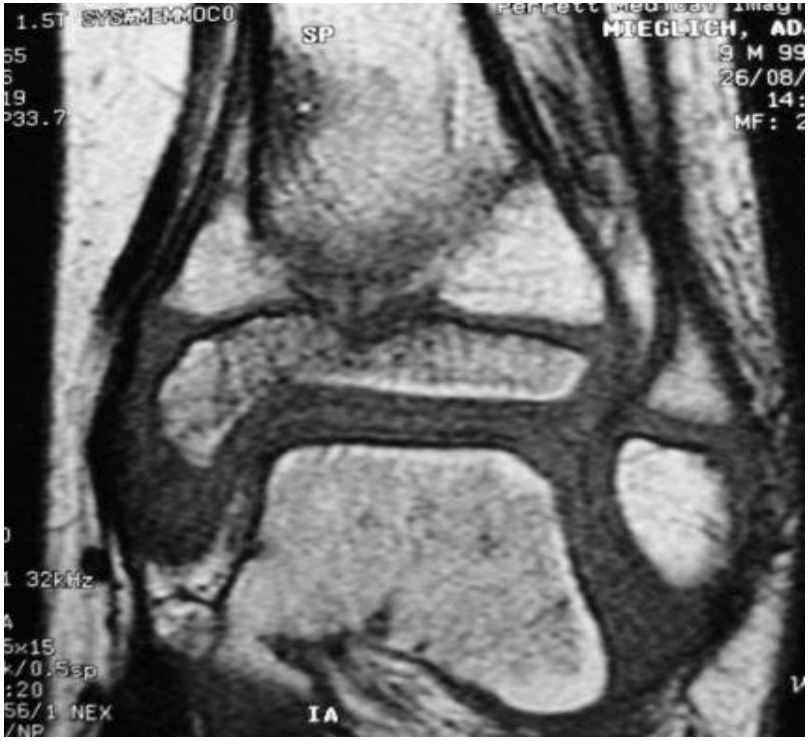

Epiphysial cartilage
Venous capillary network
(Site of bacterial seeding in
hematogenous osteomyeliti
Nutrient artery
Nutrient vein

Henman

Don’t forget the Physis!



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Neonates – pathogenesis & pathophysiology

- SA more likely to a consquence of osteomyelitis with spread to adjacent joint.
  - Neonatal vascular anatomy allows infection within bone to reach the growth plate or joint in 76%.
  - Cartilaginous epiphyses receive blood supply directly from metaphyseal blood vessel.
  - NB for hip in which metaphysis is intracapsular.
- Haematogenous spread is the commonest route of infection in neonate. Reduced blood flow in metaphysis - more susceptible
- Neonates usually have multifocal disease
- Bones & joints of lower limb most commonly affected

Incidence

- Newcastle from 1991 to 1999 was
  - 7 per 100, 000 for SA
  - 11 per 100, 000 for OM.

- Subacute OM appears to be increasing over recent years, reported to be found in 5 per 100, 000 children in Norway

Riise, O.R., et al., BMC Pediatr, 2008. 8: p. 45.

Symptoms and signs

- Bacteraemic Phase
  - Malaise and low grade fever
  - Other constitutional symptoms:
  - Night sweats, chills, loss of appetite

Septic arthritis in neonates – presenting features

- Diagnosis difficult – fewer clinical signs than older children
- May not have fever because of poorly developed neonatal immune system
- Clinical symptoms
  - Irritability
  - Poor feeding
  - Pseudoparalysis of a limb

Presenting features - children

- Toddlers & Young Children
  - Pain
  - Non weight bearing or limp: Antalgic gait
  - Decreased range of motion due to pain
  - Fever
  - Irritable/unsettled, crying
  - (Localized tenderness/swelling/redness)

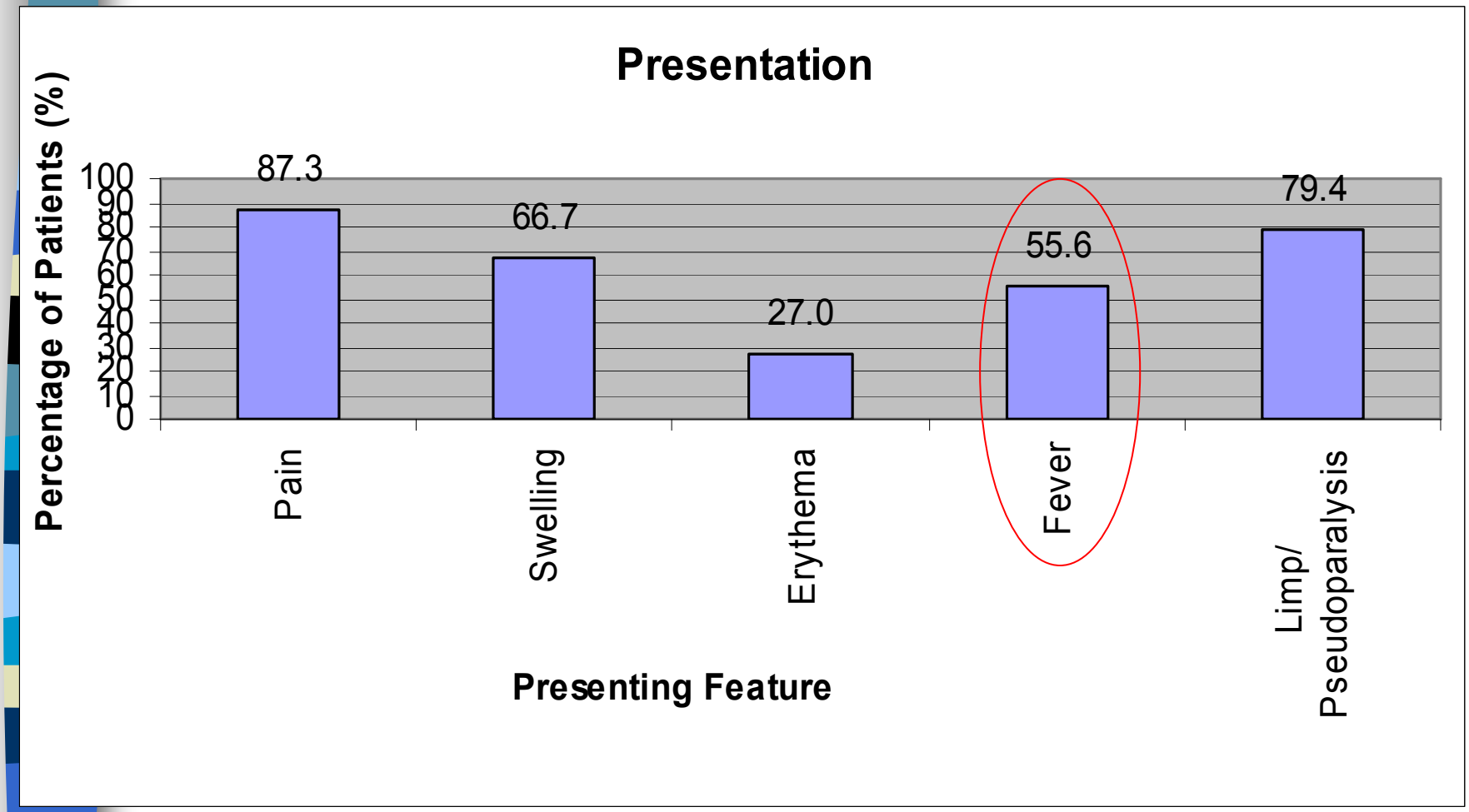
- Older Children & Adolescents
  - Focal tenderness
  - Fever
  - Malaise
  - May have less restriction of activity or only mild limp

Dissemination…..

- Pneumonia, respiratory distress
- Sepsis
- Shock

Presentation:

Symptoms and Signs: 63 children



Current Guidelines: Investigation

- Investigations to be done:
  - FBC, ESR, CRP
  - Antistaphylolysin, ASOT
  - Blood culture
  - X-ray (NB: X-ray changes are a LATE sign)

Note: normal WCC, CRP, ESR does not exclude OM or SA.

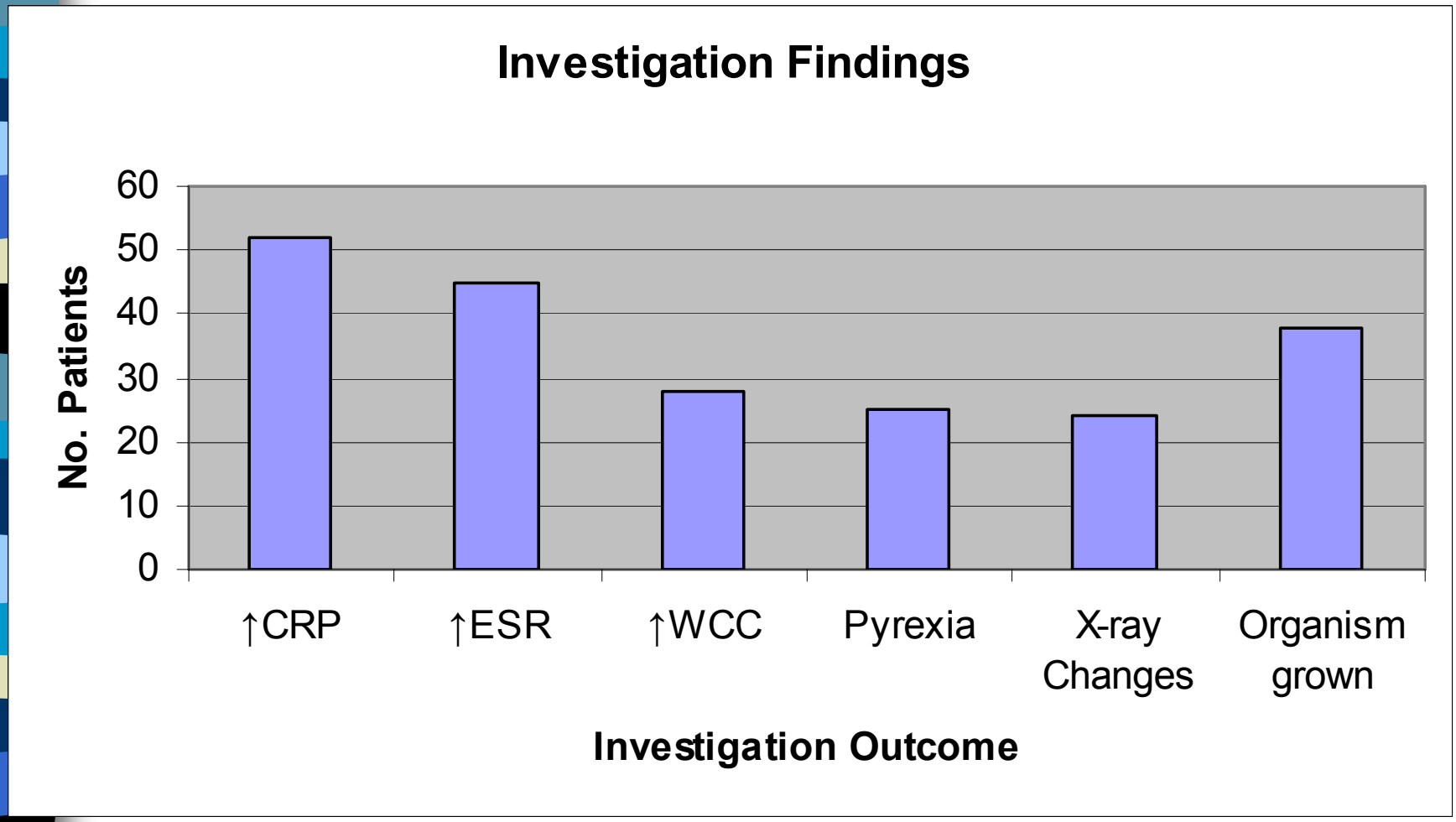
Investigations - audit

- ↑CRP in 52/63 patients (82.5%)
  - CRP not documented in 3 patients
- ↑ESR in 45/63 patients (71.4%)
  - ESR not documented in 8 patients and not requested in 3 patients
- ↑WCC in 28/63 patients (44.4%)
- Pyrexia (>38.0^{o}C) on temp chart at presentation in 25/63 patients (39.7%)

Investigations (2)

- X-ray changes were seen in 24 patients (38.1%)
  - No X-ray report in 2 patients
  - No evidence of request for X-ray in 2 patients
- Blood cultures or aspiration sent in all cases
  - Organism isolated in 38 patients (60.3%)

Investigations (3)



Imaging

- X-ray – late changes

SA

- Ultrasound – subperisosteal abscess, adjacent joint effusion
- Bone scan - Technetium diphosphonate (supply)
  - New bone formation (osteoid), reflects osteoblastic activity
  - Higher sensitivity with longer duration of illness
  - Bone Scan can be –ve
    - early osteomyelitis
    - Absent blood supply
  - Neonates have less mineralization (30% sensitivity)
  - Useful for occult multifocal lesions

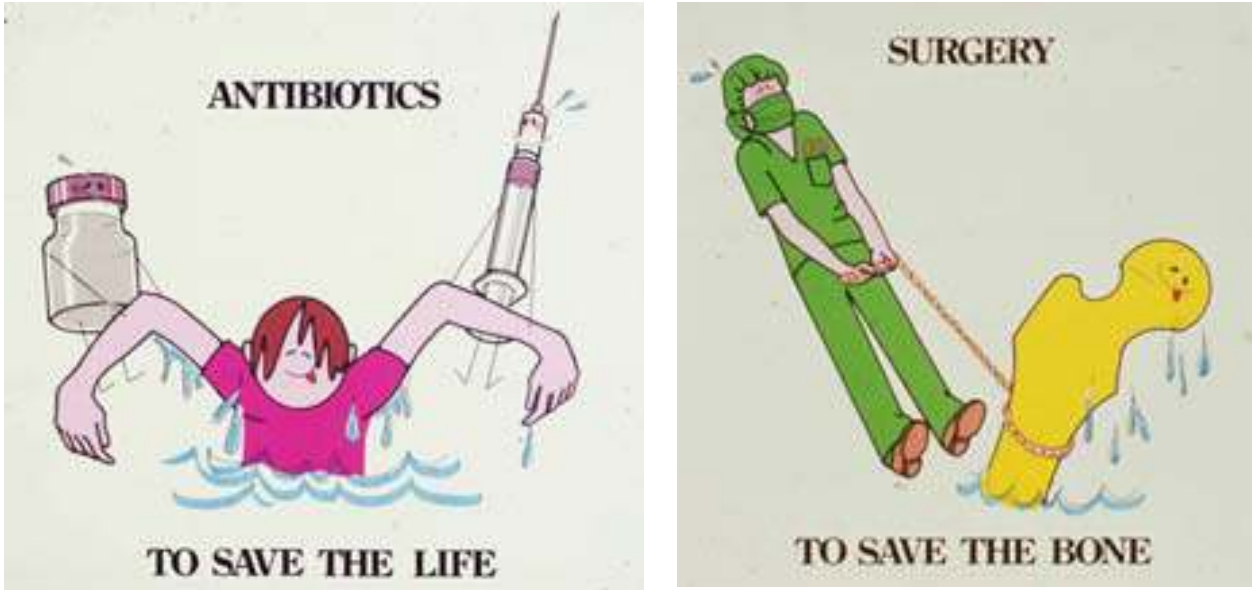
MRI – Gold standard

- Soft tissue & bony changes, changes appear early, accurately localizes subperiosteal or soft tissue collections.
- Sensitivity of 100% for bone marrow oedema,
- No ionizing radiation

OM

- (CT)

Management



From; Unni G. Narayanan, University of Toronto

Management

- Antibiotic choices depend on knowledge of infecting pathogen
- In all areas of use – not just bone and joint infection!

Newcastle

	SA	OM	SA	OM
MSSA		17(27%)	6%	29%
SA PVL	1	2(3%)		
MRSA	1	1		
GAS	2(3%)	3 (5%)	19%	0
Spn			8%	4%
GBS	2(3%)	1		
KK		1		
N.m	1			
Pseud		2(3%)		
Fuso				
TB	2(3%)			

32%

Oxford

OM – 30% I&D

SA – 80% washout

PCR

Tissue/pus innoculated into BC bottle

Case 1

- 7 year old boy
- 2 day hx left ankle pain, fever, local tenderness, swelling
- U/S joint effusion and distal tibial subperiosteal swelling
- I & D tibia, ankle washout
- Elevated CRP, ESR
- Pus (tibia) – gram +ve cocci
- Started flucloxacillin

Case 1 (2)

- Ankle improved symptomatically
- Remained febrile, CRP, ESR same
- 2/7 later increasing respiratory distress
- CXR diffuse infiltrates
- Hypotensive, poor cap return
- Fluid resus, oxygen requirement
- What do you want to do?

Case 1(3)

Consider:

- Extent of local infection
- Disseminated foci
- Pathogen
  - Antibiotic resistance
  - Toxin production
- Host response

SA – Panton Valentine Leucocidin (PVL)

- Toxin destroys white blood cells
- Gene encoding PVL on SA in <2% isolates
- Seems to be increasing
- Soft tissue infection
- Necrotising pneumonia, sepsis
- Disseminated bone infection, DVT
- MSSA (62%)

SA – PVL treatment

- MSSA - flucloxacillin
- PVL Toxin inhibitied by clindamycin, linezolid, rifampicin
- Unaffected by fusidic acid

=

- Flucloxacillin in combination with any of clindamycin, linezolid or rifampicin

Dumitrescu O. Clin Micro Infect. 2008

MRSA

- Low rate MRSA in UK
- Rapidly increasing in US
- Worrying disease profile
- “Difficult” disease – disseminated, multiple sites, sepsis, respiratory involvement, DVT frequent.
- Flucloxacillin resistant
- Teicoplanin, vancomycin, clindamycin, rifampicin, linezolid.

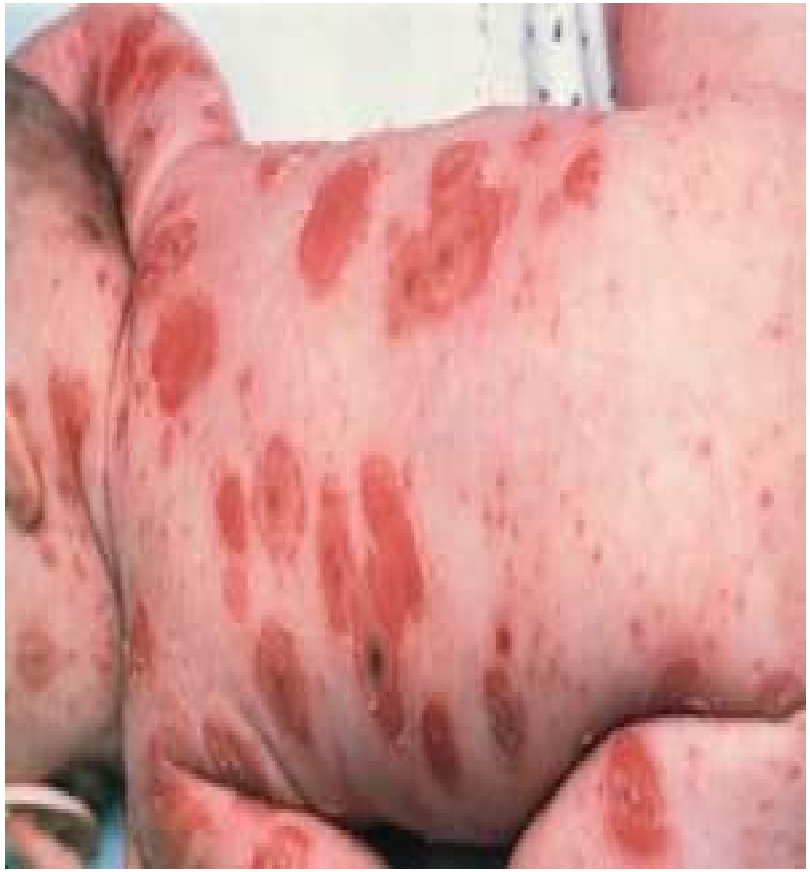
Crary, J Peds. 2006.

Case 2

- What viral infection?
- What bacterial pathogens are you concerned about?

Case 2

- Chicken pox
- Continuing fever day 4-5
- Local limb pain, restriction movt
- Joint effusion



Case 2

- GAS – often with toxin mediated disease; toxic shock
- Requires aggressive operative exploration
- Rapid empiric antibiotic treatment
- Toxin mediating antibiotics; clindamycin
- IVIG

Case 3

- 13 year old boy - 6 week history of left knee pain and tenderness.
- Two weeks later seen in orthopaedics - x-ray reported as normal.
- One week later reluctant to weight bear and stopped attending school.
- A week later he noticed some mild swelling.
- At orthopaedic review, 5 weeks after onset,
  - continued pain with limitation of movement
  - bone scan showed diffusely increased uptake in the left tibial epipyseal plate and was therefore followed by MRI.
  - MRI appearances suggested infection involving the left epiphyseal plate of the proximal tibia with evidence of bone destruction and marrow oedema. There was a soft tissue mass extending into the overlying gastrocnemius muscle. Gadololinium scanning showed extensive enhancement of the latter.

- He was systemically well until just before admission, when he started to complain of nausea and lethargy. There was no history of pyrexia, trauma to the knee, recent infections or other joint pain.

Case 3

- On examination he was afebrile, with a normal systemic examination.
- Tender, some swelling, skin was warm and range of movement was significantly reduced.
  - normal WCC 10.4 x109 with a neutrophil count of 7.8 x109.
  - CRP was 19mg/l and ESR 60mm/hr.
  - CRP rose to a maximum of 90mg/l on day 7 of admission.
- He was admitted for surgical debridement and commenced on empirical treatment of parenteral flucloxacillin and cefuroxime.
- Tibial abscess cavity was explored, debrided and washed-out.
  - Larger than expected from the MRI and involved the growth plate.
  - A significant proportion of the growth plate was destroyed. Histology showed active chronic inflammation consistent with infection.
- A swab grew *P. aeruginosa* sensitive to ceftazadime, gentamicin and ciprofloxacin. Antibiotic therapy was changed to intravenous ceftazidime 25mg/Kg every 8 hours.

Case 3

- In view of the unexpected causative organism the history was reviewed.
- There was no past medical history of note and immunological investigations were normal, including neutrophil oxidative burst.
- There was no clear history of injury to his foot, however his left big toe nail had fallen off two months previously due to minor trauma and had been kept by the patient.
- It was reported that it was green in colour. The nail was cultured and produced a heavy, pure growth of *P. aeruginosa*

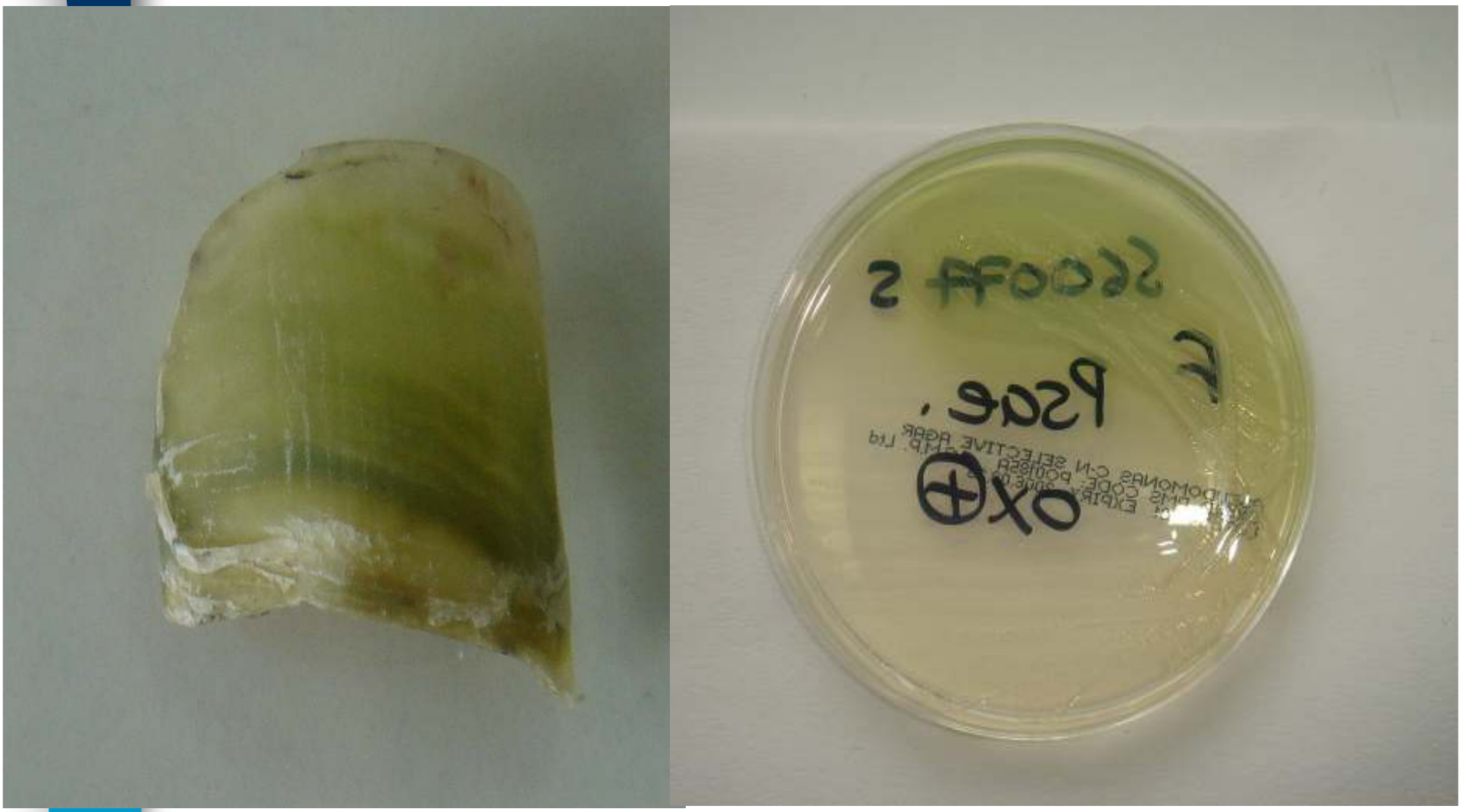


Figure 1 Left: big toe nail, Right: P. aeruginosa grown from culture of toe nail

Case 3 - Lessons

- Because of the relatively insidious onset of symptoms and signs together with the lack of systemic symptoms, diagnosis of osteomyelitis was delayed,
- leading to extensive bone and physeal necrosis at the time of treatment.
- Difficulties in managing *Pseudomonas* osteomyelitis include few oral antibiotics active against the organism and an apparent poorer prognosis compared to *S. aureus* and other organisms

Pathogen and risk factor

Varicella	GAS
Sneaker	Pseudomonas
Sickle cell	Salmonella
CGD	Mycobacteria/fungi
Unimmunised < 2	HIB
neonate	GBS, e.coli, candida
< 5 years	SA, KK, HI, gm neg.

Empiric treatment

Neonatal to <=3 months **SEEK MEDICAL REVIEW**	intravenous cefotaxime	< 7 days 7-21 days 21-28 days	50 mg / kg / 12 hourly 50 mg / kg / 8 hourly 50 mg / kg / 6 hourly
	plus if sepsis/meningitis considered: intravenous amoxicillin	< 7 days 7-28 days	50 mg / kg / 12 hourly 50 mg / kg / 8 hourly
	(stop amoxicillin when Listerial meningitis excluded)		
3 months to <=5 years old	intravenous cefuroxime		50 mg /kg / 8 hourly
>=6 years old	intravenous flucloxacillin *or* intravenous clindamycin		50 mg / kg / 6 hourly 10 mg / kg / 6 hourly to maximum 675 mg 6 hourly

Add clindamycin if varicella or shocked

Length of antibiotics

- Length of intravenous
- Length of total treatment

IV to Oral Switch

- Currently there is no international and little UK consensus regarding the route or duration for antibiotic treatment of acute OAI in children.
- Sequential intravenous and oral therapy is usual as it is less inconvenient and painful for the patient, has fewer complications and is cheaper.
- A Canadian systematic review of short (≤7 days) versus long course (>7 days) parenteral antibiotic treatment for acute haematogenous OM in children due primarily to *Staphylococcus aureus* showed no difference in the overall cure rate after 6 months between short course and long course parenteral antibiotic therapy. (Le Saux. BMC. 2002)

Prolonged Intravenous Therapy Versus Early Transition to Oral Antimicrobial Therapy for Acute Osteomyelitis in Children

Theoklis Zaoutis, A. Russell Localio, Kateri Leckerman, Stephanie Saddlemire, David Bertoch and Ron Keren

Pediatrics 2009;123;636-642
DOI: 10.1542/peds.2008-0596

- 1969 children, uncomplicated infection
- 29 hospitals, local practice

- 1021 – prolonged iv
- 948 – oral switch , <10 days iv.

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No difference in outcome:
5% v 4% treatment failure

3.4% CVL associated complications

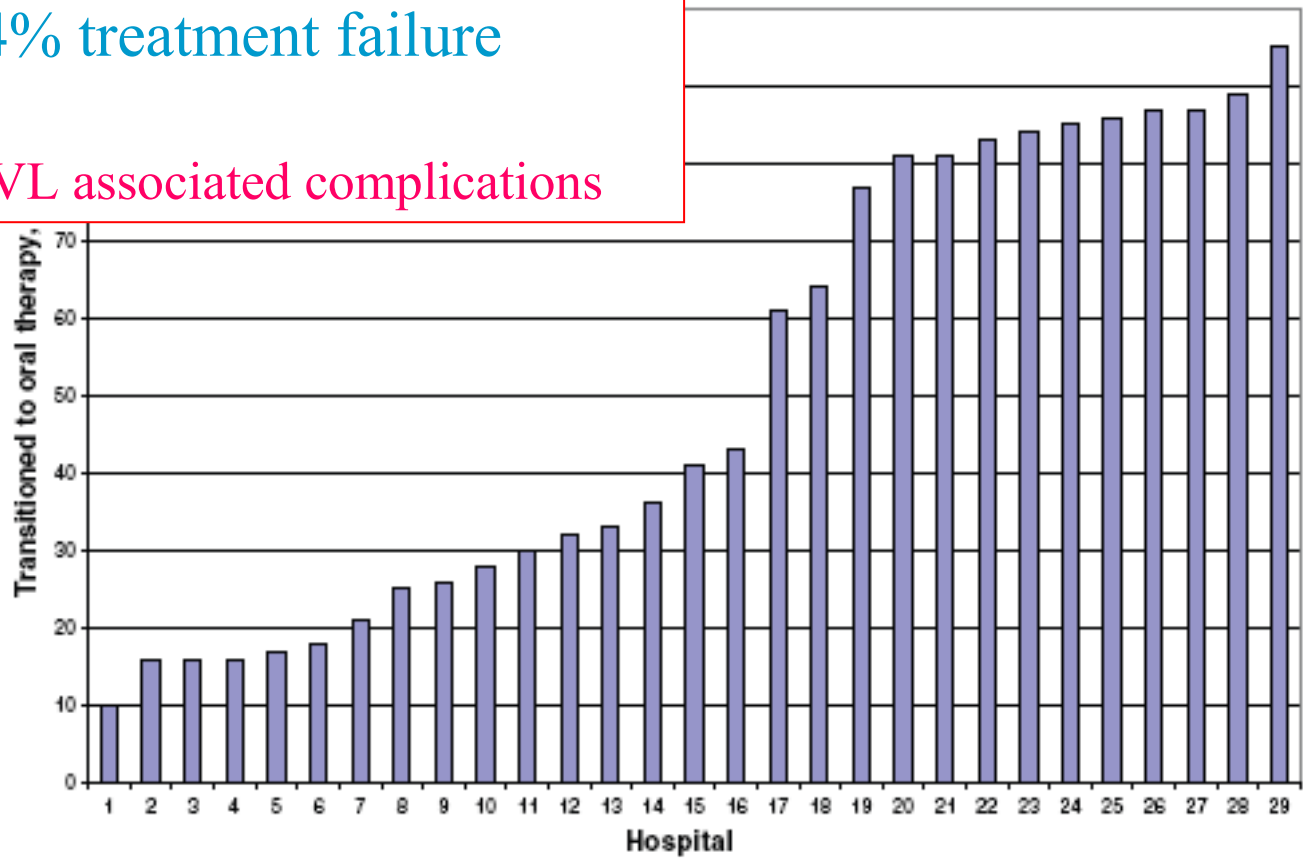


FIGURE 2
Proportion of children in each hospital transitioned to oral therapy before discharge.

CVC complications

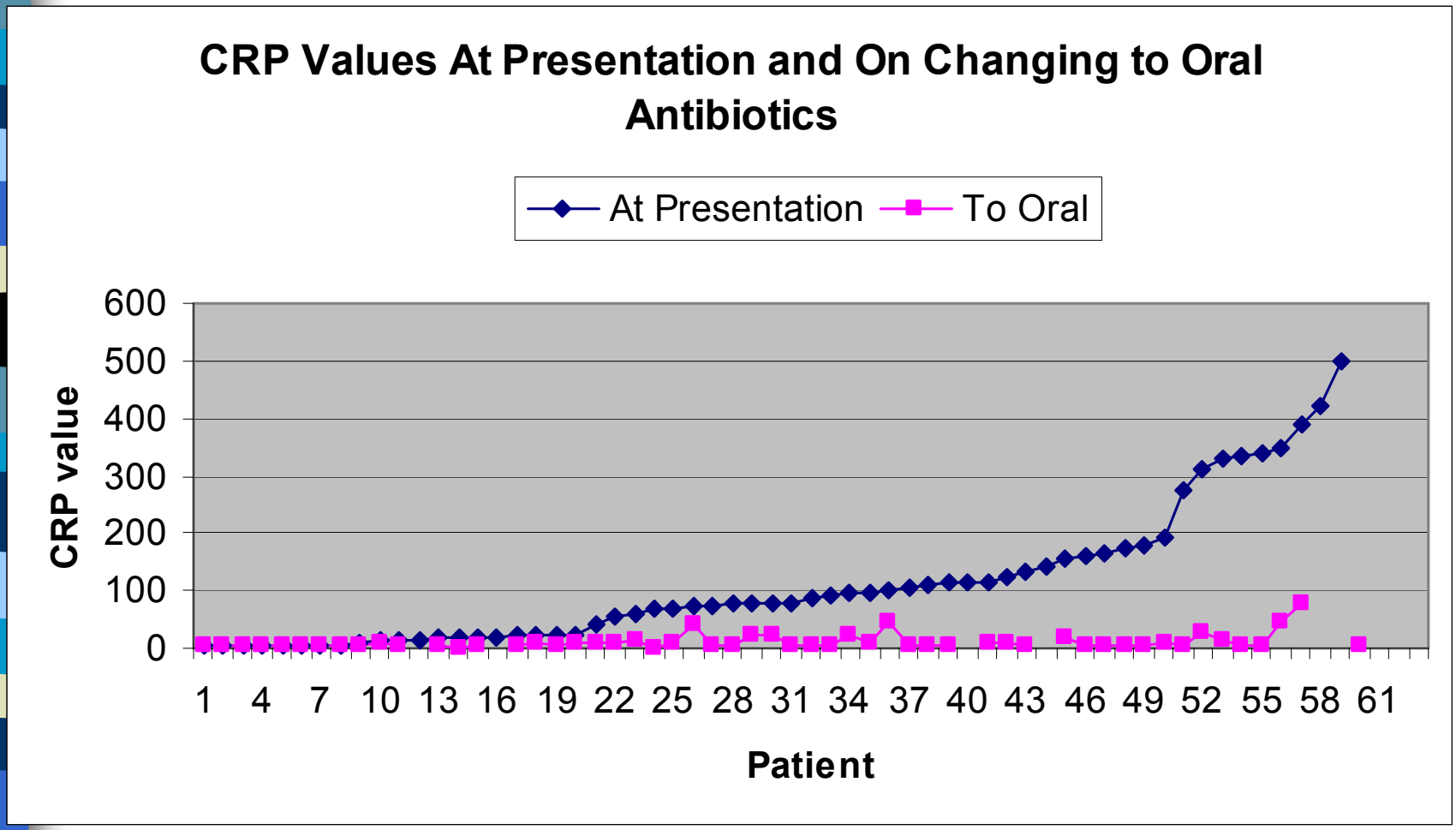
- Of the 75 patients who received 2 weeks of IV therapy for AHO:
  - 41% had 1 CVC-associated complication.
  - 23% had a CVC malfunction or displacement,
  - 11% had a catheter-associated bloodstream infection,
  - 11% had fever with negative blood culture results,
  - 5% had a local skin infection at the site of catheter insertion. (Ruebner et al. Peds. 2006)

When to switch from iv to oral?

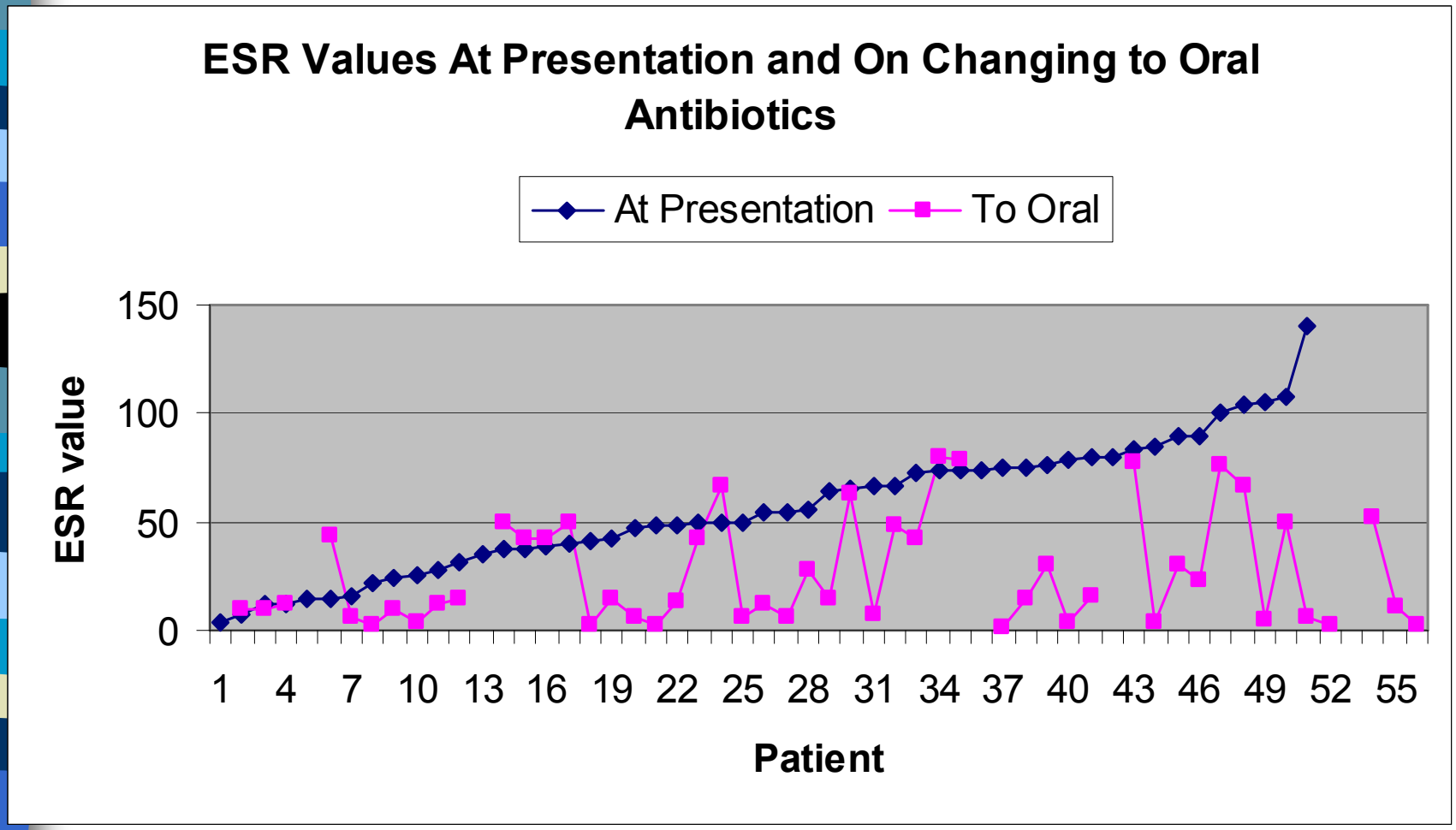
- Most UK clinicians continue intravenous antibiotics until:
  - clinical improvement
  - afebrile
  - oral fluids and medication established.
  - C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) decreased. *(CRP < 20 or 2/3rds of initial).*
- Studies have shown that serum CRP level decreases more rapidly than ESR.
- A Finnish clinical trial showed good long term results and no failure rates using CRP to change from iv (4 days) to oral. (Peltola et al. Peds. 1997)

- No evidence specifically for neonatal short course treatment.
- A more than two fold increase in recurrence rates with *pseudomonas* infection compared with *S. aureus*. There are also far fewer oral antibiotics to treat *Pseudomonas* than to treat *S. aureus* with the choice limited to quinolones. (Tice et al. *Journal of Antimicrobial Chemotherapy*. 2003)

Monitoring Response:
CRP



Monitoring Response:
ESR



Total length

- Historical observational studies showed an association between short duration of antibiotic therapy and poor outcome or relapse.
- Dich (1975); 19% failure rate in 37 patients treated for 3 weeks or less;
- Blockey (1970); 15% failure rate in 113 patients treated 3 weeks or less;
- In contrast a more recent prospective study by Peltola (1997) showed that a 3-week course of total antibiotic therapy was sufficient, with no relapse rates or adverse outcomes reported.

Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis.

- Finnish study group
- 20 years, 130 children, septic arthritis
- 88% - SA, HI, SPn
- randomized to receive clindamycin or a first-generation cephalosporin for 10 days or 30 days (intravenously for the first 2-4 days).
- No difference in outcome
- < 2 weeks antibiotics sufficient if good response and normalising CRP.

Peltola. 2009. CID

Septic arthritis in neonates – potential for long term damage

- Lax muscles + effusion -> ↑risk subluxation or dislocation
- Accumulation of inflammatory exudate in joint may lead to vascular compression & AVN
- Damage to articular cartilage dt proteolytic enzymes released from synovial fluid

- ~40% neonates with SA of hip develop serious complications & long-term f/u is crucial

Complications

- Damage to growth plate with premature &/or asymmetrical closure of growth plate
- AVN of femoral head with/without dissolution of femoral head & neck
- Pseudoarthrosis
- Limb length discrepancies – more obvious as child grows
- Angular deformities at joints
- Joint dislocations
- Joint arthrodesis

Summary

- Clinical index of suspicion in young children with limp, non weight bearing, pain with or without fever
- FBC, CRP, ESR, BC useful initial investigations
- Observation may be needed
- U/S, MRI
- Antibiotics mainstay of treatment
- Uncomplicated infection; iv - oral switch can be guided by clinical response and markers of infection
- Neonatal iv courses usually longer (2-3 weeks)

- 4-6 weeks antibiotics until more evidence re short total course
- Tailor to clinical response and pathogen
- Surgery required
  - SA
  - OM with collections, abscesses or non responding to iv antibiotics
- Management requires close interaction and joint care between orthopaedics and paediatrics
- National Guidelines being developed