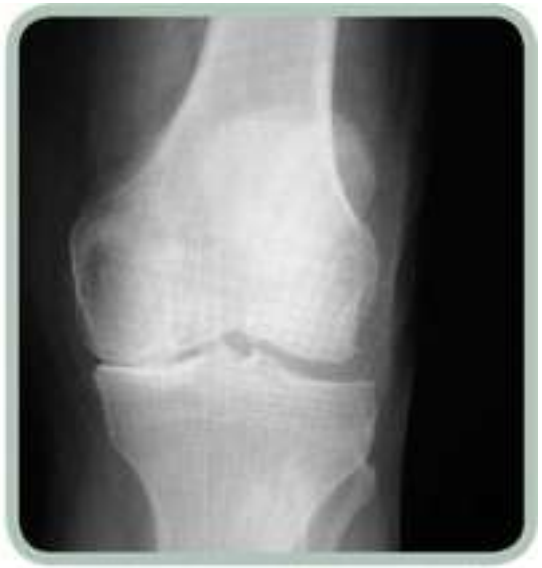
ARTRITE SETTICA



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TOPICS

- Introduction
- Epidemiology: eziology, risk factors
- Presentation
- Diagnosis
- Treatment options

Introduction

"Septic Arthritis, also called infectious arthritis, is an inflammatory disease of the joints that is started by an infectious agent". Organisms may invade the joint by:

- Direct inoculation(trauma, surgery, animal bites)
- Contiguous spread from infected periarticular tissue
- Bloodstream(The most common route!)
- Reactive arthritis (generally not classified as septic arthritis)

Incidence:

- 4-10/100000/ yr in general population[1]
- 30-100/ 100000/ yr in RA[1]
- 5- 12/ 100000/ yr in Children
- post prosthetic joint surgery
  - Old case series: 0.04-0.86%[2]
  - Recent case series: 0.14-2.25%[3]

Epidemiology

1:Kaandorp Cj et al Ann Rheum Dis 1997:56:470-5
2:Coudane H et al Symposium de la Société francaise d'arthroscopie 2001
3:Yeranosian MG et al Arthroscopy 2013;29(8)1355-61

Etiology

0 m -2 m → *S. aureus*, *S. agalactiae*

→ *S. pneumoniae*, *S. pyogenes* — Gram +

2 m -5 y → *H. influenzae*, *Kingella kingae* — Gram -

> 5 y → *S. Aureus* (*N.gonorrhoeae*)

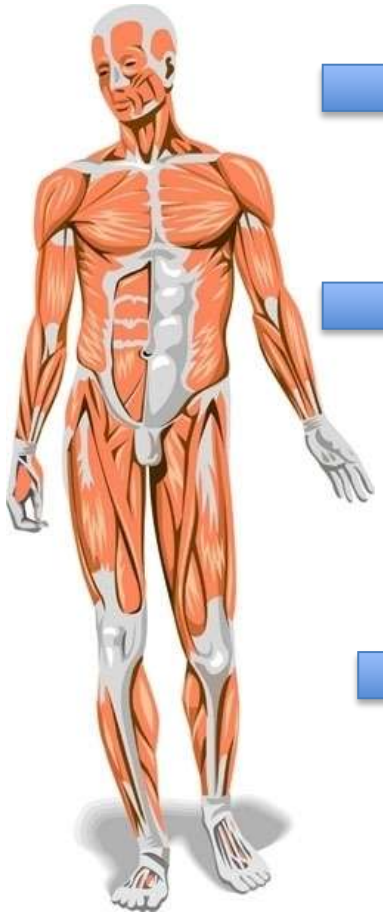
Best Practice & Research Clinical Rheumatology 25 (2011) 407–421

Risk factors

- Rheumatoid arthritis or osteoarthritis
- Elderly or young children
- Low socioeconomic status
- Intravenous drug abuse
- Alcoholism
- Diabetes
- Previous intra-articular corticosteroid injection*
- Cutaneous ulcers
- Joint surgery/prosthesis

* 40/100.000 injections

Eziology



S. aureus **(37-56%)** the most common agent in both childen and adult

*Streptococcus spp.**(20%)***

- *Str. pyogenes*
- - Str. gruppo B
- *Str. pneumoniae*

- bacilli G neg
- *N. gonorrhoeae*

Specific populations

Eziology stratified by risk

- RA → S.aureus
- Developing countries → M. tuberculosis
- Skin infection, wounds → S.aureus, Str. spp. Gram-neg
- Elderly with UTI → Gram -neg, S. aureus
- Immunosuppressed → S.aureus, Gram- neg, fungi
- STIs population or complement deficiency → N. gonorrhoeae

Best Pract Res Clin Rheumatol. 2015 Apr;29(2):275-89

Eziology stratified by risk(2)

- Drug abusers
- HIV

→ S.aureus, fungi, Gram-neg, rare microrganisms

- Neutropenic patients

→ Gram-neg

- joint surgery and prosthetics

→ Staphylococci coag-neg, S.aureus

Why is S. aureus dangerous?

- Increasing in susceptible individuals.

  Increasing MRSA infections in:
  - Health-care system
  - Drug abusers
  - Elderly people
  - Orthopaedic procedures
- Some strains are positive for Panton-Valentine leucocidin(PVL) that is associated with fulminant infections.

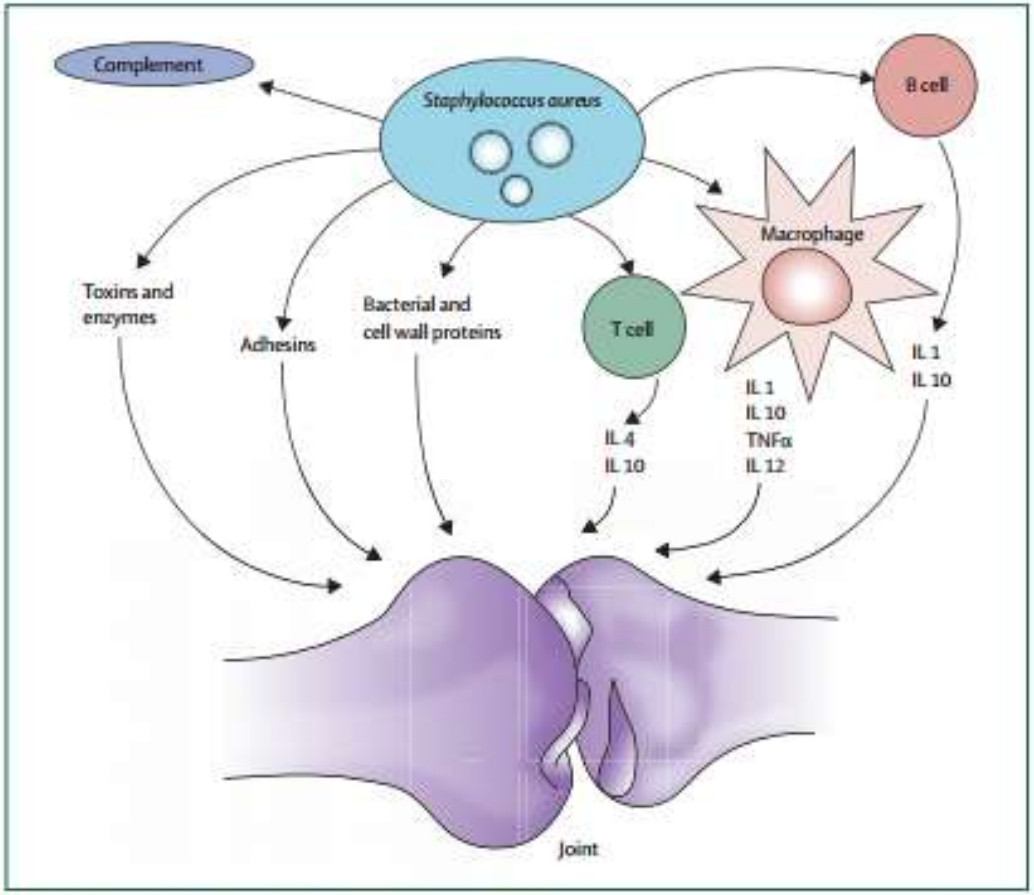


Figure 1: Pathogenesis of staphylococcal septic arthritis
TNFα=tumour necrosis factor α. IL=interleukin. Adapted from ref 30, with permission of Future Medicine.

microrganism based flow chart

MONOARTICULAR SEPTIC ARTHRITIS

ACUTE

IST RISK

YES

- *N. gonorrhoeae*
- *S. aureus*
- *Str.* spp.
- G neg

NO

- *S. aureus*
- *Str.* spp.
- G neg

CRONIC

- *Brucella* spp.
- *Nocardia* spp.
- Mycobacteria
- Fungi

POLIARTICULAR SEPTIC ARTHRITIS

- *N. gonorrhoeae*
- *B. burgdorferi*
- RAA
- *Virus: HBV, rubella vaccine, parvo-B19*

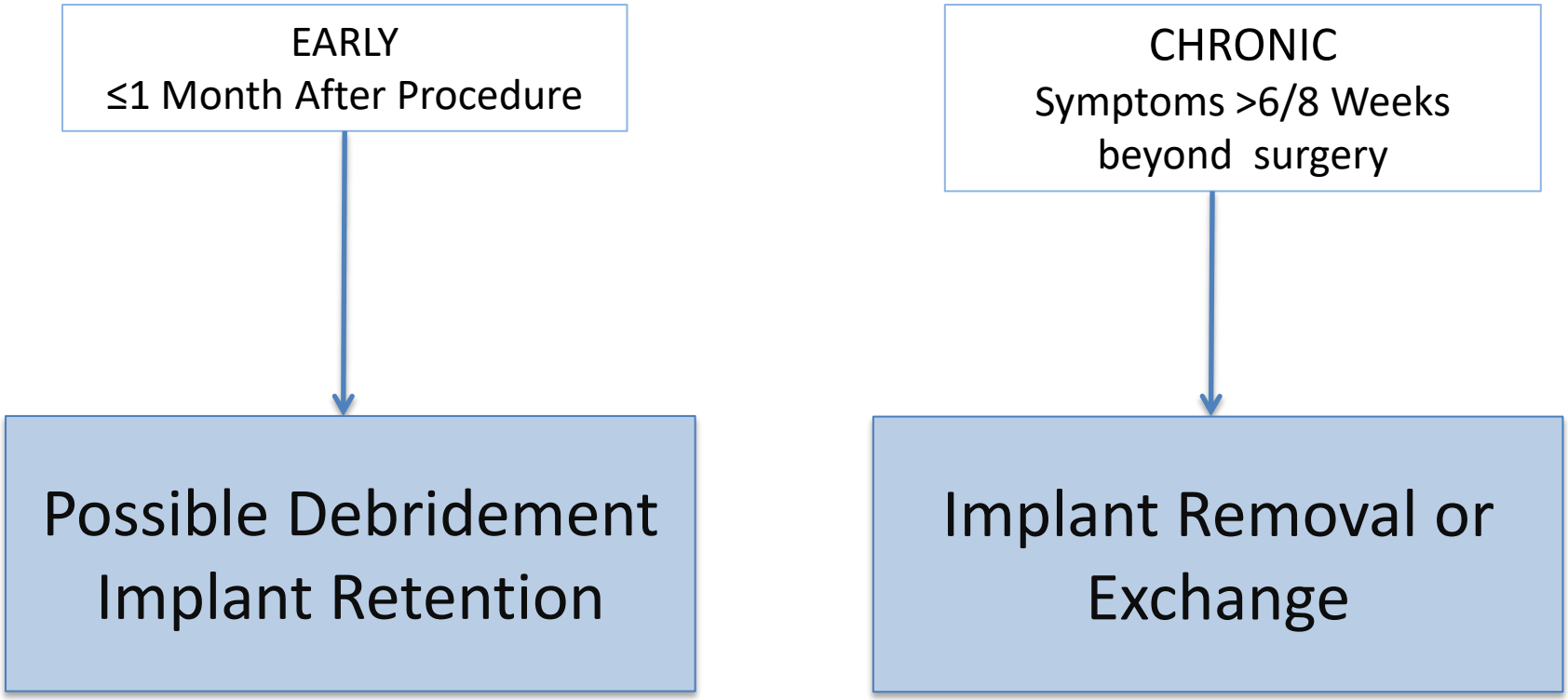
Epidemiology

Incidence:

- 4-10/100000/ yr in general population [1]
- 30-100/ 100000/ yr in RA [1]
- 5- 12/ 100000/ yr in Children

- **Implant associated septic arthritis**
  - **Old case series: 0.04-0.86%** [2]
  - **Recent case series: 0.14-2.25%** [3]

1:Kaandorp Cj et al Ann Rheum Dis 1997:56:470-5
2:Coudane H et al Symposium de la Société francaise d'arthroscopie 2001
3:Yeranosian MG et al Arthroscopy 2013;29(8)1355-61



Highest Risk within 3 months

Implant-associated septic arthritis

Hot Topics

- ✓S.aureus and CONS account for 38-82% of infections
- ✓Exogenous route is much more frequent as hematogenous
- ✓MRI and CT have limited diagnostic role because of interference in the vicinity of implant
- ✓Prolonged AB therapy(6w -6m)

Implant-associated septic arthritis

Clinical manifestation: adults

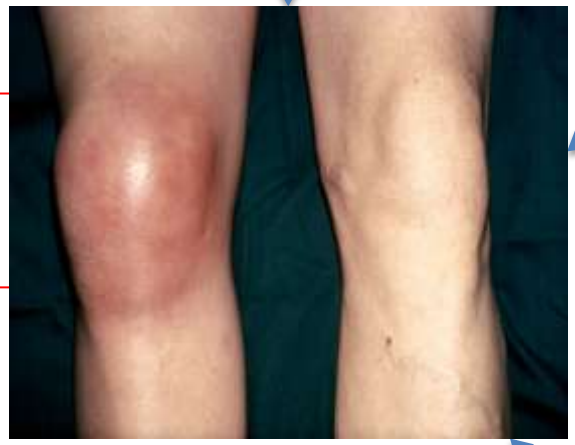
•DOLOR
•RUBOR
•TUMOR
•FUNCTIO LESA

POSITION OF COMFORT

LEUKOCYTOSIS

N.gonorrhoeae

- Dermatitis
- Tenosynovitis
- migratory polyarthralgia/arthritis



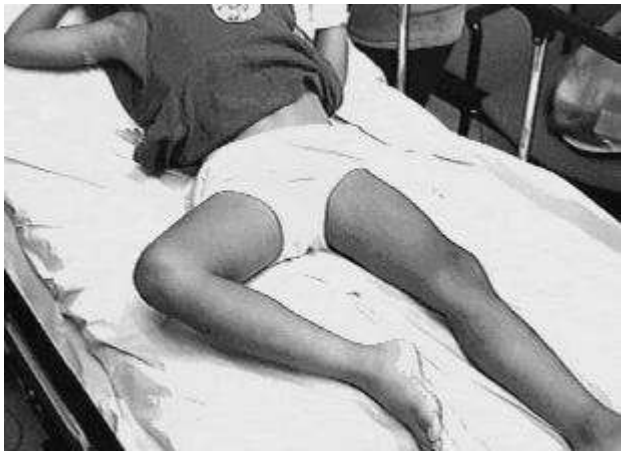
FEVER

DECREASED RANGE OF MOVEMENT

Pseudoparesis: all movements are restricted due to muscle spasm

Rapid pulse

Moviment are restricted by pain or spasm

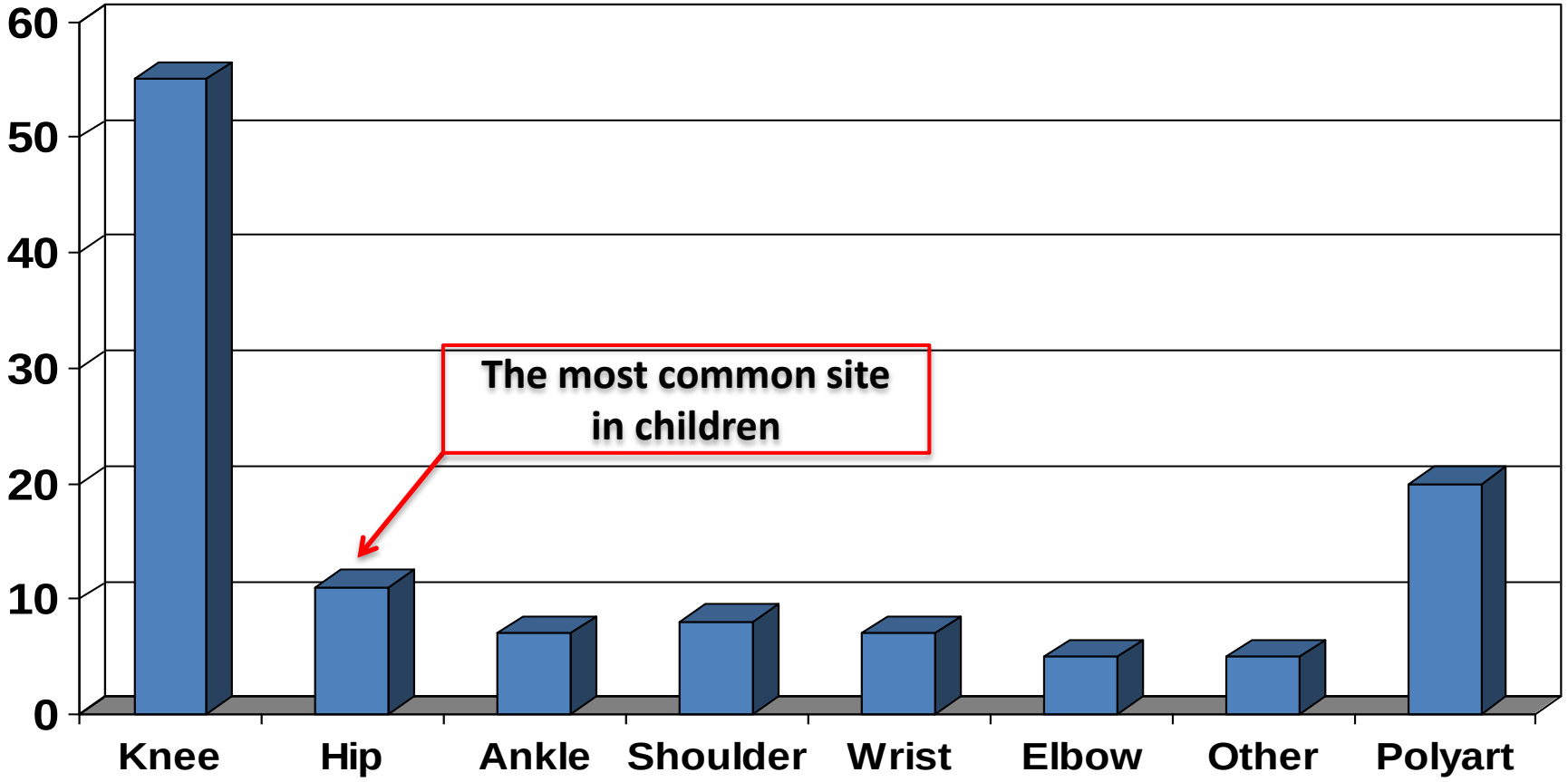


Child is irritable

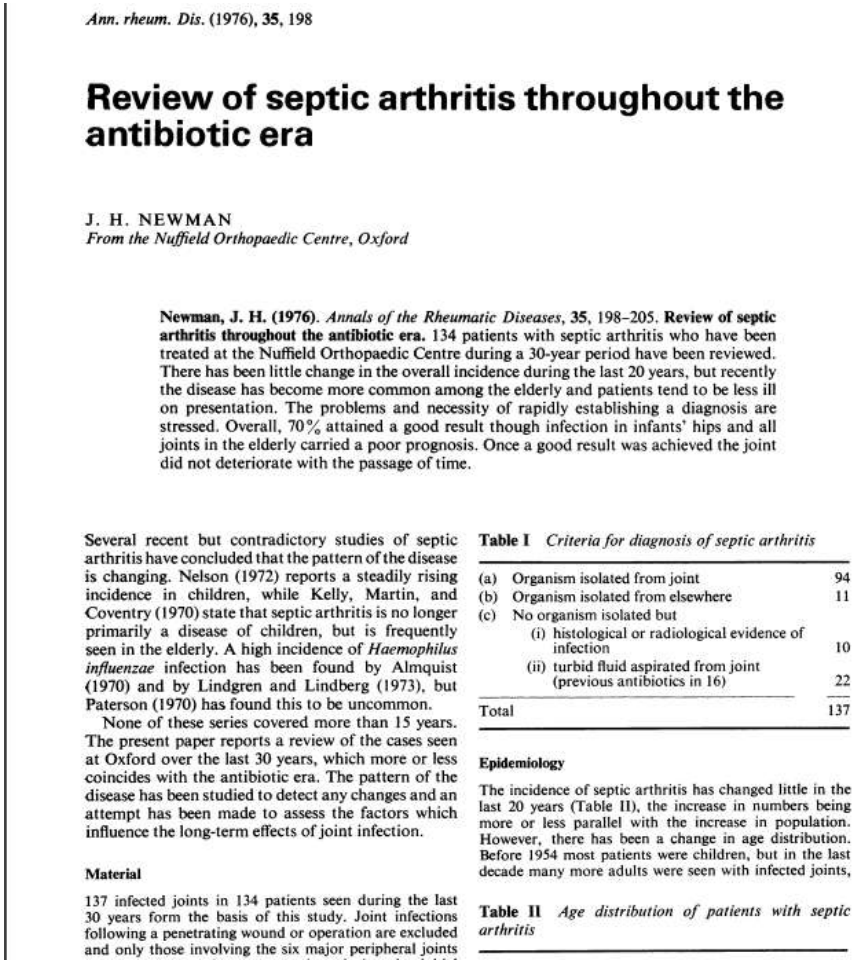
Anxiety

Signs and symptoms: Children

Septic Arthritis joints involved in adults



Case definition



Ann. rheum. Dis. (1976), **35**, 198

Review of septic arthritis throughout the antibiotic era

J. H. NEWMAN
From the Nuffield Orthopaedic Centre, Oxford

Newman, J. H. (1976). *Annals of the Rheumatic Diseases*, **35**, 198–205. **Review of septic arthritis throughout the antibiotic era.** 134 patients with septic arthritis who have been treated at the Nuffield Orthopaedic Centre during a 30-year period have been reviewed. There has been little change in the overall incidence during the last 20 years, but recently the disease has become more common among the elderly and patients tend to be less ill on presentation. The problems and necessity of rapidly establishing a diagnosis are stressed. Overall, 70% attained a good result though infection in infants' hips and all joints in the elderly carried a poor prognosis. Once a good result was achieved the joint did not deteriorate with the passage of time.

Several recent but contradictory studies of septic arthritis have concluded that the pattern of the disease is changing. Nelson (1972) reports a steadily rising incidence in children, while Kelly, Martin, and Coventry (1970) state that septic arthritis is no longer primarily a disease of children, but is frequently seen in the elderly. A high incidence of *Haemophilus influenzae* infection has been found by Almquist (1970) and by Lindgren and Lindberg (1973), but Paterson (1970) has found this to be uncommon.

None of these series covered more than 15 years. The present paper reports a review of the cases seen at Oxford over the last 30 years, which more or less coincides with the antibiotic era. The pattern of the disease has been studied to detect any changes and an attempt has been made to assess the factors which influence the long-term effects of joint infection.

Material

137 infected joints in 134 patients seen during the last 30 years form the basis of this study. Joint infections following a penetrating wound or operation are excluded and only those involving the six major peripheral joints

Table I *Criteria for diagnosis of septic arthritis*

(a)	Organism isolated from joint	94
(b)	Organism isolated from elsewhere	11
(c)	No organism isolated but	
	(i) histological or radiological evidence of infection	10
	(ii) turbid fluid aspirated from joint (previous antibiotics in 16)	22
Total		137

Epidemiology

The incidence of septic arthritis has changed little in the last 20 years (Table II), the increase in numbers being more or less parallel with the increase in population. However, there has been a change in age distribution. Before 1954 most patients were children, but in the last decade many more adults were seen with infected joints,

Table II *Age distribution of patients with septic arthritis*

One of the four points to be fulfilled to define case:

a) Isolation of pathogenic organism from an affected joint.
b) Isolation of pathogenic organism from another source-blood or body fluid in suspicious of joint originated sepsis
c) Typical clinical features and turbid synovial fluid in presence of previous antibiotic therapy
d) Postmortem or pathological features suspicious of septic arthritis

Ann. rheum. Dis. (1976), 35,

Laboratory investigations: 1 step

Blood sample

- Leukocytosis
- VES,PCR
- PCT?

useful to monitor AB therapy

Collect blood cultures:

- 24% positive of cases in whom organism were identified in the synovial fluid
- +/-**Urine culture and urethral swab** if STI is suspected
- **Collect ulcer skin cultures** if present

Diagnosis

Procalcitonin levels in fresh serum and fresh synovial fluid for the differential diagnosis of knee septic arthritis from rheumatoid arthritis, osteoarthritis and gouty arthritis

CHENGGONG WANG, DA ZHONG, QIANDE LIAO, LINGYU KONG, ANSONG LIU and HAN XIAO

Table I. Characteristics of the SA, RA, OA and GA groups.

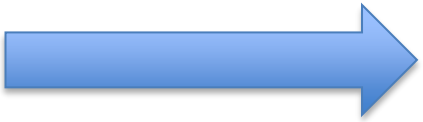
Characteristic	SA	RA	OA	GA
Number of cases	23	21	40	11
Male/female (n)	15/8	6/15	19/21	10/1
Average age (years)	46.6±3.6	35.0±2.2	66.2±2.6	60.8±5.6
Types and numbers of pathogenic bacteria				
Staphylococcus aureus	12	0	0	0
Hemolytic *Streptococcus*	5	0	0	0
Tubercle bacillus	2	0	0	0
Escherichia coli	2	0	0	0
Streptococcus pneumoniae	2	0	0	0

The mean ± stadard deviation is shown for the average ages. SA, septic arthritis; RA, rheumatoid arthritis; OA, osteoarthritis; GA, gouty arthritis.

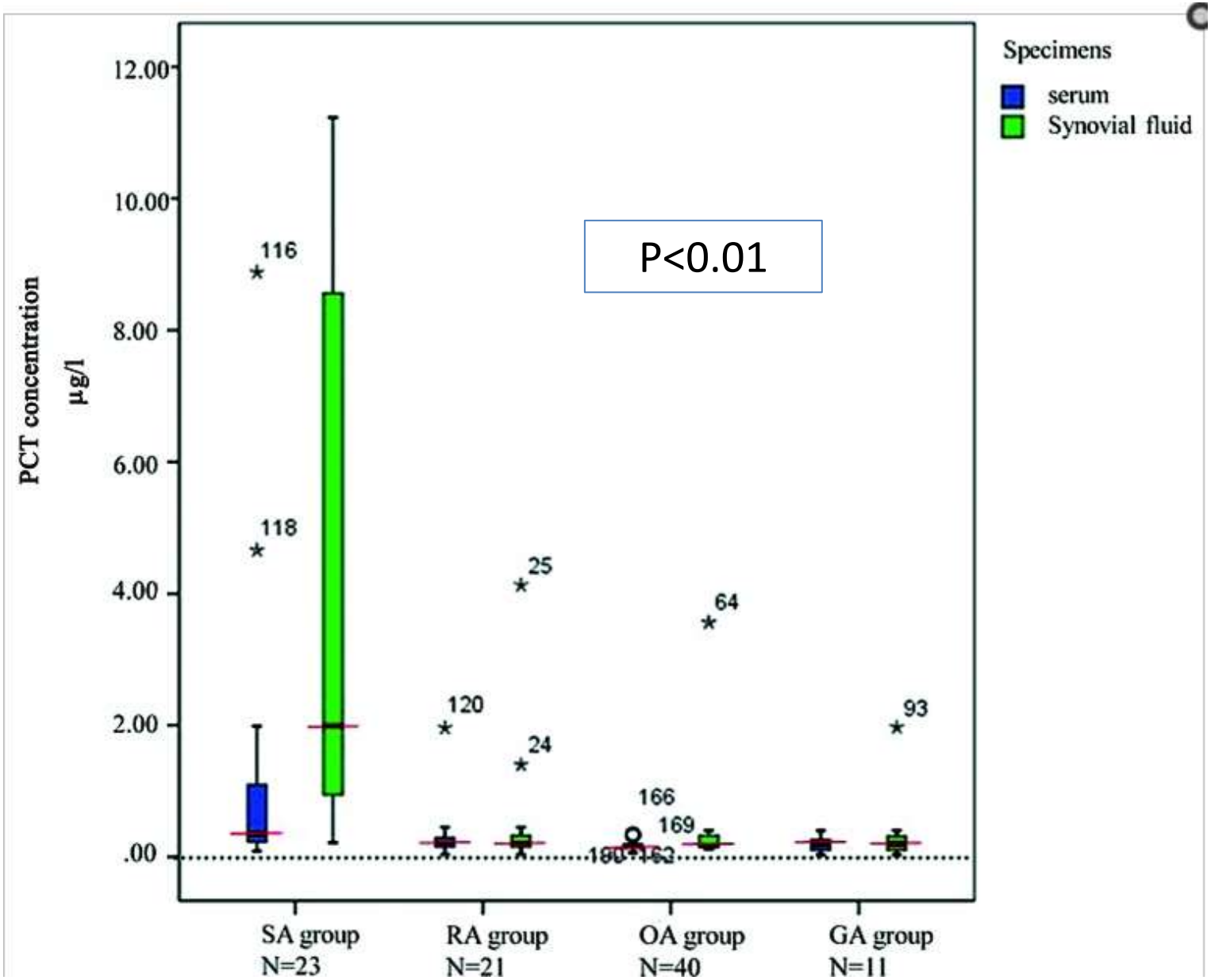
- Patients with various types of arthritis: SA, RA, OA or GA
- The patients had not received any prior antibiotic or joint puncture treatments
- Levels of PCT were tested within 24 h after serum and fluid collection

Table II. Serum and synovial fluid levels of PCT in the knees of patients with SA, RA, OA and GA.

	SA (n=23)		RA (n=21)		OA (n=40)		GA (n=11)			
PCT (μg/l)	Cases	%	Cases	%	Cases	%	Cases	%	χ^2	P-value
Serum										
<0.5	15	65.21	21	100.0	39	97.50	11	100.00	23.002	0.001
0.5-2.0	6	26.09	0	0.00	1	2.50	0	0.00		
2.0-10.0	2	8.70	0	0.00	0	0.00	0	0.00		
>10.0	0	0.00	0	0.00	0	0.00	0	0.00		
Total	23	100.00	21	100.00	40	100.00	11	100.00		
Synovial fluid										
<0.5	3	13.04	20	95.24	38	95.00	10	90.90	62.669	<0.001
0.5-2.0	9	39.14	0	0.00	1	2.50	1	9.10		
2.0-10.0	7	30.43	1	4.76	1	2.50	0	0.00		
>10.0	4	17.39	0	0.00	0	0.00	0	0.00		
Total	23	100.00	21	100.00	40	100.00	11	100.00		



HIGH NPV


PCT concentration
µg/l
12.00
10.00
8.00
6.00
4.00
2.00
.00
Specimens
serum
Synovial fluid
P<0.01
116
118
25
120
24
64
166
169
93
SA group
N=23
RA group
N=21
OA group
N=40
GA group
N=11

PCT<0.5 g/l

High specificity in d.d. among septic arthritis and other arthritis

Laboratory investigations: 2 step

SYNOVIAL FLUID ASPIRATION

- **Leucocyte** >50.000/uL(˜ 10 fold less for prosthetics joint infections) with neutrophils predominance
- **Gram stain + culture***(*before antibiotic tp!!!*.) → 67% positive
- **PcR** if available(TBC, *Streptococcus*, anaerobia, *K. kingae*)
- **DD**: crystal arthrisis, reactive arthritis……

Absence of organisms on grain strains or a negative synovial culture does not exclude the diagnosis, although it does make it less likely

Diagnosis

IMAGING

- Although radiographs, CT, MRI can be used to assess and determine the extent of inflammation, tissue destruction or responce, they cannot distinguish among SA and other arthritis, however…

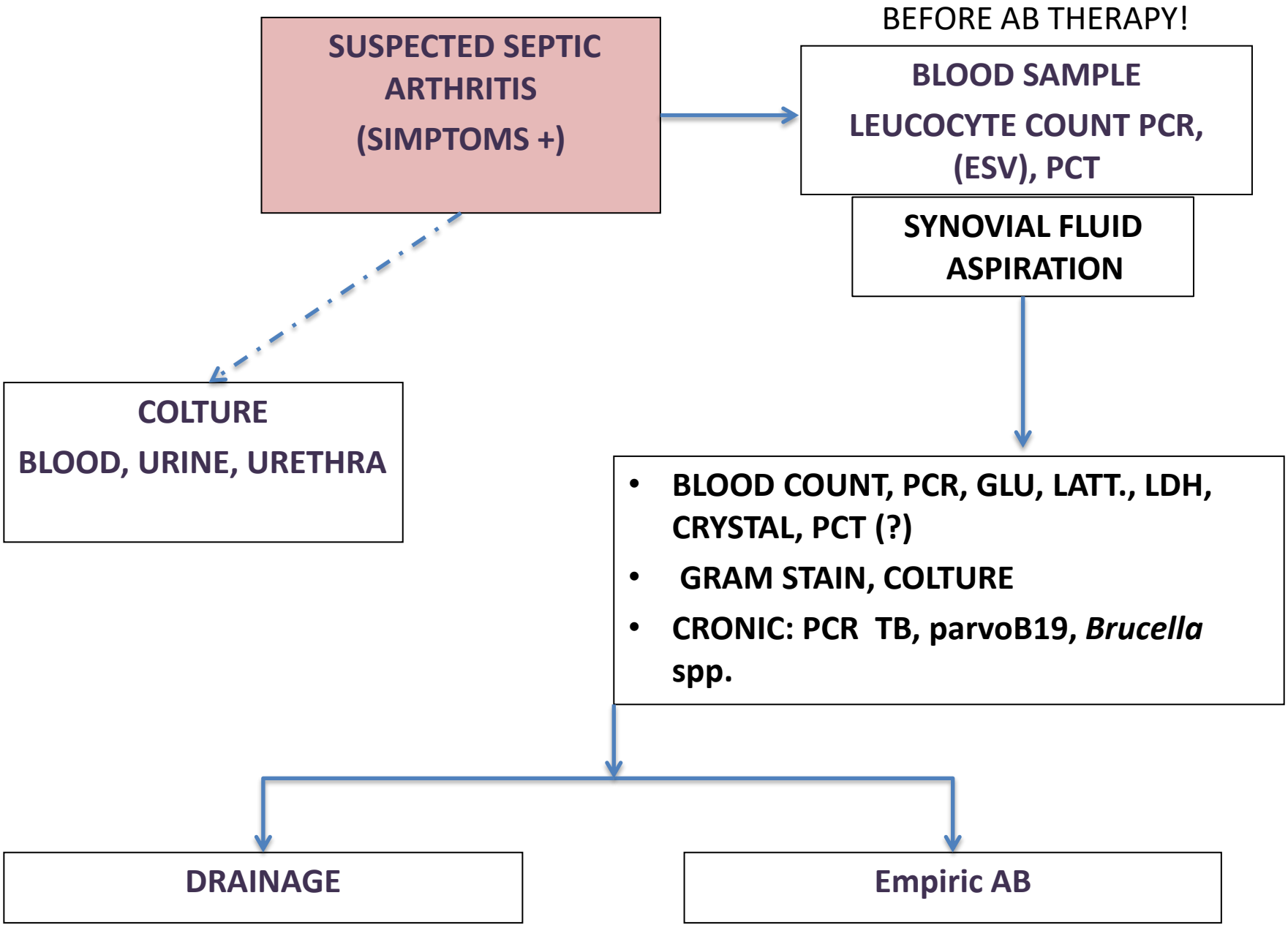
  MRI can help to assess a coexistent osteomyelitis or indicate tracking of purulent material into surrounding tissues

Diagnosis

DIFFERENTIAL DIAGNOSIS

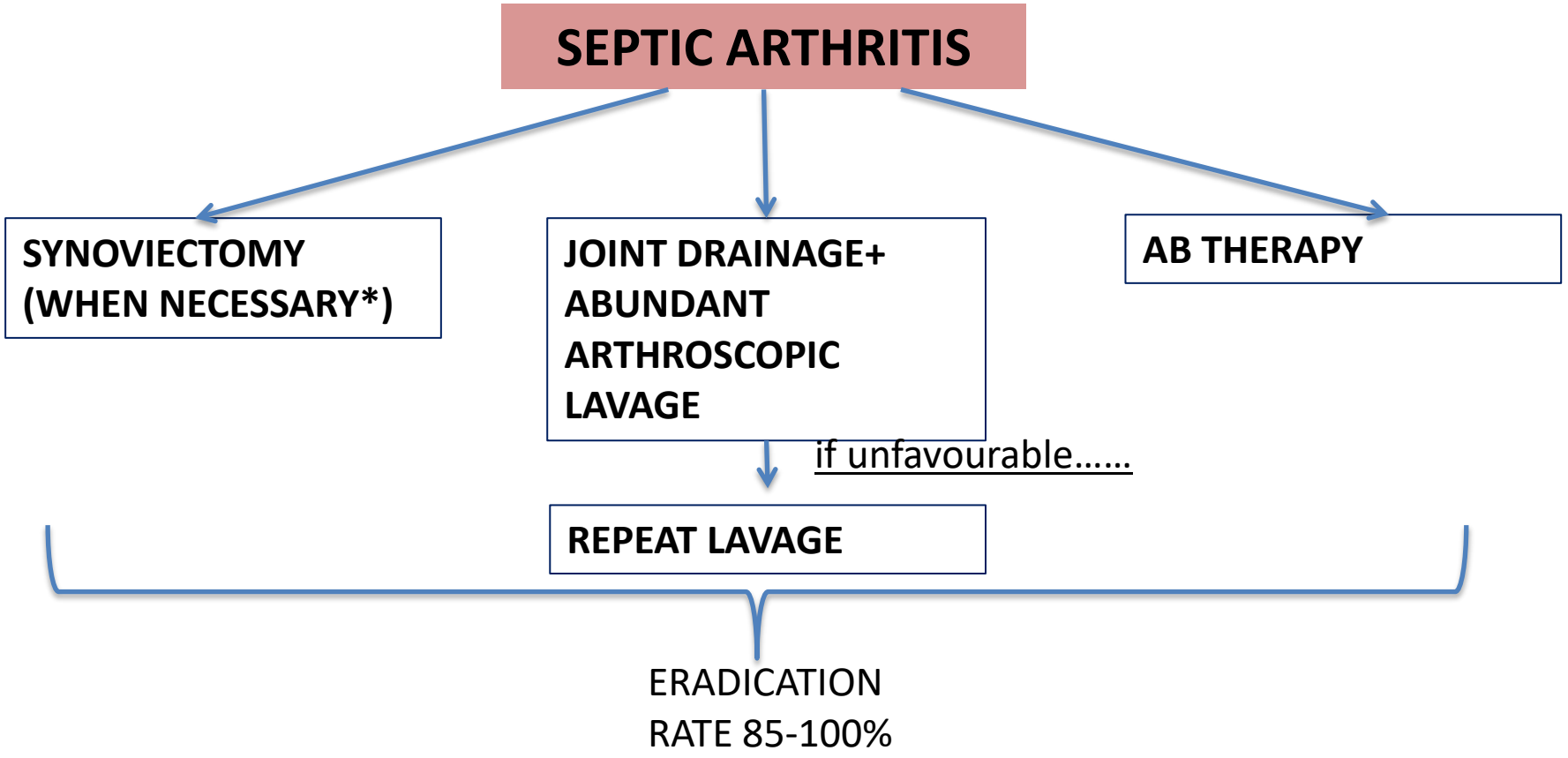
- ✓ TRAUMATIC EFFUSIONS
- ✓ HEMARTHROSIS
- ✓ CRYSTAL ARTHROPATHY
- ✓ BURSITIS
- ✓ CELLULITIS
- ✓ TRANSIENT SYNOVITIS
- ✓ RA
- ✓ REACTIVE ARTHRITIS

Diagnosis


BEFORE AB THERAPY!
SUSPECTED SEPTIC ARTHRITIS
(SIMPTOMS +)
BLOOD SAMPLE
LEUCOCYTE COUNT PCR, (ESV), PCT
SYNOVIAL FLUID ASPIRATION
COLTURE
BLOOD, URINE, URETHRA
• BLOOD COUNT, PCR, GLU, LATT., LDH, CRYSTAL, PCT (?)
• GRAM STAIN, COLTURE
• CRONIC: PCR TB, parvoB19, Brucella spp.
DRAINAGE
Empiric AB

- In view of *11% mortality*, patient should be admitted to hospital and treated with IV antibiotic treatment. **Lancet**. 2010;375:846–55.
- Evidence on which to base choice or *duration of antibiotic* treatment for septic *arthritis is scarce*. **Lancet**. 2010;375:846–55.
- the mainstay of treatment *should combine abundant arthroscopic lavage, with synovienctomy as indicated by stage of infection and coadministration of 2 effective antibiotics for at least 6 weeks*. **Knee Surgery, Sports Traumatology, Arthroscopy** September 2000

Management

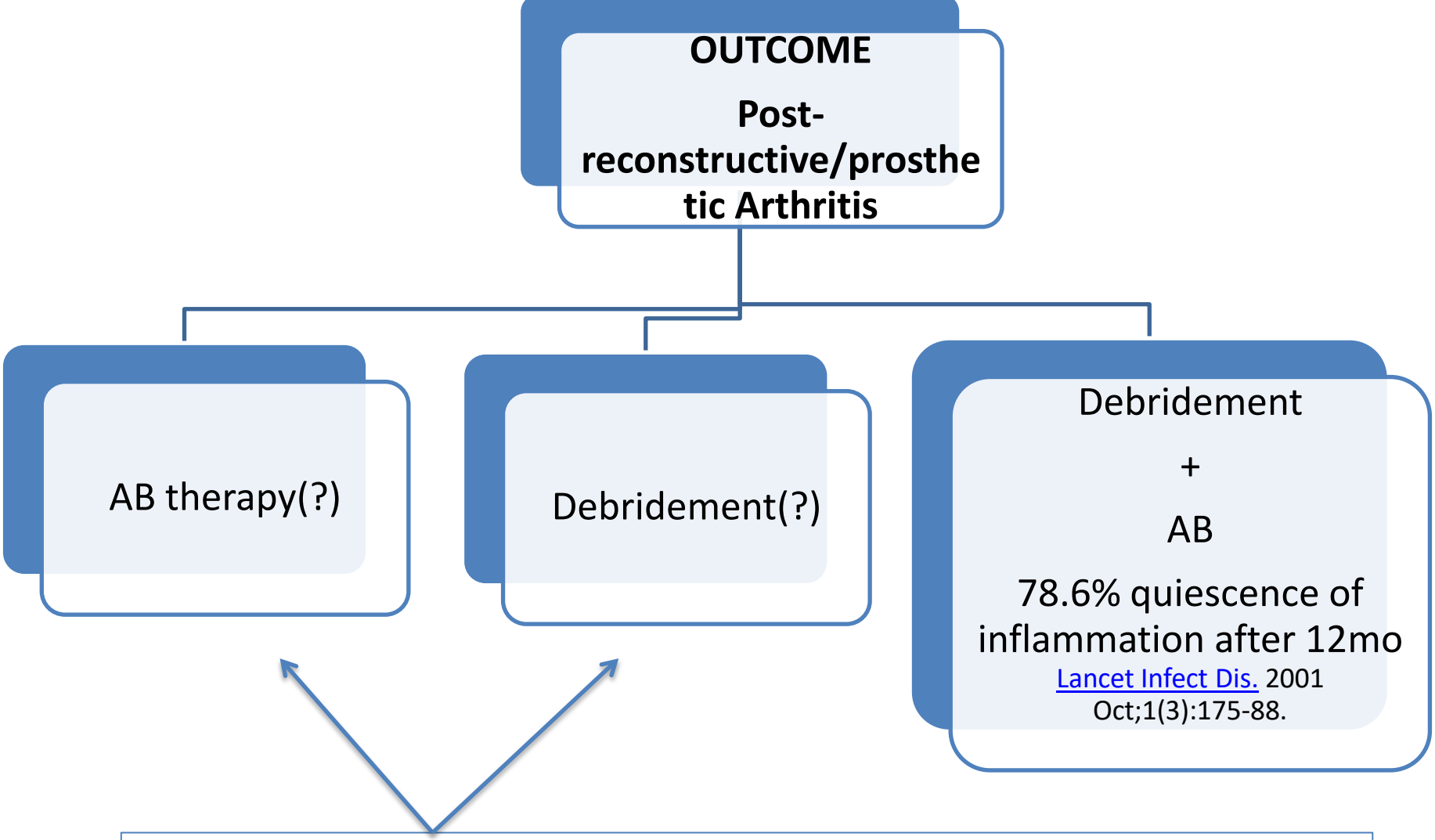


INCREASING AGREEMENT THAT IMPLANTS AND TRANSPLANTS CAN BE LEFT IN PLACE

***SYNOVIECTOMY IN PATIENTS WITH MARKED HYPERTROPHY AND INTRA-SYNOVIAL ABSCESSES. IT'S SHOULD BE AS COMPLETE AS POSSIBLE TO MAXIMALLY DECREASE BACTERIAL LOAD**

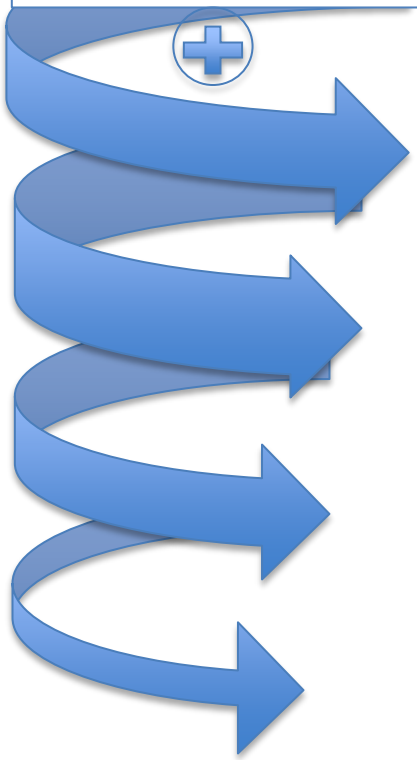
MANAGEMENT

Orthop Traumatol Surg Res. 2015 Dec;101(8 Suppl):S347-50



Although literature exists regarding the efficacy of antibiotic therapy, no articles prospectively comparing outcomes following the use of antibiotics alone *versus* debridment and antibiotics in combination could be identified

COLLECT A JOINT ASPIRATION → (−) **LOW RISK OF INFECTION**



(+)

PERFORM JOINT ASPIRATE CULTURE

START EMPIRIC ANTIBIOTICS

JOINT LAVAGE(NO NEEDLE IRRIGATION)

CONSIDER SYNOVECTOMY

Post-arthroscopy septic arthritis MANAGEMENT

Empiric Antibiotic Treatment

Acute monoarticular

STD RISK

GRAM STAIN	EMPIRIC ANTIBIOTIC THERAPY
Cocchi GRAM pos	Vancomicyn 15–20 mg/kg/8–12 h (ITALY: Teicoplanin 10-12 mg/kg/24h; 3 loading doses 12 mg/kg/12 h)
Cocchi GRAM neg/ neg. GRAM stain (*N. gonorrhoeae*)	Ceftriaxone 1 g/24 h + azitromicina 1 g x 1 dose (or doxiciclina 100 mg/12h per 7 gg); Ceftazidime 2 g/8 h,
Bacilli GRAM neg	Cefepime 2/8–12 h, piperacillina/tazobactam 4.5 g/6 h, or meropenem 1 g IV/8 h. B-lactam allergy: levofloxacina 750 mg/24h or Ciprofloxacin 400 mg IV/12h

Empiric Antibiotic Treatment

Acute monoarticular **NO STD RISK**

GRAM STAIN	EMPIRIC ANTIBIOTIC THERAPY
Negative GRAM stain	Vancomicyn** 15–20 mg/kg/8–12 h + Ceftriaxone 1 g/24 h or Vancomicina** 15–20 mg/kg/8–12 h + Cefepime 2g/8–12 h (elderly, id, *healthcare-associated infections*)
GRAM pos; cocci	Vancomicyn 15–20 mg/kg/8–12 h (ITALY: Teicoplanin 10-12 mg/kg/24h; 3 loading doses 12 mg/kg/12 h)
GRAM neg; bacilli	Cefepime 2/8–12 h, piperacillina/tazobactam 4.5 g/6 h, or meropenem 1 g IV/8 h. B-lactam allergy: levofloxacina 750 mg/24h or Ciprofloxacin 400 mg IV/12h

** or teicoplanin

Antibiotic Treatment

- Difficult infections(es. prosthetic joints) — Glycopeptides+Rifampicin [1]

- Vancomycin-interm. *S.aureus (VISA)* — Daptomycin or Linezolid published experience with daptomycin in bone e native joint is limited to case report, retrospective, observational and post hoc. [2-3]

1 J Antimicrob Chemother. 2014 Sep;69 Suppl 1:i47-52
2 Ann Pharmacother. 2008 Feb;42(2):213-7
3 Curr Med Res Opin 21:1923–1926

Dalbavancin & Oritavancin: Features of Trial

Chambers HF et al, NEJM 2014; 370:2238-2239

- **Trials similar**
  - Dalbavancin iv 1000-mg dose, with a 500-mg dose administered 1 week later
  - Oritavancin was given as a one-time dose of 1200 mg
  - Vancomycin 15 mg/Kg q12h was the comparator in both drugs
    - Step-down option to oral linezolid in the dalbavancin trials
- **In accordance** with the **2010 FDA draft guidance**
  - & the final October 2013 guidance for ABSSSIs
- **The primary efficacy end point:**
  - Clinical response of the wound, cellulitis, or major abscess (i.e., no progression and reduction in lesion size as compared with baseline in a patient who is alive and did not receive rescue therapy) determined 48 to 72 hours after the initiation of therapy
- **Substantial departure from most previous registrational trials**
  - Using the ABSSSI definition with more objective criteria of success

Dalbavancin & Oritavancin: Features of Trial

Chambers HF et al, NEJM 2014; 370:2238-2239

- **Dalbavancin trials**
  - Higher percentage of sicker patients
    - With fever 85% vs. 15%
    - With elevated WBC count 40% vs. 22%
    - With SIRS 51% vs. 18%
    - Patients' lesions were 46% larger on average (345 cm^2 vs. 237 cm^2)
- **Outcomes similar to vancomycin**
  - Both exceeded the noninferiority thresholds of 10% for the primary and secondary efficacy end points
  - There was 86% concordance of outcomes between lesion response at 48 to 72 hours and investigator-assessed success or failure of the treatment
- **The efficacy of vancomycin was remarkably similar**
  - No significant effect on outcome caused by differences in design or patients

Tedizolid

ESTABLISH-1 (TR701-112)[1]

- A Phase 3 Randomized, Double-blind, Multicenter Study Comparing the Efficacy and Safety of 6-Day Oral Tedizolid Phosphate FA and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

  Key endpoints

  - Early clinical response at the 48- to 72-hour assessment (defined as: no increase in lesion area from baseline and afebrile, confirmed by second temperature measurement within 24 hours)
  - Investigator-assessed clinical response at PTE

ESTABLISH-2 (TR701-113)[2,3]

- A Phase 3 Randomized, Double-blind, Multicenter Study Comparing the Efficacy and Safety of IV to Oral 6-Day Tedizolid Phosphate FA and IV to Oral 10-Day Linezolid for the Treatment of ABSSSI

  Key endpoints

  - Early clinical response at the 48- to 72-hour assessment (defined as: at least 20% decrease in lesion area from baseline)
  - Investigator-assessed clinical response at PTE

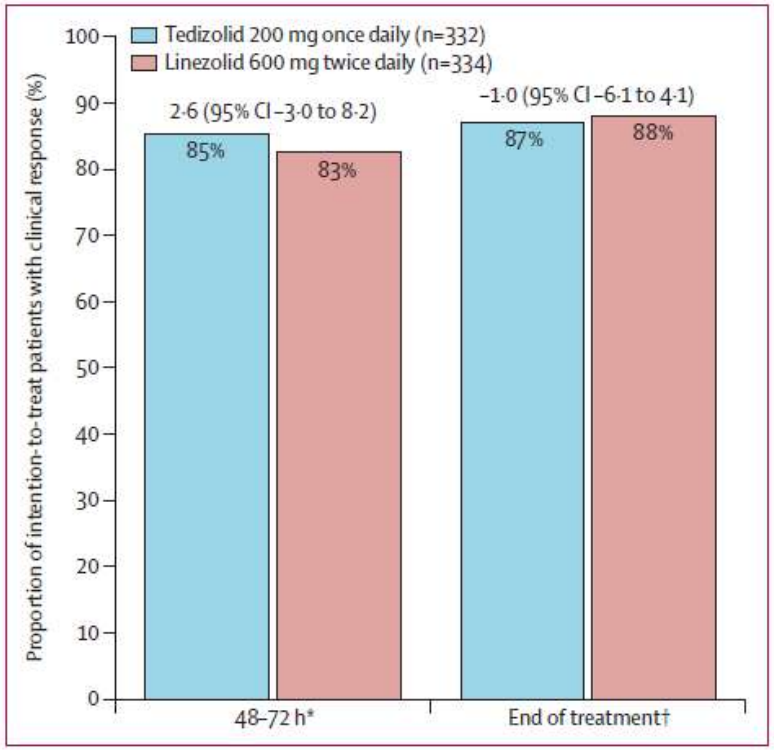
FA=free acid; PTE = post therapy evaluation; IV=intravenous; ABSSSI=acute bacterial skin and skin structure infections.

1. Prokocimer P, et al. JAMA. 2013;309(6):559-569; **2.** http://www.clinicaltrials.gov/ct2/show/NCT01421511; **3.** Fang E, et al. Efficacy and safety results from the ESTABLISH-2 ABSSSI study comparing IV and oral tedizolid phosphate and linezolid. Poster presented at: 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 27-30, 2013; Berlin, Germany. (LB2964).

Tedizolid in ABSSSIs: ESTABLISH-2

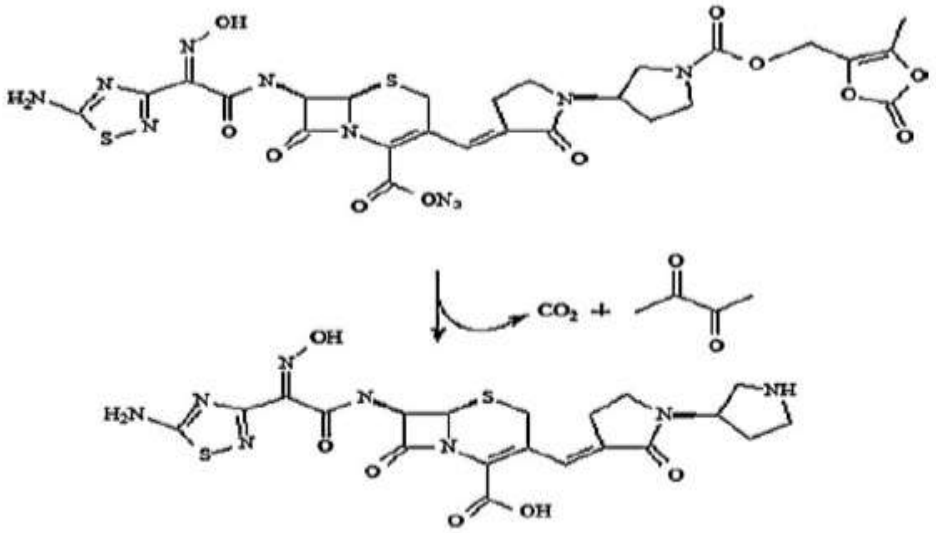
Moran GJ et al Lancet Infect Dis 2014;14:696-705

- 666 patients were randomly assigned to Tedizolid (n=332) or Linezolid (n=334)
  - 283 (85%) patients in the tedizolid group and 276 (83%) in the linezolid group achieved early clinical response (difference 2·6%, 95% CI -3·0 to 8·2), meeting the prespecified non-inferiority margin
- Gastrointestinal & treatment-emergent adverse event
  - Less frequent with tedizolid



- indications for treating skin and skin structure infections (SSSI) or community-acquired pneumonia (CAP)
- activity against aerobic and anaerobic gram-positive and aerobic gram-negative bacteria associated with skin and respiratory infections. It also **has activity against MRSA and *Str.pneumoniae*. vancomycin-resistant *E. faecalis* (not *E. faecium*)**. includes many Gram-negative pathogens but **does not extend to extended-spectrum β-lactamase-producing or AmpC-derepressed or Carbapenemase.**

CEFTAROLINA fosamil



- Activity against **MRSA, penicillin-resistant *Str. pneumoniae*, *Pseudomonas aeruginosa*, and Enterococci** and appears to be less susceptible to development of resistance.
- approved drug in Europe for the treatment of CAP and HAP (excluding patients with VAP) in adults
- Limited experience in bone/joint infections [1]

CEFTOBIPROLE

Can J Infect Dis Med Microbiol. 2010 Autumn; 21(3): 138–140.