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Simplified Treatment of Childhood Acute Bone and Joint Infections

ACADEMIC DISSERTATION

University of Helsinki

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Simplified Treatment of Childhood Acute Bone and Joint Infections

Hospital for Children and Adolescents
University of Helsinki
Finland

ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty of the University of Helsinki, for public examination in the Niilo Hallman lecture hall, Hospital for Children and Adolescents, Helsinki University Central Hospital on April 15th, 2011, at 12 noon.

Helsinki 2011
This book is dedicated to those countless children in non-privileged countries who succumbed to or became disabled due to septic bone and joint infections during the time this work was undertaken. Children, who could have been saved but were not.
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ORIGINAL ARTICLES

The thesis is based upon the following original publications, referred to in the text by roman numerals (I-V).


III Pääkkönen M, Kallio MJ, Kallio PE, Peltola H. Antimicrobial treatment for childhood osteomyelitis complicated by adjacent septic arthritis. (Submitted)


Original communications are reproduced with permission of the following journals: Clinical Orthopaedics and Related Research, Journal of Pediatric Orthopaedics B, Clinical Infectious Diseases and Pediatric Infectious Disease Journal.
ABBREVIATIONS

c-a-MRSA  community acquired methicillin-resistant *S. aureus*
CI  confidence interval
CRP  C-reactive protein
CT  computerized tomography
ESR  erythrocyte sedimentation rate
Hib  *Haemophilus influenzae* type b
IQR  interquartile range
iv  intravenous
mg/L  milligrams per liter
/mm³  per cubic millimeter
mm/h  millimeters per hour
MRI  magnetic resonance imaging
OM  osteomyelitis
OM+SA  osteomyelitis with adjacent septic arthritis
po  peroral
qid  quater in die, four times a day
SA  septic arthritis
*S. aureus*  *Staphylococcus aureus*
SD  standard deviation
SEM  standard error of mean
*S. pneumoniae*  *Streptococcus pneumoniae*
*S. pyogenes*  *Streptococcus pyogenes*
US  ultrasound
WBC  white blood cell count
ABSTRACT

Acute childhood osteomyelitis (OM), septic arthritis (SA), and their combination osteomyelitis with adjacent septic arthritis (OM+SA), are treated with long courses of antimicrobials and immediate surgery.

We conducted a prospective multi-center randomized trial among Finnish children at age 3 months to 15 years in 1983-2005. According to the two-by-two factorial study design, children with OM or OM+SA received 20 or 30 days of antimicrobials, whereas those with SA were treated for 10 or 30 days. In addition, the whole series was randomized to be treated with clindamycin or a first-generation cephalosporin. Cases were included only if the causative agent was isolated. The treatment was instituted intravenously, but only for the first 2-4 days. Percutaneous aspiration was done to obtain a representative sample for bacteriology, but all other surgical intervention was kept at a minimum.

A total of 265 patients fulfilled our strict inclusion criteria and were analyzed; 106 children had OM, 134 SA, and 25 OM+SA. In the OM group, one child in the long and one child in the short-term treatment group developed sequelae. One child with SA twice developed a late re-infection of the same joint, but the causative agents differed.

Regarding surgery, diagnostic arthrocentesis or corticotomy was the only surgical procedure performed in most cases. Routine arthrotomy was not required even in hip arthritis. Serum C-reactive protein (CRP) proved to be a reliable laboratory index in the diagnosis and monitoring of osteoarticular infections. The recovery rate was similar regardless of whether clindamycin or a first-generation cephalosporin was used.

We conclude that a course of 20 days of these well-absorbing antimicrobials is sufficient for OM or OM+SA, and 10 days for SA in most cases beyond the neonatal age. A short intravenous phase of only 2-5 days often suffices. CRP gives valuable information in monitoring the course of illness. Besides diagnostic aspiration, surgery should be reserved for selected cases.
INTRODUCTION

Acute osteomyelitis (OM) is an acute infection of the bone or bone marrow (Harik and Smeltzer 2010). Septic arthritis (SA) is a purulent infection of the joint. The combination of these two entities is called osteomyelitis with septic arthritis (OM+SA). The disease is defined to be acute if the symptoms of OM, SA or OM + SA have lasted for less than two weeks. If the history is longer than two weeks the disease is defined to be subacute or – in case the duration is several months – chronic (Krogstad 2004, Harik and Smeltzer 2010).

Acute bone and joint infections were once common killer diseases (Smith 1874, Toziano et al. 1993). Under normal circumstances bone and joint resist infections fairly well, but predisposing illnesses or environmental factors – often associated with poverty- greatly increase the infectious disease burden (Khan and Bhutta 2010). Thus today bone and joint infections are rare in high income countries with generally healthy children and efficient health care (Geirsson et al. 2008). This is not the case in most other parts of the word, as OM, SA and OM+SA are rampant in many developing countries due to many underlying illnesses and malnourishment affecting children (Tekou 2000, Ntsiba 2006).

We launched a prospective study in Finland in the early 1980s in hope that the treatment for these potentially devastating infections could be simplified from the traditional months-long medication and aggressive surgery. The goal was to shorten the duration of antimicrobials, and hence, to reduce the costs of treatment. Furthermore, unnecessary surgery was to be avoided. The rationale behind our aim stemmed from realizing that unfortunately medical resources are scarcest in settings where the need is greatest (Goudge 2009).
REVIEW OF LITERATURE

1. Definition of terms

“Osteomyelitis” (OM) and “septic arthritis” (SA) are taken here as acute, hematogenous diseases of children at age 3 months to 15 years (if not otherwise mentioned). “Osteomyelitis with adjacent septic arthritis” (OM+SA) is a combination of these two entities. Neonatal infections, OM and SA among adults, infections caused by Mycobacterium tuberculosis, and chronic OM are not primarily discussed in this context.

2. History

OM and SA were likely rare diseases among ancient populations, and affected mainly adult population (Vuorinen 2002). In the late 19th century acute osteomyelitis was reported to be a common illness among adults in Finland (Spoof 1885, Roos 1894). In modern days, OM and SA primarily affect children, and no explanation exists for this difference (Vuorinen 2002). Effective treatments for osteoarticular infections followed the invention of modern anesthetics – primarily ether and chloroform – in the 1840s, with the support of antiseptics during the latter part of the 19th century; now the surgeon could drain the infectious focus of a bone or joint (Tröhler 1993). Regarding surgery one must also mention the work of the great anatomist Andreas Vesalius, who already in 1543 published the exact anatomy of the musculoskeletal system in his book “De humani corporis fabrica libri septem”. His work had an immense impact on the development of orthopedic surgery in the subsequent centuries (Forsius 1996).

The pathogenesis of osteoarticular infections became better understood after the work of such pioneers of modern bacteriology as Louis Pasteur (1822-1895) and Robert Koch (1843-1910) (Sigerist 1931). Pasteur was among the first to isolate S. pneumoniae, a common causative agent in these infections. Even a more common organism is Staphylococcus aureus whose discovery is attributed to Sir Alexander Ogston (1844-1929) from Scotland. He
viewed pus under a microscope and took advantage of Joseph Lister’s (1827-1912) earlier work on antiseptics (Smith 1965). These pioneers paved way to more accurate diagnostics and understanding of these diseases, but still, OM and SA continued to be mortal diseases (Smith 1874, Mynter 1889).

A dramatic change occurred once sulphonamides and penicillin were discovered by teams led by Gerhard Domagk (1895-1964) (Silverman 1944) and Alexander Fleming (1881-1955), respectively (Kranz 1974, Fleming et al. 1970). Finally, clinicians had effective medications to combat these severe infections (Tiitinen 1944, Sulamaa 1945). Mortality and morbidity were significantly reduced (Koistinen 1956, Torppi and Uurasmaa 1962). One important new 20th century surgical treatment was the introduction of cancellous bone chip grafts for the treatment of chronic OM (Mowlem 1944).

3. Pathogenesis and epidemiology

3.1. Pathogenesis

Bacteria may reach a bone or a joint by three routes: direct inoculation following a trauma or a surgical intervention, local invasion (from for example cellulitis), or hematogenically. The spread via blood is the most common route in children (Krogstad 2004, Conrad 2010).

There are essentially two distinct types of bone: compact dense bone and soft cancellous bone. The distinguishing feature in the growing skeleton of a child is the presence of epiphyseal growth plates. Immediately adjacent to the epiphysis is the “resting cell zone”, which supplies the developing cartilage cells. Next, in the “zone of proliferating cartilage” bone length is created by active growth. In the “maturation zone” the chondrocytes differentiate and calcification occurs. Similarly, a vertebral body grows in height from the superior and inferior endplates of the vertebrae, these are comparable to the growth plates of long bones (Doskocil et al. 1993, Krogstad 2004, Conrad 2010).

OM usually begins in the metaphysis of a long tubular bone as shown in Figure 1. As there is no direct blood flow from the metaphysis to the
epiphysis, the proliferative epiphyseal chondrocytes receive nutrition mainly from the epiphyseal arteries. All parts of the growth area, epiphysis, growth plate, metaphysis and perichondrium, have their own distinct blood supply (Krogstad 2004, Conrad 2010). Hence, the growth plate functions as a barrier against infection. On the other hand, joints where the metaphysis is intracapsular such as hip, shoulder and ankle are thought to be especially at risk for infection (Jackson et al. 1992, Perlman et al. 2000). The synovial membrane of the joint has abundant blood flow, and large numbers of bacteria may enter the synovial membrane during bacteremia (Krogstad 2004). Most of these episodes are transient, but occasionally and largely for unknown reasons, bacteria stick onto a particular site and launch an infection which, in turn, triggers massive inflammatory reaction in the host. *S. aureus* is able to attach to the type I collagen fibrils and establishes microcolonies surrounded by a glycocalyx (Zavin et al. 1993, Krogstad 2004).

Burn injuries may also cause hematogenous septic seeding leading to OM (Fodor et al. 2004) or SA (Smoot et al. 1993).

**Figure 1.** Slow blood flow in the sinusoidal arteries of the metaphyseal-epiphyseal junction predisposes children to hematogenous osteomyelitis. The infection is initiated by bacteremic seeding.
3.2. Causative agents

3.2.1. *Staphylococcus aureus*

Gram-positive *S. aureus* - literally “golden cluster seed” due to the carotenoid pigment staphyloxanthin (Marshall and Wilmoth 1981) - is the most common causative organism both in OM and SA (Krogstad 2004). Besides osteoarticular infections it causes a wide range of diseases such as skin infections (Frei et al. 2010), pneumonia (Li et al. 2010), meningitis (Aguilar et al. 2010), endocarditis (Slabbe Koorn et al. 2010) and wound infections (Suljagic et al. 2010). *S. aureus* is part of the normal flora of skin and is also involved in impetigo, pimples, boils and abscesses. Depending on the strain, *S. aureus* is capable of secreting several toxins causing toxic shock syndrome (Kare and Dang 2008). *S. aureus* has proven its capability to develop antimicrobial resistance. After penicillin resistance had developed already in the 1940s (Plough 1945) methicillin has been used as an anti-staphylococcal agent in many countries. The evolution and spread of methicillin-resistant (ca-MRSA) and vancomycin-resistant *Staphylococcus aureus* in the past decade has caused grave concern (Rehms and Tice 2010).

3.2.2. *Streptococcus pyogenes*

This spherical Gram-positive bacterium grows in long chains and displays streptococcal group A antigen in the cell wall. *S. pyogenes* typically produces large zones of beta-hemolysis, hence the name group A beta-hemolytic streptococcus. It is common in upper respiratory tract infections, especially in acute tonsillitis (Altamimi et al. 2010). *S. pyogenes* is part of the normal flora of the skin (Brown et al. 1975) and is a common causative agent of erysipelas (Berhard 2008). *S. pyogenes* remains sensitive to penicillin (Tempera et al. 2010).

3.2.3. *Streptococcus pneumoniae*

*S. pneumoniae* a.k.a. pneumococcus is a Gram-positive member of the genus *Streptococcus*. Apart from osteoarticular infections and pneumonia (Resti et al. 2010),
2010) this organism causes a wide variety of respiratory infections such as acute sinusitis and otitis media. Severe pneumococcal infections include meningitis, peritonitis (Rueda et al. 2010) and pedicarditis (Wei et al. 2010). While previously sensitive to penicillin now an emergence of penicillin resistant strains has been seen as well (Tempera et al. 2010). Penicillin resistance has still fortunately remained low in Europe (Cooke et al. 2010).

3.2.4. Haemophilus influenzae type b (Hib).

*Haemophilus influenzae* is a gram-negative rod that used to be a devastating pathogen causing pneumonia, meningitis (Smythe 1948) and epiglottitis (Margolis et al. 1972). Thanks to large-scale vaccinations, the Hib etiology of osteoarticular infections has been eliminated from Finland (Peltola et al. 1998). The same sequence is likely to repeat once *S. pneumoniae* vaccination is adopted to the routine childhood immunization program. Hib is mostly still sensitive to beta-lactam antibiotics and common antimicrobial used is ampicillin (iv) or amoxicillin (po). Recent study put the prevalence of beta-lactamase positive strains at 16% (Perez-Trallero et al. 2010).

3.2.5. Kingella kingae

*Kingella kingae*, a Gram-negative coccobacillus, is another important pathogen in SA in some parts of the world (de Groot et al. 1988, Lacour et al. 1991). In Israel, it can even surpass *S. aureus* in frequency (Yagupsky et al. 1995). This pathogen is thought to be underdiagnosed in SA since it’s culturing is difficult (Host et al. 2000). *K. kingae* is susceptible to beta-lactams, erythromycin and ciprofloxacin (Yagupsky et al. 2001).

3.2.6. Others

SA may also be caused by *Neisseria meningitidis* and *Neisseria gonorrhoeae*, this etiology being more characteristic of newborns (Deshpande et al. 1990) and of

3.2.7. Regional differences

S. aureus is overwhelmingly most common causative organism in OM all over the world (Craigen et al. 1992, Jenzri et al. 2008, Kharbanda and Dhir 1991, Riise et al. 2008.). The most common causative organisms in SA by region are shown in Table 1.

3.3. Epidemiology

3.3.1. Worldwide distribution

Osteoarticular infections are rather common in the developing world (Onyemelukwe and Sturruck 1979, Molyneux and French 1982, Smith et al. 2002), but much less frequent in industrialized countries (Grimprel and Cohen 2007). Little information is available of the precise incidence of OM or SA in Africa since most reports deal only with cases presented at single institutions without a precisely defined source population (Lavy et al. 2007). Most likely these infections are much more common in low income countries and in the tropics. A recent study estimated the prevalence a tropical area to be 2-5 times that of Europe (Labbe et al. 2010). In a Nepalese study 10% of childrens’ hospital admissions were sequelae of musculoskeletal sepsis (Spiegel et al. 2010). In Finland, the annual incidence of OM or SA at age 0-14 years is less than five per 100,000 (Peltola and Vahvanen 1983, Kunnamo et al. 1986). Articles giving a current estimate of the incidence of OM or SA that has been published in recent years are shown in Table 2.
3.3.2. Incidence in boys vs girls

OM and SA universally tend to affect males more than females. The reason for this unequal distribution among genders is not known. The ratio is approximately 2.0 : 1.2 (Krogstad 2004). Interestingly, as seen in Table 3, the ratio is fairly similar in all over the world.

3.3.3. Concomitant OM +SA

High proportion of children with OM or SA have concomitant bone or joint involvement. One third (Perlman et al. 2000) or even half the cases (Chen et al. 2010) may have OM+SA.

3.3.4. Predisposing factors

Factors generally contributing to child health also influence the prevalence of OM and SA. Poverty, lack of purchasing power, household food insecurity and low education lead to malnourishment and high infectious disease burden (Khan and Bhutta 2010). Immunodeficiencies predispose to OM or SA. A special characteristic among immunodeficient patients is the presence of low virulence infections (Bloom et al. 2008). Blunt trauma preceding osteoarticular infections has been described in up to 63% of the cases (Labbe et al. 2010). Burns may precipitate OM. Surgery of a bone or joint always carries a risk of postoperative infection.

3.3.5. Recent changes

Iatrogenic SA, due to increasing use of arthroscopy, seems to have slightly increased in frequency in the affluent countries (Geirsson et al. 2008). Most troubling development in the rise of community acquired methicillin resistant Staphylococcus aureus. Current rate of ca-MRSA varies around the world, with a
rate of 24% published in Hawaii (Erdem et al. 2010), or even 74% in Taiwan (Fang et al. 2004).

**Table 1.**

**Most common causative organisms in septic arthritis by region**

<table>
<thead>
<tr>
<th>Country</th>
<th>Most common bacteria (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td><em>S. aureus</em> 74%</td>
<td>Peltola et al. 1998</td>
</tr>
<tr>
<td></td>
<td><em>S. pyogenes</em> 15%</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td><em>S. aureus</em> 44%</td>
<td>Moumile et al. 2005</td>
</tr>
<tr>
<td></td>
<td><em>Kingella kingae</em> 14%</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td><em>S. aureus</em> 35%</td>
<td>Eder et al. 2005</td>
</tr>
<tr>
<td></td>
<td><em>Streptococci</em> 14%</td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td><em>S. aureus</em> 39%</td>
<td>Al Saadi et al. 2009</td>
</tr>
<tr>
<td>Taiwan</td>
<td><em>S. aureus</em> 43%</td>
<td>Wang et al. 2003</td>
</tr>
<tr>
<td></td>
<td><em>Streptococci</em> 10%</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td><em>S. aureus</em> 41%</td>
<td>Ryan et al. 1997</td>
</tr>
<tr>
<td></td>
<td><em>Streptococci</em> 28%</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.

Incidence pediatric of OM or SA by region among (per year)

<table>
<thead>
<tr>
<th>Country</th>
<th>OM or SA</th>
<th>Incidence/100 000</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>SA</td>
<td>9</td>
<td>Morgan et al. 1996</td>
</tr>
<tr>
<td>Iceland</td>
<td>SA</td>
<td>11</td>
<td>Geirsson et al. 2007</td>
</tr>
<tr>
<td>Finland</td>
<td>SA</td>
<td>4</td>
<td>Peltola and Vahvanen 1983</td>
</tr>
<tr>
<td>Norway</td>
<td>SA</td>
<td>4</td>
<td>Riise et al. 2008</td>
</tr>
<tr>
<td>Norway</td>
<td>OM</td>
<td>13</td>
<td>Riise et al. 2008</td>
</tr>
<tr>
<td>Norway</td>
<td>OM</td>
<td>10</td>
<td>Dahl et al. 1998</td>
</tr>
<tr>
<td>Malawi</td>
<td>SA</td>
<td>20 (children &lt;5years)</td>
<td>Lavy et al. 2005</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>SA</td>
<td>2</td>
<td>Al Arfaj 2008</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>OM</td>
<td>4</td>
<td>Craigen et al. 1992</td>
</tr>
</tbody>
</table>

Table 3.

Boys vs girls affected by OM or SA by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Boys : Girls</th>
<th>Note</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>2.5 : 1</td>
<td>SA</td>
<td>Peltola and Vahvanen 1983</td>
</tr>
<tr>
<td>India</td>
<td>2.7 : 1</td>
<td>OM</td>
<td>Kharbanda and Dhir 1991</td>
</tr>
<tr>
<td>Italy</td>
<td>1.9 : 1</td>
<td>OM, SA</td>
<td>Faesch et al. 2009</td>
</tr>
<tr>
<td>Malawi</td>
<td>2.0 : 1</td>
<td>SA</td>
<td>Lavy and Thyoka 2005</td>
</tr>
<tr>
<td>Nigeria</td>
<td>3.0: 1</td>
<td>OM</td>
<td>Tindimwebwa et al. 1983</td>
</tr>
<tr>
<td>Tunisia</td>
<td>1.4 : 1</td>
<td>Calcaneal OM</td>
<td>Jenzri et al. 2008</td>
</tr>
<tr>
<td>Turkey</td>
<td>1.2 : 1</td>
<td>SA</td>
<td>Caksen et al. 2000</td>
</tr>
<tr>
<td>Zambia</td>
<td>2.2 : 1</td>
<td>Salmonella SA</td>
<td>Lavy et al. 1996</td>
</tr>
</tbody>
</table>
4. Diagnostics

4.1. Classic OM, SA and OM+SA

A child with a typical OM is clinically less ill than a child with SA. The patient may have fever and refuse to walk. In a closer examination the anatomic region is found to be warm, tender and hyperemic as seen in Figure 2. The most common localization is around the metaphyseal area of a long bone, but may be anywhere in the osseal structures. Even rare cases of primary patellar osteomyelitis have been recorded (Waris 1938). Sometimes the child presents only with fever, malaise and refusal to eat (Krogstad 2004).

Figure 2. Clinical presentation of calcaneal osteomyelitis can be deceptively inconspicuous. Picture courtesy of Dr. Heikki Peltola.
In contrast, a patient with SA is usually more ill than a patient with OM. Fever is often high, and the affected joint is swollen, warm and tender. Motion causes considerable pain. The history reveals no prior trauma (Shaw et al. 1990). SA usually only affects one joint (Krogstad 2004), but septicemic seeding may also initiate the infection in several joints simultaneously, an entity called septic multiple joint involvement. The slogan “mono means gono” stems from times when gonorrhea used to be a common etiology.

Once suspicion of an osteoarticular infection has arisen, the diagnosis should be confirmed. Prompt corticotomy (drilling) in OM, aspiration of pus in case of a periosteal abscess and an aspiration of the joint in SA are methods to verify the clinical entity and to obtain a representative sample for bacteriology (Tetzlaff 1978). Both Gram-staining and culture should be performed (Brannan and Jerrard 2006). Traditionally, synovial fluid has been scrutinized by a microscope, but for example, the leucosyte count overlaps with other types of arthritis in such a manner (Kunnamo et al. 1987, Kortekangas et al. 1992) that its usefulness is questionable. In contrast, the blood culture may be positive although the local sample remains negative.

4.2. Differential diagnostics

Options to be considered in the differential diagnosis of OM or SA are listed in Table 4. A bone or soft tissue tumor or dysplastic change within bone may show symptoms suggesting OM (Sluga et al. 2002, Gomoll 2007) or SA (Jordanov et al. 2009). Ultrasound or magnetic resonance imaging (MRI) are valuable in this differential diagnosis (Sluga et al. 2002). Computerized tomography (CT) is also informative (Ma et al. 1997). A trauma, overuse osteopathy or a tress-fracture may show symptoms compatible with OM (Roth et al. 2008). Pyomyositis, a common disease in the tropics but rare in Nordic countries may also resemble OM in such a way, that the differential diagnosis may be extremely difficult (Abdullah et al. 2010). Child abuse may be a possible cause of musculoskeletal symptoms.

In SA, the most common likely confounding diagnoses are non-bacterial arthritides such as reactive arthritis and juvenile idiopathic arthritis.
In case of coxitis, transient synovitis of the hip is the first entity to be distinguished from SA (Kocher et al. 1999). A number of viruses may cause joint manifestations; among those are infections caused by sindbis (Kurkela et al. 2008), chikungunya (Sebastian et al. 2009), rubella and parvovirus (Franssila and Hedman 2006).

Systemic diseases such as sickle cell anemia for example may also present musculoskeletal symptoms that may resemble OM or SA (Balogun et al. 2010). Conditions such as growing pains rarely resemble OM in children, as the child moves normally and the symptoms appear periodically (Asadi-Pooya and Bordbar 2007).

Table 4.
Diseases to be considered in the differential diagnosis OM or SA.

<table>
<thead>
<tr>
<th>OSTEOMYELITIS</th>
<th>SEPTIC ARTHRITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Aseptic arthritis</td>
</tr>
<tr>
<td>Stress fracture</td>
<td>Transient synovitis of the hip</td>
</tr>
<tr>
<td>Pyomyositis</td>
<td>Legg-Calve-Perthes disease</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Slipped capital femoral epiphysis</td>
</tr>
<tr>
<td>Benign/malignant tumours</td>
<td>Viral arthritis</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>Juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>Child abuse</td>
<td>Reactive arthritis</td>
</tr>
<tr>
<td>Scurvy</td>
<td>Sickle cell anemia</td>
</tr>
</tbody>
</table>

4.3. Laboratory measurements in the diagnostics of osteoarticular infections

The erythrocyte sedimentation rate (ESR) is the traditional laboratory marker used in the diagnostics of osteoarticular infections (Lorrot 2007). ESR increases in 1-3

Finnish researchers were probably the first to utilize serum C-reactive protein (CRP) in the diagnostics and follow-up of osteoarticular infections (Peltola and Räsänen 1982, Peltola and Vahvanen 1984; Unkila-Kallio et al. 1994 [1], Unkila-Kallio et al. 1994 [2], Kallio et al. 1997).

White blood cell count (WBC) is too unspecific a marker to be of value in a clinical setting, especially since it may be normal in up to 80% of cases (Lorrot 2007). Recently, serum procalcitonin concentrations have been used in the differentiation of OM and SA (Butbul-Aviel et al. 2005, Hugle et al. 2008), but no study shows it to serve the clinician better than CRP.

4.4. Radiological findings

Plain radiograph has been used in OM almost since the times of Wilhelm Konrad Röntgen (Smith 1896), because when positive, it is a strong argument for the diagnosis. The problem is that significant bone matrix destruction is required for a positive x-ray with leading to sensitivity as low as 15% in an early x-ray (Malcius et al. 2009). In a Finnish study (Peltola et al. 1997), lytic x-ray changes were found in only 19% of the cases at the beginning of treatment, but in 68% of the cases at day 29 from the onset of treatment. On the other hand, plain radiograph can be used to rule out other possible causes of joint pain or limp, such as traumatic/stress fractures or slipped upper femoral epiphysis (Reed 2009).

Scintigraphy a.k.a bone scan and more recently magnetic resonance imaging (MRI) have paved their ways to be used in diagnostics as seen in Figure 3, albeit they too, might be negative in an early stage of the disease (Hughes and Aronson 1994, Jenzri et al. 2008). Especially during the first 3 days a bone scan may yield a false negative result (Conrad 2010), but still changes to positive much earlier than the traditional radiograph (Azoulay et al. 2007).

Apart from differential diagnosis a plain radiograph is of little relevance in recognizing SA, because if anything it usually only identifies a
swollen joint space. Ultrasound is slightly better for detecting swelling and facilitating aspiration (Lavy et al. 2003). Good accuracy has been demonstrated with MRI which also adds to the difficult differential diagnosis between OM and SA (Hammond and Macnicol 2001). Fat-enhancement or using gadolium contrast does not improve accuracy of MRI (Averill et al. 2009, Kan et al. 2010). Computer tomography (CT) has few indications, but it may be performed when a sequestrum in chronic osteomyelitis is suspected, or when MRI is not possible.

In the routine follow-up a plain x-ray is often sufficient as it reveals a pathological fracture or chronic processes sequestrum. In a recent study routine repeat MRI did not offer additional benefit (Courtney et al. 2010). However, if the recovery is slow or absent, a repeat MRI can affect treatment in 10% of the cases (Courtney et al. 2010).

![Figure 3](image.png)

**Figure 3.** Previously healthy 15-year-old boy suffered a mild distorsion injury of the hip while playing ice hockey. In the following days the patient developed fever and pain in the left sacro-iliacal region. US suggested sacroilitis. MRI showed an abscess of 23 millimeters adjacent to the sacro-iliacal joint. *S. aureus* grew from the blood culture.
5. Treatment

5.1. Antimicrobial therapy, and other medications

Antimicrobial treatment for osteoarticular infections should be started without delay after the relevant samples have been obtained. Because no sufficiently-powered study comparing different antimicrobials or examining dissimilar durations of treatments has been available, clinicians have been forced to base their choice on the experts’ recommendations and own experience. Sometimes the initial treatment requires an adjustment according to the causative agent (Krogstad 2004).

The primary antimicrobial should cover the most common organisms. In high-income countries these are essentially gram-positive bacteria (Krogstad 2004, Shaw and Kasser 1990, Smith et al. 1995) since Hib has been eliminated by vaccination (Peltola et al. 1997). The agent must have good joint and bone penetration (Nelson et al. 1978). Clindamycin and first-generation cephalosporins fulfill these criteria. Large doses were recommended decades ago and probably with good reasoning as these antimicrobials are time dependent and thus their efficacy depends on the time their tissue concentration exceeds the minimal inhibitory concentration (Nelson et al. 1978). For clindamycin, 40 mg per kilogram per 24 hours should be administered divided in 4 daily doses (qid), and for the first-generation cephalosporins no less than 150 (-200) mg per kilogram qid. Because beta-lactams and lincosamides (clindamycin) are time-dependent antimicrobials, it is probably important that administration occurs four, not three, times, per 24 hours. Antimicrobial recommendations vary greatly in different regions, as seen in Table 5.
Table 5.

Recommended empiric antimicrobial treatments vary greatly between countries or even between hospitals. A list of some recommended primary antimicrobial agents in osteoarticular infections by country.

<table>
<thead>
<tr>
<th>Country</th>
<th>Antimicrobial recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chile</td>
<td>Cloxacillin + Ceftriazone (age&lt;5)</td>
<td>Prado et al. 2008</td>
</tr>
<tr>
<td></td>
<td>Cloxacillin+Aminoglycoside (age&gt;5)</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Beta–lactam</td>
<td>Cohen and Grimprel 2007</td>
</tr>
<tr>
<td>Malawi</td>
<td>Chloramphenicol</td>
<td>Peek et al. 2006</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Flucloxacillin or Cefuroxime</td>
<td>Jagodzinski et al. 2009</td>
</tr>
<tr>
<td>United States</td>
<td>Beta-lactam + Vancomycin</td>
<td>Saphyakhajon et al. 2008</td>
</tr>
</tbody>
</table>

The optimal duration of antimicrobials is under continuous discussion. Many authorities opine that the initial intravenous phase should last for at least a week (Krogstad 2004, Glorion et al. 1993, Ross et al. 2003). Then, a shift to oral administration may be possible, circumstances permitting (Feigin et al. 1975, Nelson et al. 1978, Tetzlaff et al. 1978, Kolyvas et al. 1980, Toziano et al 1993). The total course, both for OM and SA, is globally recommended to last several weeks as shown in Table 6 (Mollam and Biggott 1977, Syrogiannopoulos and Nelson 1988, Syrogiannopoulos and Nelson 1988, Shaw et al. 1990, Smith an Piercy 1995, Dahl et al. 1998, Christiansen et al. 1999, Bonhoeffer et al. 2001, Lew and Waldvogel 2004, Malcius 2005, Krilov and McCracken 2006), even though the risks involved with prolonged treatments have been documented (Ceroni et al. 2003). Retrospective studies have shown early transition from intravenous to oral therapy to be safe even in OM (Zaoutis et al. 2009).

One study on SA examined the value of adjuvant dexamethazone (Odio 2001). It slightly quickened healing but did not influence long-term outcomes. Non-steroidal anti-inflammatory drugs to relieve pain and fever should be given at the discretion of the attending clinician (Autrec-Leca 2003).
Table 6.

Recommended length of total antimicrobial treatment of pediatric OMSA by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Treatment length</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3 weeks</td>
<td>Vinod et al. 2002</td>
</tr>
<tr>
<td>Chile</td>
<td>4 - 6 weeks</td>
<td>Prado et al. 2010</td>
</tr>
<tr>
<td>France</td>
<td>5 - 6 weeks</td>
<td>Abuamara et al. 2004</td>
</tr>
<tr>
<td>India</td>
<td>3 - 4 weeks</td>
<td>Shetty and Gedalia 2004</td>
</tr>
<tr>
<td>Iran</td>
<td>5 weeks</td>
<td>Shetty and Gedalia 2004</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2 - 4 weeks</td>
<td>Eyichukwu et al. 2010</td>
</tr>
<tr>
<td>Taiwan</td>
<td>5 weeks</td>
<td>Kao et al. 2003</td>
</tr>
<tr>
<td>United States</td>
<td>4 weeks</td>
<td>Ballock et al. 2010</td>
</tr>
</tbody>
</table>

5.2. Surgical treatment of OM

Traditional surgical treatment of OM comprises drainage of the subperiosteal abscess by drilling of the bone (trepanation). If adjacent joint is involved, capsulotomy or continuous lavage is often performed (Tetzlaff et al. 1978, Kolyvas et al. 1980, Karwowska et al. 1998, Vinod et al. 2002, Gutierrez 2005). Since no high-quality studies have been available, such active surgical intervention is largely empirical, or based on retrospective analyses of variable patient series (Kenney 1944).
5.3. Surgical treatment of SA

In SA, the traditional surgical treatment includes prompt surgical drainage of the joint (Welkon 1986, Parsch 1997, Gordon 2005, Nunn 2007). This has been deemed especially important for the hip and shoulder joints because of the tight surrounding capsule (Krogstad 2004). Although no study has documented the need for routine arthrotomy, the rationale is to drain pus, to decrease intra-articular pressure, and thus, to decrease the risk of avascular necrosis of the femoral head, or prevent the pressure induced dislocation of the hip joint (Hunka 1982, Vidigal 1997). In recent years, researchers have also challenged this view (Lavy et al. 2006). Interestingly, SA in an adult patient is more often treated with arthrotomy/arthroscopy and lavage if the attending physician is a surgeon; if not, the patient is more often treated with daily arthrocentesis (Manadan and Block 2004). The results have not differed.

Some clinicians have moved to repeated (ultrasound guided) aspirations (Griffet and Hayek 1996, Lavy et al. 2003, Manadan and Block 2004, Smith et al. 2002, Givon 2004), or conservative treatment which consists only of antimicrobials and possibly immobilization of the affected joint (Lipczyk 2001). The results have equaled to those deriving from the traditional approach.

5.4. Treatment of OM+SA

Although there is no consensus on the treatment modalities for OM+SA (Tetzlaff et al. 1978, Kolyvas et al. 1980, Karwowska et al. 1998, Carek et al. 2001, Dieckmann et al. 2008, Weichert et al. 2008), the approach is traditionally more aggressive than for plain OM or SA (Hartwig 2006, Shetty and Kumar 2007) because OM+SA is considered to have a poorer outcome (Gafur et al. 2008, Jenzri et al. 2008). Since the differential diagnosis between OM and OM+SA may be difficult (Hammond and Macnicol 2001), especially at an early stage of disease, the clinician often has to treat the patient without precise knowledge of the extent of the infection.
5.5. Monitoring of the treatment

Measuring the effect of antimicrobials and/or surgical treatments warrants repeated clinical examination, combined with a follow-up of the parameters of infection/inflammation. ESR and WBC are the traditional markers used (Gold 1991, Del Beccaro et al. 1992). Being an excellent tool for monitoring response to a chosen treatment, serum CRP has challenged both these laboratory indices (Peltola and Räsänen 1982, Peltola and Vahvanen 1984, Unkila-Kallio et al. 1994, Andreola et al. 2007). A special advantage of CRP is its rapid reaction to changes in the clinical situation compared to ESR (Unkila-Kallio 1994, Andreola 2007). Furthermore, a precise CRP value is currently obtainable quickly (in 10 minutes) from a whole-blood sample taken with a finger prick. CRP costs 1.40-6.00 € and is thus much cheaper than procalcitonin measurement that costs 20.00-30.00 € (Tykslab 2010).

5.6. Prevention of osteoarticular infections

Before the era of conjugate vaccines, Hib used to be the second most common causative agent of SA in Finland. Large-scale vaccinations wiped out this etiology, and as a consequence, the initial antimicrobial spectrum could be narrowed (Peltola et al. 1998). Conjugate vaccines against *S. pneumoniae* can be expected to decrease the incidence of osteoarticular infections caused by pneumococci (McClure et al. 2006), although its role is smaller than what Hib used to be. So far, there is no effective vaccine against *S. aureus* (Stranger-Jones et al. 2006, Clarce et al. 2006).

### 6. Outcomes

6.1. Natural course of OM and SA

Although large series of various osteoarticular infections have been published since or even before the beginning of last century (Smith 1874, Homans 1912),
their natural course is not well characterized. A study of 110 patients in India showed that sequelae such as chronic osteomyelitis and sequestrum are fairly common in OM if antimicrobial treatment has been delayed or not instituted (Kharbanda and Dhir 1991). In a Finnish study early treatment in under 72 hours did not correlate with a more favorable outcome compared to children presenting within a week (Lindell and Parkkulainen 1960).

By experience we have learned that sequelae may develop slowly (Spindler et al. 1998, Nunn and Rollison 2007), and therefore a long follow-up for at least a year is needed. If a new episode develops later, it is likely that it is not a true recrudescence of the same disease but a late re-infection (Uckay et al. 2006).

The risk of recrudescence in OM, SA, or OM+SA is not well known. A large retrospective study on 168 cases of osteoarticular infections in the United States from the 1974-83 (Syrogiannopoulos and Nelson 1988) found four (3.8%) recurrences of OM, and other sources (Cole et al. 1982, Kharbanda and Dhir 1991, Tindimwebwa et al 1983) suggest an incidence of somewhere around. However, if a new episode develops later, it is not-at-all clear that the case has recrudesced. A Swiss report (Uckay et al. 2006) demonstrates that it may only be a late re-infection in the same anatomical site caused by a different agent, perhaps a similar phenomenon as observed with endocarditis. Whatever the sequence, a recrudescence or a late reinfection tend to occur within months, or at least, in the few years after the primary affection.

6.2. Long-term sequelae

The feared complications of OM include pathological fractures, abscesses, sequestrum and periosteal necrosis. Acetabulum dysplasia is a severe sequela that develops after an enlarged femoral head – caput magna – is formed because of overgrowth of cartilage after SA. Pathological fractures most commonly develop due to chronic osteomyelitis (Akinyoola et al. 2008), which is unfortunately common in less privileged countries (Agaja and Ayorinde 2008) and may require extensive surgical procedures as seen in Figure 4. Sequestrum is a segment of bone that has been avascularised by necrosis. Involucrum is the
formation of new bone around a sequestrum during the healing process (Jones et al. 2009).

Growth disturbance is a devastating sequela that may lead to severe functional disability (Suger et al. 2000, Nunn and Rollison 2007). For example, a partial closure of the growth plate of a single femoral condyle leads to angular varus or valgus deformity (Langenskiöld 1984). These deformities may be asymptomatic even for decades before arthrosis develops. Compartment syndrome secondary to pediatric OM has also been described (Mulcaney et al. 2009).

A series of 110 patients from India showed that sequelae such as chronic OM and sequestrum are fairly common if the antimicrobial treatment has been delayed or not instituted (Kharbanda and Dhir 1991). The sequelae may develop slowly (Spindler et al. 1998, Nunn and Rollison 2007). Therefore, a long follow-up for at least a year post-hospitalization is well founded.

Complications of SA include the avascular necrosis of the subchondral bone or joint cartilage destruction leading to arthrosis (Hunka et al. 1982, Vidigal Junior EC et al. 1997). Even death may occur. The length of antimicrobial administration needed to avoid recrudescences or sequelae – if such exists – is not known (Krogstad 2004). Reported global complication rates in OM and SA are given in Table 7ab. Articles often use different criteria for reporting complications making definitive comparisons between different regions and patient populations difficult.
Figure 4. Hematogenous osteomyelitis is the most common cause of chronic osteomyelitis, a devastating and sometimes lifelong disease that is unfortunately common in impoverished countries (Agaja and Ayorinde 2008). A Kenyan boy required extensive surgical debridement because of a chronic infection focus of the right femur. Courtesy of Dr. Jukka Tiittanen.
**Table 7a**

Outcome of OM by country.

<table>
<thead>
<tr>
<th>Country</th>
<th>Sequelae/Cases (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1/75 (1)</td>
<td>Cole et al. 1982</td>
</tr>
<tr>
<td>India</td>
<td>32/110 (29)</td>
<td>Kharbanda and Dhir 1991</td>
</tr>
<tr>
<td>Nigeria</td>
<td>3/28 (11)</td>
<td>Tindimwebwa et al. 1983</td>
</tr>
<tr>
<td>Russia</td>
<td>6/348 (2)</td>
<td>Rusak et al. 1991</td>
</tr>
<tr>
<td>Tunisia</td>
<td>7/26 (27)</td>
<td>Jenzri et al. 2008</td>
</tr>
<tr>
<td>United States</td>
<td>1/77 (1)</td>
<td>O’Brien et al. 1982</td>
</tr>
</tbody>
</table>

**Table 7b**

Outcome of SA by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Sequelae/Cases (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1/75 (1)</td>
<td>Cole et al. 1982</td>
</tr>
<tr>
<td>India</td>
<td>32/110 (29)</td>
<td>Kharbanda and Dhir 1991</td>
</tr>
<tr>
<td>Nigeria</td>
<td>3/28 (11)</td>
<td>Tindimwebwa et al. 1983</td>
</tr>
<tr>
<td>Russia</td>
<td>6/348 (2)</td>
<td>Rusak et al. 1991</td>
</tr>
<tr>
<td>Tunisia</td>
<td>7/26 (27)</td>
<td>Jenzri et al. 2008</td>
</tr>
<tr>
<td>United States</td>
<td>1/77 (1)</td>
<td>O’Brien et al. 1982</td>
</tr>
</tbody>
</table>
THE PURPOSE OF THE STUDY

1. To determine if the duration of antimicrobial treatment for OM/OM+SA could be shortened to 20 days (V).

2. To determine if the duration of antimicrobial treatment for SA could be shortened to 10 days (IV).

3. To compare clindamycin with first generation cephalosporin in the treatment for OM, SA or OMSA (IV, V).

4. To assess the need for surgery in OM, SA or OM+ SA (II, III, IV, V).

5. To evaluate the usefulness of serum CRP determinations in the diagnostics of and monitoring the course of acute osteoarticular infections of childhood (I, II, III, IV, V).

6. To estimate to which extent concurrent adjacent SA complicates the treatment of OM (III).
PATIENTS AND METHODS

1. Study design

The study was a randomized controlled, multicentre, open labeled, parallel group, non-inferiority trial carried out in 7 referral hospitals (Aurora Hospital, Etelä-Saimaa Central Hospital, Helsinki University Central Hospital, Jorvi Hospital, Kuopio University Hospital, Päijät-Häme Central Hospital, Seinäjoki Central Hospital) in Finland in 1983-2005. The study protocol was approved by each institution’s ethical committee, and the child was included only if consent was given by the legal guardian. The trial was designed, conducted, and analyzed independently of any medical companies or manufacturers. Only previously healthy children were included.

Once a child with OM (painful and swollen limb without trauma, restriction of motion, often a tender and warm area combined with fever), acute SA (painful and swollen joint without trauma, restriction of motion, tenderness and warmth combined with fever) (Shaw and Kasser 1990) or OM+SA (combined symptoms of OM and SA) was suspected in a 3-month to 15-year-old child, the clinician obtained a randomized study number by telephone from a computer-generated list held at Children’s Hospital, Helsinki, 24 hours a day. The number was marked in the hospital chart, and it dictated the length of the treatment, 20 or 30 days in OM or OM + SA and 10 or 30 days in SA. The antibiotic, clindamycin or a 1st generation cephalosporin was chosen according to the child’s birthdays (even or odd) as seen in Figure 5.
**Figure 5.** Study protocol. Adjuvant ampi-/amoxicillin was also given to children under 5 years.
2. Patients

Patients from age 3 months to 15 years with culture positive OM, SA, or combined OM+SA were enrolled in the study. 131 children with OM or OM+SA were randomized between 20 days (67 cases) or 30 days (64 cases) of antimicrobials. 130 children with SA were randomized to receive the 10-day-treatment (63 cases) or the 30-day-treatment (67 cases). A quasirandomization was done between clindamycin and cephalosporin treatments. As four post-enrollment cases were included in the subanalysis of the surgical treatment and laboratory monitoring, the final series comprised 265 patients. The patient characteristics are described in Table 8. Proportion of cases from each participating hospital is described in Figure 6. Number of cases in proportion to the pediatric source population of each participating hospital is described in Figure 7. Average enrollment of enrolled patients in proportion to source population was 2.4/100 000/year among 0-15 year olds. Localization of OM or SA in proportion to the whole series is described in Figure 8a. Figure 8b depicts the rate of adjacent joint involvement in OM by localization. 8c shows the proportion of OM cases by localization in proportion to all OM cases and SA by localization in proportion to all SA cases.

![Figure 6. Patients (%) from participating hospitals.](image)
Table 8. Patient characteristics on admission (N=265)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Males/Females</td>
<td>161/104</td>
</tr>
<tr>
<td>Age, years, median</td>
<td>8.4</td>
</tr>
<tr>
<td>History, days (median, IQR)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>134</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>106</td>
</tr>
<tr>
<td>Osteomyelitis with adjacent septic arthritis</td>
<td>25</td>
</tr>
<tr>
<td><strong>Agent cultured from</strong></td>
<td></td>
</tr>
<tr>
<td>Joint and blood</td>
<td>55</td>
</tr>
<tr>
<td>Bone and blood</td>
<td>21</td>
</tr>
<tr>
<td>Joint only</td>
<td>75</td>
</tr>
<tr>
<td>Bone only</td>
<td>33</td>
</tr>
<tr>
<td>Blood only*</td>
<td>81</td>
</tr>
<tr>
<td><strong>Causative agent</strong></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>199</td>
</tr>
<tr>
<td><em>Haemophilus influenzae type b</em></td>
<td>26</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>25</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>12</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

*provided that the patient had an indisputable evidence of an osteoarticular affection by US, radiograph and/or MRI, or local pus was obtained.

Figure 7. Number of enrolled patients during the study period from each hospital in proportion to the pediatric source population of the hospital in question (/100000).
Figure 8a. Localization of osteoarticual infections in this series of 265 cases in all. Skeleton used as a model was originally drawn by the great anatomist, physician and genius Andreas Vesalius (1514-1564).
Figure 8b. Proportion of OM cases complicated by SA by localization. Special predisposition of the proximal tibia is surprising.
Figure 8c. The anatomical site of OM/OM+SA (N=131) and SA (N=130), shown as percentage of their total numbers, respectively.
3. Treatment

3.1. Antimicrobial treatment

Since a gram-positive agent was the likely pathogen (Krogstad 2004, Glorion et al. 1993, Nelson et al. 1978, Syrogianopoulos and Nelson 1988, Shaw and Kasser 1990, Smith and Piercy 1995, Peltola and Vahvanen 1983, Christiansen et al. 1999), the children were given clindamycin (Feigin et al. 1975, Nicholas et al. 1975, Kaplan et al. 1982) 40 mg per kilogram per 24 hours divided qid (Kolyvas et al. 1980), or a first-generation cephalosporin (cephradine/cephalothin i.v., cephradine/cehalexin/cephadroxil orally) 150 mg per kilogram per 24 hours divided qid (Kolyvas et al. 1980). In the first years of the study Hib was still common, the children with SA at age 0-4 years received initially additional ampicillin (Kolyvas et al. 1980) intravenously, followed by amoxicillin orally, each 200 mg per kilogram per 24 hours qid until the etiology was identified. The course was completed with one antimicrobial only.

Being the only first-generation cephalosporin available for parenteral and oral use, cephradine (Kolyvas et al. 1980, Zaki et al. 1974, Brossof et al. 1979, Leigh et al. 1989) was our first choice, but its later withdrawal from Scandinavia forced us to change to cephalothin (iv), and oral cephalexin (Tetzlaff et al. 1978) or cephadroxil; the doses were the same as for cephradine. This switch was not deemed critical for the study, because all these cephalosporins are very similar (Lambert and O’Grady 1992).

Antimicrobial was instituted intravenously for 2-4 days, and completed orally with the same high doses. Serum or joint fluid concentrations were not assayed. Nor was adjuvant dexamethasone (Odio et al. 2003) used. Instead, non-steroidal anti-inflammatory drugs were given routinely.

3.2. Agent identification

To identify the causative agent, drilling or trepanation for OM, and a needle aspiration for SA was recommended. Gram-staining and bacterial culture of the
synovial fluid and/or bone sample were done. Blood culture was to be taken from all patients. To avoid debate whether the diagnosis was correct only bacterial positive patients were included in the final analysis.

3.3. The role of surgery

Beyond initial drilling, no surgery was recommended for OM, unless considered essential by an experienced pediatric or orthopedic surgeon. Surgery was kept at minimum for SA as well, and repeated aspirations, or arthroscopy and lavage were not recommended even in shoulder or hip arthritis, unless the clinical response was unsatisfactory, or the responsible orthopedic surgeon deemed it mandatory.

3.4. Monitoring the course of disease

Preset laboratory and radiographic investigations comprised plain radiograph on admission, and on days 10 and 19; basic blood analysis at presentation, and on day 5 and 10. CRP (Peltola and Räsänen 1982, Peltola et al. 1984) and ESR were measured sequentially during the entire follow-up. At the last visit, the child was examined thoroughly, and radiography, ESR and CRP were checked. Values exceeding 20 mg/L for CRP or 20 mm/h for ESR were deemed increased. CT and MRI were done on demand. The findings were recorded in special forms from which the data were computerized and analyzed in Helsinki. A researchers’ meeting was held once a year.

3.5. Dealing with special problems, control visits

Medication was discontinued if most (though not all) symptoms and signs had subsided and CRP declined to less than 20 mg/L; current ESR value did not affect this decision. If CRP remained elevated or the signs were still prominent, medication was continued until two normal CRP values (extra checks) were obtained. In case of likely allergy, medication was switched from 1st generation cephalosporin to clindamycin or vice versa.
Because of the potential late problems of osteoarticular infections (Howard et al. 1976, Spindler et al. 1998, Nunn et al. 2007, Tice et al. 2003) control visits were scheduled at 2 weeks, 3 months, and at least 1 year from discharge. A study group member executed all investigations, paying special attention to potential sequelae. Plain radiograph, and the ESR and CRP determinations were included in the check-ups.

4. Outcome measures and statistical analysis

The primary endpoint was full clinical recovery without reinstitution of treatment for an osteoarticular infection within the follow-up of 12 months. Secondary endpoints comprised all potential sequelae.

Regarding the comparative treatment trials (IV, V), the sample size calculation took into consideration the 95% confidence interval (CI_{95%}) for the difference in success rates using the normal approximation to the binomial distribution. The non-inferiority test was based on the lower bound of the confidence intervals being within pre-specified non-inferiority margin of 15% and the upper bounds containing 0%. Assuming a 90% efficacy in both groups, a statistical power of 80%, and a one-sided significance level of 0.025, 63 patients were needed in the groups to test the null hypothesis (difference of at least 15% in treatment). All P-values were two-sided and not adjusted for multiple analysis.

After the conclusion of the original trial the gathered data was also to be used in retrospective analyses.

RESULTS

1. Shortened duration of antimicrobial treatment for OM

The number of cases affecting bone was 131 (V). Bacteria grew from bone and blood in 35 cases, from bone alone in 44 cases, and from blood alone in 52 cases as depicted in Figure 9. S. aureus, all methicillin-susceptible strains, was the
overwhelmingly most common agent being responsible for 89% (117/131) of cases. Causative organisms are presented in Figure 10.

![Venn Diagram: Bone 34%, Blood 40%, Blood and Bone 27%]

**Figure 9.** Isolation of causative organisms from bone or blood in OM.

![Pie Chart: S. aureus, Str. Pyogenes, Hib, Other]

**Figure 10.** Causative organisms in OM.

All age groups were affected as the median age was 9.0 years in the short-term and 9.3 years in the long-term treatment group (V). Medical attention was sought within 3 days and 7 days in 47% (N=61) and 84% (N=110), respectively. An adjacent joint (OM+SA) was involved in 13 and 11 cases in the short and long treatment groups (III, V). OM+SA induced significantly greater changes in ESR and CRP than OM (p<0.05) (III, IV).
Antimicrobials were administered intravenously for 3.7 (median) and 4.1 days in the short-term or long-term treatment group, respectively. The duration of entire antimicrobial medication in the former group was 20.0 days (interquartile range 0 day, 90% range 10-21 days), the shortest course (of cephalosporin) being no more than 9 days (V). In the long-term treatment group, the children were administered antimicrobials for 30 days (III, IV, V). The extreme prolongations in medication were 108 days in the short-term, and 91 and 80 days in the long-term treatment group (V).

The children in both groups recovered fast without difference between groups in the follow-up indices. Importantly, no laboratory or clinical marker in the 20-day group deviated from the other group after the antimicrobial had been discontinued (IV, V).

At the 1-year checkup, 15 children in the short-term, and 18 in the long-term treatment group did not show up since they considered themselves already fully recovered. There were 98 attendees at the final control. Complications are described in Results 7: Problem cases. One child in the long and one child in the short treatment group had major sequelae (V).

No case relapsed, nor was corrective surgery needed (II, V).

2. Shortened duration of antimicrobial treatment for SA

This series comprised 130 SA patients who represented all age groups, with some preponderance among under 2-year-olds. The mean age was 6.5 years. Medical attention was sought within six days in 93% of the patients. No clear association prevailed between the length of history and the presenting status.

The lower extremities were usually affected, with hip, knee and ankle comprising 85% of the cases (III, IV, Figure 8a). The joints were affected rather similarly in the short-term and long-term treatment groups. Synovial fluid and blood grew bacteria in 32%, synovial fluid alone in 46% and blood only in 22% (IV) as seen in Figure 11.
The majority of cases were caused by *S. aureus*, Hib, *S. pyogenes* and *S. pneumoniae* (I, II, IV). Proportion of causative organisms is given in Figure 12. 63 children were in the short-term and 67 children in the long-term treatment group. Antibiotics were given intravenously, on average, for 3 days (I, II, IV).

![Figure 11. Isolation of causative organisms from joint or blood in SA.](image)

![Figure 12. Causative organisms in SA.](image)

There was no difference between the treatment groups in any of the follow-up indexes. In the short-term treatment group, the median of the entire
antibiotic course was 10 days, whereas in the long-term treatment course the median was 30 days (II, IV). Percutaneous aspiration was performed in 110 cases. Arthrotomy was carried out in 15 cases, occasionally with drilling of adjacent bone to exclude OM (II, IV, V).

One case in the long treatment group relapsed. One child with previous Erb-palsy showed extension deficit of the affected elbow. Two children had asymptomatic radiographic abnormalities [Results 7. Problem cases].

3. Clindamycin and first generation cephalosporin in the treatment of OM, OM+SA or SA

Of the 265 enrolled children, 96 were excluded from this analysis, because of a full course of ampi-/amoxicillin, or another agent had been used (data to be published). A short initial course of ampi-/amoxicillin was given to 6 clindamycin and 8 cephalosporin recipients; they were analyzed. The final series consisted of 169 patients treated primarily with clindamycin 1st generation cephalosporins (data to be published).

S. aureus, invariably susceptible to methicillin, was overwhelmingly the most common agent in both groups (I, II, III, IV, V). Both groups were treated intravenously for a median of three days (data to be published). The total median lengths of the antimicrobial course were 23 and 24 days for the clindamycin and the cephalosporin groups, respectively. Despite high doses, both antimicrobials were tolerated without major problems (III, IV, V). Loose stools were reported in 1% of the clindamycin and 7% of the cephalosporin recipients. Two clindamycin recipients developed rash (data to be published).

In general, the patients responded well to treatment, no matter which antimicrobial was used (IV, V). The peak CRP appeared one day sooner in the clindamycin group, but the difference was not significant (p=0.13). Otherwise, CRP and ESR normalized to the level of 20 mg/L and 20 mm/h (I) on days 9 and 29 in both groups, respectively (to be published). Discontinuation of the antimicrobials did not lead to a re-increase of any of these parameters (IV, V, data
to be published). At two weeks after discharge 36% of the children had symptoms, with no difference between groups.

The children were followed up for one year (II, III, IV, V). As characteristic of osteoarticular infections, the symptoms and signs subsided gradually. Complications are described in Results 7. As mentioned above, one SA patient initially treated with cephradine experienced two late re-infections (IV,). The antibiotics used in cases that developed complications are described in Results 7.

4. Need for surgery in OM or SA

4.1. Need for surgery in OM

Among the 131 OM patients, corticotomy (drilling or bone biopsy) was performed in 62 cases, combined with arthrocentesis in 14 cases. Percutaneous bone aspiration was performed in 26 cases. Seeking for arthritis, 8 children underwent joint aspiration and a subperiosteal abscess was drained in 4 cases. The length of medication, or the choice of antimicrobial treatment did not affect the need for surgical intervention, no matter which treatment group was in question (III, V). Thirty-one OM patients (24%) did not undergo procedures. Proportions of surgical interventions among OM patients are described in Figure 13.

![Figure 13. Surgical procedures among OM patients](image)
4.2. Need for surgery in SA

Because the hip joint is perhaps deemed to be the most perilous entity of all SAs (Vidigal et al. 1997), the 62 children with septic coxitis were analyzed separately (II). The median age was 7.2 years, and medical attention was sought within 7 days in 97% of the cases. In 21/62 (34%) cases bacteria grew from the synovial fluid only, from blood only in 17/62 (27%) cases and from both joint and blood in 24/62 (39%) cases. The most common causative agent was \textit{S. aureus} in 71%. Multiple joint involvement was seen with 2 children, both having the shoulder joint affected. An adjacent bone was involved in 10 cases (16%) (II).

The mean initial CRP was 91 mg/L, ESR rate 57 mm/h and leukocyte count 13,400 /mm³. The duration of total antimicrobial treatment depended on the randomization to 10 or 30 days (IV, V). The mean CRP peak level was slightly higher among operated (162 mg/L) vs. non-operated patients (134 mg/L) (II). In both groups CRP peaked on the second day of treatment (I, II).

One patient escaped all procedures under anesthesia, whereas 61/62 (98%) children underwent one or more joint aspirations as shown in Figure 14. The majority of the patients underwent 1 aspiration only (II). Arthrotomy was carried out in 12 cases.

95% of the coxitis patients who showed-up in a control visit of at least 12 months post-hospitalization were either asymptomatic or were found to be asymptomatic in an additional follow-up control arranged later on (II, III, IV). Two patients had radiographic abnormalities [Results 7.].

In reviewing the series of SA (all localizations, N=130) we found that 85% of the patients were treated with aspiration alone. We also performed a subanalysis of shoulder arthritis – another entity previously thought to be especially perilous (data to be published). The series was small, but anyway 8/9 cases had been treated with a mere diagnostic aspiration after which antimicrobial was promptly administered.
Figure 14. A child with a hip arthritis undergoes a diagnostic aspiration from the inguinal angle under fluoroscopic control. Courtesy of Dr. Pentti Kallio.

5. Usefulness of serum CRP in the diagnostics and monitoring of the course of OM, OM+SA or SA

The entire series of our 265 patients are summarized in Table 8+. ESR on admission was elevated in 94% of the cases (I). Although the peak was reached approximately as soon as with CRP, on day 2 (I, II, IV), ESR normalized significantly slower (p<0.05) (I). The mean ESR values (mm/h ± SEM) on days 1, 3, 5, 7, 10, 14, 19 and 29 were 51 ± 2, 67 ± 2, 66 ± 2, 62 ± 2, 52 ± 2, 45 ± 3, 30 ± 2 and 20 ± 1 as seen in Figure 15.

The initial CRP value was elevated in 95% of cases (I), mean being 87 ± 4 mg/L. CRP peaked on day 2, but normalized rapidly in 10 days (I); the mean values (mg/L ± SEM) on days 2, 3, 5, 7, 9, 10, 12, 14, 17, 19, 23, 26, and 29 were 107 ± 5, 100 ± 5, 58 ± 3, 35 ± 3, 23 ± 3, 21 ± 2, 20 ± 3, 15 ± 1, 16 ± 1 ,
12 ± 1, 13 ± 2, 15 ± 4 and 12 ± 1, respectively. CRP was higher in OM+SA than in SA, whereas the lowest values were found in OM (I). Patients undergoing extensive surgery had on average higher CRP values than others (II).

![Figure 15](image.png)

**Figure 15.** Mean CRP (mg/L) on days (D) from admission.

The mean WBC on admission was 12,600 (± 400) per mm³, and on days 5, 10, 19 and 29 it was 7,900 ± 200, 8,100 ± 200, 6,900 ± 200, 6,900 ± 200, respectively. WBC on admission exceeded >15,000 per mm³ in 25% (65/265) of cases. The only difference between the disease manifestations was that the mean WBC was lower in OM than SA or OM+SA.

The duration of symptoms before hospitalization was reflected in the CRP and the ESR but not the WBC values. Had the history been 3 days or less, ESR, CRP and WBC on admission for the whole series was 46 ± 2 mm/h, 85 ± 5 mg/L, and 13,700 ± 600 per mm³, respectively. If the history was more than three days, initial ESR, CRP and WBC 58 ± 3 mm/h, was 90 ± 6 mg/L, and 11,000 ±
500 per mm$^3$. In this group ESR peaked on day four ($\pm 0.5$), CRP on day two ($\pm 0.3$).

6. Treatment of OM + SA in respect to the treatment of OM

Of the 131 patients with OM, we excluded cases where there was no logical potential to clinically, bacteriologically or radiologically separate OM from OM+SA. This left us 117 cases. In those, an adjacent joint was found affected in 25 (21%) cases. The antimicrobials were administered according to the protocol for 20 or 30 days (III, IV), and a quasi-randomization was done between clindamycin and a 1$^{st}$ generation cephalosporin (V).

Overall, the mean duration of antimicrobials was 26 days ($\pm$SEM=1.3), the median being 21 (IQR 20-30) days (I). Both the intravenous and the total course of antimicrobials lasted about a week longer in OM+SA than OM group, the mean total duration in OM+SA being 32 days ($p<0.05$) and 25 days in OM (III). Compared with plain OM, OM+SA induced greater initial CRP, ESR and WBC response (I), and normalization took longer than in plain OM (II).

Two patients in this series - one with OM and one with OM+SA - showed major sequelae when controlled at 1-year or later (V) [see below 7.2, 7.3].

7. Problem cases

7.1. SA, boy, 10-years, late reinfection

Staphylococcal tibiotalar arthritis of a 10-year-old boy was treated with cephradine for 28 days. Seventeen months later the same joint was affected, and $S. aureus$ was isolated. Cephradine was reinstated, but due to suboptimal response, the course was completed with clindamycin orally for 30 days. Again, the recovery seemed uneventful until eight months later the same ankle was once more affected, this time by coagulase-negative staphylococci. Clindamycin was administered for 30 days. Since 1990 the child has remained well. No surgery besides aspiration was ever carried out (IV).
7.2. OM+SA, boy, 12-years, symptomatic arthrosis of the tibiotalar joint

In the long treatment group a 12-year-old boy with ankle OM+SA was treated with iv clindamycin for 3 days and oral penicillin for 77 days. This remarkable prolongation of medication occurred because of slow clinical recovery. Only diagnostic arthrocentesis was carried out.

At the 1-year-control the patient told he felt pain during exercise (V). Radiography identified joint destruction in the tibiotalar joint.

7.3. OM, boy, 1-years, 8 degree varus deformity

1.6-year-old boy with S.aureus tibial osteomyelitis was assigned to the short-term treatment group of 20 days. Antimicrobial administration was prolonged to 108 days due to slow recovery. The treatment was started with cephalosporin, but was changed to clindamycin after 10 days. Surgical abscess drainage was carried out on day 26 of treatment.

At the final control the patient presented with 8 degree varus deformity of the affected limb.

7.4. SA, boy, 11-years, extension deficit of the elbow joint

An 11-year-old boy with perinatal Erb’s palsy and elbow arthritis. He was left with a mild extension deficit of the affected elbow joint (considered to be related with previous palsy) (IV). The boy had received clindamycin for 30 days.

7.5. SA, boy, 2-years, radiographic abnormality

A mild coxa magna was found in a 2-year-old boy who had been treated with aspiration and lavage for hip arthritis. Antibiotic therapy was started with cephradine but changed to ampi-/amoxicillin after 2 days. Total course was 11 days. The patient was asymptomatic.
7.6. SA, boy, 5-years, radiographic abnormality

A slightly narrow hip joint space in a 5-year-old boy who had undergone repeated aspiration for hip arthritis. The patient was asymptomatic. He had been treated with clindamycin for 30 days.

7.7. Minor sequelae

A 14-year-old boy with a previous hip arthritis showed one centimeter limb shortening at the one-year control. The defect normalized in the following 12 months (II). Fibular osteomyelitis with adjacent tibiotalar arthritis of an 11-year-old boy recovered uneventfully. A possibility of a developing postural flat foot was suspected in the 1-year-control. An additional control was arranged at 2 years, but no postural flat foot was detected and the function of the ankle joint was normal.

7.8. Adherence to the protocol

Deviations from the preassigned protocol occurred (II, III, IV, V). Most common was a prolongation of the total duration of the antimicrobial course. The intraquartile range of treatment in the short treatment groups was 10-15 days for SA (IV), but most often this prolongation occurred with OM+SA patients (III), who received antimicrobials for approximately a week longer than OM patients on average (mean 32 days in OM+SA vs 25 days in OM). CRP normalization was also the slowest in OM+SA (I).
DISCUSSION

1. Shortened duration of antimicrobial treatment for OM

The traditional view is that acute pediatric OM requires a long treatment course of antimicrobials (Mollam and Biggott 1977, Syrogiannopoulos and Nelson 1988, Syrogiannopoulos and Nelson 1988, Shaw et al. 1990, Smith an Piercy 1995, Dahl et al. 1998, Christiansen et al. 1999, Bonhoeffer et al. 2001, Lew and Waldvogel 2004, Malcius 2005, Krilov and McCracken 2006). Our study (V) showed that OM is often curable without a notable risk of recrudescence or sequelae with antimicrobials for only 20 days. The intravenous phase can last only a few days (if needed at all) and the course can be completed orally (IV, V). No serum assays are needed, but large doses of well-absorbing agent such as clindamycin or 1st generation cephalosporin and qid dosing are probably mandatory.

With this approach we did not have any recrudescences among our patients, even though short courses were used (V). Sequelae were found in 2 cases, one in both treatment groups. This does not in any way suggest that the short course would have been inferior.

For the first time it was shown that antimicrobials fulfilling the above mentioned criteria for a total of 20 days in OM is not inferior to 30 days, provided the clinical response is good and CRP normalizes soon.

Our data on shorter and cheaper treatment courses should be good preliminary news especially in the resource-poor settings, where most cases of osteomyelitis occur.

2. Shortened duration of antimicrobial treatment for SA

SA is also a disease in which tradition mandates a lengthy course of antimicrobials (Ross et al. 2006, Vinod et al. 2002). Our study challenges this view too (II, III, IV).

Only a 10-day course sufficed in most cases of pediatric SA (IV). The rate of a recrudescence in SA is not known. Interestingly, among 168 cases in
the USA (Syrogiannopoulos and Nelson 1988) there were no recrudessences. In our series we had only one patient experiencing two late re-infection among 130 cases (IV). These interesting episodes were not true recrudessences but rather late re-infections. Thus it seems SA has a lower tendency to reoccur than OM. Two patients had asymptomatic radiographic abnormalities, but the overall clinical relevance of these findings remained unclear as no symptoms developed during the follow-up period or came to attention at a later stage. Caput magna may develop into acetabulum dysplasia or joint degeneration may develop even decades later, and thus cannot be totally excluded.

Again it was shown that the antimicrobial course can often – though indisputably not always – be considerably shortened from that which is routine in most institutions dealing with childhood SA.

3. Clindamycin and 1st generation cephalosporin in the treatment of OM, OM+SA or SA

Both clindamycin and 1st generation cephalosporins proved in our hands effective and safe agents. They have a good activity against the most common bacteria causing OM or SA (S. aureus and streptococci). They are also well absorbed and the tissue penetration is so good that oral administration is possible (IV, V). No serum assaying is needed, but good adherence to treatment is necessary. Oral administration is much easier to the patient and personnel, and lowers the costs. This is especially important in low income settings as oral agents are considerably cheaper than parenteral antimicrobials.

No major difference was observed between clindamycin and the cephalosporins we used. Most children responded well to either antimicrobial, and this was soon reflected in the declining CRP and ESR values. Interestingly, CRP began to normalize one day sooner in the clindamycin group, although the difference was not significant. The difference may perhaps suggest a slightly greater activity of clindamycin. Thus clindamycin successfully defends its position as a relevant alternative to the newer, costly antimicrobials. Diarrhea was not especially common, although we used large doses (IV, V). Instead, two
patients developed rash, but it remained unclear whether the association was causal. If it was, a low two-percent incidence seems acceptable in light of the aforementioned advantages of clindamycin.

One patient developed two late infections as described in Results 7.1. This may not have been an antimicrobial agent failure. First of all, the causative agents differed and secondly, the intervals between episodes were very long, 17 and eight months (IV). One can also question whether a prolonged medication would have prevented this late re-infection from occurring (Uckay et al. 2006).

Two patients treated with clindamycin monotherapy developed radiographic abnormalities as mentioned earlier, but the clinical significance was not confirmed during the study period. One patient with Erb palsy was treated with clindamycin and developed an extension deficit of the elbow. The extension deficit remained but was suspected to be related to the previous palsy.

Clindamycin and first-generation cephalosporins are effective and safe agents for the treatment of osteoarticular infections of childhood if local antimicrobial resistance permits their use. We proved that most childhood OM, SA and OM+SA cases can still be safely treated with a first generation cephalosporin or clindamycin.

4. Need for surgery in OM or SA

4.1. Need for surgery in OM

Minimal surgery in OM (percutaneous aspiration or drilling) aiming primarily to obtain a representative sample for bacteriology, sufficed in most cases of OM. No less than 24% of our patients escaped all procedures – and recovered uneventfully. Primary routine surgery besides a diagnostic sample did not seem to offer additional benefit to the patient.

An old study from 1944 (Kenney 1944) showed that when acute osteomyelitis was operated early, mortality increased but late sequelae decreased. In our material most early presenting cases do not require extensive surgical
procedures. This said, our protocol did not give strict criteria to suggest when to operate, because it left the ultimate decision to the clinician in charge. Even keeping this shortcoming in mind, we opine that most early presenting cases do not require routine extensive surgery. Modern imaging (US, MRI) help today’s colleagues to detect better abscesses or other processes that may warrant drainage. In our series a subperiosteal abscess was drained in 4 cases. We believe that extensive surgery should be reserved to cases showing no or little improvement during the first days of treatment, or cases of chronic infection.

4.2. Need for surgery in SA

Our analysis on pediatric septic hip showed that among our 62 cases arthrotomy could be avoided with most patients (II, IV). The series comprised of consecutive patients who were carefully followed-up to reveal any possible sequelae. We think the finding is important and should raise some rethinking.

Actually, as similar results have been published previously by other authors (Lavy et al. 2003, Manadan and Block 2004) one may wonder why aggressive routine arthrotomy is still favored by most orthopedic surgeons. Perhaps a historical aspect may offer one explanation. Before the antimicrobial era SA was a killer disease and, if the child survived, caused major disability for life (Smith 2007). Thus, understandably, decompressive surgery for especially the hip and the shoulder joint were recommended by experienced clinicians (Welkon et al 1986, Parsch and Savvidis 1997, Gordon et al. 2005) because of the fear of avascular necrosis of the femoral head or pressure induced dislocation of the femoral head leading to acetabular dysplasia. Accepting the logic of the fear of pressure–induced avascular necrosis, it might be a surprise that evidence proving this sequence to be true is lacking. Extremely high, position dependent intra-articular hydrostatic pressures have been measured in experimental animals (Levick 1979) and children (Kallio and Ryöppy 1985), but in a prospective follow-up on children with hip joint effusion, hyperpressure did not result in avascular necrosis in any patient (Kallio et al. 1985).
Pressure conditions in entirely encapsulated joints are much dependent on the positioning of the extremity. Position-induced hyperpressure can be produced experimentally, but it decreases rapidly with time (Kallio and Ryöppy 1985). Thus, combining all information deriving from animal experiments and from prospective clinical studies on children to our experience of 62 consecutive cases, one has good grounds to cast doubts to this old hypothesis of pressure-induced avascular necrosis.

Thus, the value of decompressive arthrotomy can rightly be disputed (Lavy et al. 2003, Manadan and Block 2004, Griffet and Hayek 1996). In fact, both CRP and ESR normalize considerably slower if surgery/arthrotomy has been performed (Peltola et al. 1984, Kallio et al. 1997, II). This finding agrees with the observation on trauma surgery in which inflammatory parameters have been monitored sequentially (Kallio et al. 1990).

Routine arthrotomy in the septic hip and also in shoulder (results to be published) arthritis should generally be avoided. Instead, percutaneous aspiration for diagnostic purposes should be done. Sometimes, in non-responding cases, arthrotomy should be carried out.

As we have shown that routine arthrotomy offers no benefit even these perilous hip and shoulder joints, we can safely assume that routine arthrotomy can be avoided in the majority of cases in other localizations as well. This hypothesis was confirmed by our large series of cases (IV, V) – including among others ankle, knee and elbow arthritides– mostly treated successfully with aspiration and antimicrobials.

5. Usefulness of serum CRP in the diagnostics and monitoring of the course of OM, OM+SA or SA

ESR and CRP and WBC behaved similarly in OM, SA, and OM+SA: a fast ascent with highly increased values usually found on admission, a peak on the 2nd or 3rd day of treatment, and then a fast descend. The speedy normalization differed significantly in favor of CRP (I).
ESR should be measured on arrival, because in rare cases, the first CRP value was unincreased being <20 mg/L (I). We assume that the inflammatory process is sometimes too weak to trigger hepatocytes to produce CRP in large quantities, and in this respect, ESR is useful (I). Measuring WBC has little value (I).

Sequential CRP determinations were of great value in the monitoring of the course of disease. Between OM, SA and OM+SA, there were however, differences as OM induced a low, SA greater, and OM+SA the greatest CRP response. Although this was the case, we could not always distinguish OM+SA from SA or OM with CRP alone (Unkila-Kallio et al. 1994).

To maximize the informative value of CRP, sequential determinations are needed, and the test results should arrive the same day (we receive them in 2-3 hours) (I). One should be acquainted with the dynamics of this valuable yardstick: even when an osteoarticular infection heals uneventfully, CRP usually increases for 1-2 days after the institution of an antimicrobial, but then descends soon reaching 20 mg/L in 7-10 days. If CRP continues to rise, or remains high on the 4th day, a complication is likely (Roine et al. 1995).

Today CRP can be measured fast and reliably from a whole-blood sample which has been taken from a finger or heel prick. The costs are also tolerable.

6. Treatment of OM + SA vs treatment of OM

Although children with OM+SA were treated along the lines of OM with antimicrobial for 20 or 30 days there were no recrudescences among our 25 OM+SA patients. Sequelae developed in two cases. Our treatment was significantly shorter than still recommended by many (Karwowska et al. 1998, Dieckmann et al. 2008). In fact, antimicrobials for no more than 20 days generally did as well as 30 days (III, V). This was often the case OM+SA. The intravenous phase was short, 4 days in OM and 6 days in OM + SA, on average. As might be expected, OM+SA patients were treated somewhat longer – on average about a week – than those with OM. Since the discontinuation of antimicrobials was
bound to lowering of CRP this might reflect the slower decline of inflammatory parameters we have already reported (I). It may even be that cases might have recovered even with a shorted medication, but we have no data to evaluate this assumption.

No difference in the clinical effectiveness of clindamycin vs. a 1st generation cephalosporin was observed. However, we intentionally used exceptionally large doses, both intravenously and orally, as recommended long ago (Nelson et al. 1982), and a qid regimen was used. We believe that both of these aspects are important.

7. Limitations of the study

7.1. General

Since our study did not include neonates or immunodeficient patients (I, II, III, IV, V) we have no comment on how treatment should be modified in these cases. As no prospective trials on these populations have been published, the clinicians have to tailor treatments according to the present recommendations.

All our S. aureus strains were susceptible to methicillin (III, IV, V). Therefore we have little to say how to cope with resistant staphylocoCCI, except that those strains have still mostly remained susceptible to clindamycin (Rehms and Tice 2010). The emergence of ca-MRSA no doubt poses a true challenge to the treatment.

Not a single case caused by Salmonella spp or K. kingae were found in this series whose enrollment lasted more than two decades. Salmonella is a rather common pathogen in the developing world (Lavy et al. 1996), and it may require longer treatments than we used. Regarding K. kingae, we made sure with the bacteriologists that there were no methodological problems in the detection of this pathogen, and this was not the case. Evidently, K. kingae is rare in Finland (as it is in many other countries as well), at least so far. Interestingly, since 1995, K. kingae has been isolated with an increasing frequency in pediatric OM in Iceland
(Masson et al. 2007). It will be interesting to see whether the same will also happen here, in the eastern part of Scandinavia.

Our enrollment rate was less than the presumed incidence, as we enrolled 2.4 patients/100,000/year from the pediatric population. OM is rare in Finland; the annual incidence at age 0-14 years is only 4.5 per 100,000 for OM and essentially the same for SA (Peltola and Vahvanen 1983). The incidence may have reduced somewhat because of the decline in Hib arthritis (Peltola et al. 1998). Still, we cannot call our study population based. Many reasons probably contributed to the low enrollment rate. As neonatals, immunodeficient patients and patients with underlying illnesses were excluded this also reduced the enrollment rate. Cases where the causative organism was not identified were also excluded. Hib vaccination also reduced the incidence of Hib arthritis during the last years of the study (Peltola 1998). Despite the low rate we are happy to note that the enrollment was fairly even in most of the participating hospitals.

Our study was collected in a well developed high income country and thus cannot be directly applied in a low income setting, where health facilities are not always available. Our patients presented early – usually in 2-4 days from the onset of symptoms – so we cannot comment whether surgery or longer treatment would have been needed had the history been much longer.

7.2. Randomized study on treatment length and the choice of antimicrobial

Collecting 131 culture-positive cases took long, because our strict enrollment criteria our enrollment rate was fairly low. We felt it necessary to limit our study to cases where the diagnosis was well confirmed and this slowed the enrollment considerably. However, yearly researchers’ meetings kept the rules the same. We are happy to note that the enrollment rate was fairly similar in most of the attending hospitals.

A special concern was the withdrawal of the primarily chosen cephalosporin (cephradine) from the market. Fortunately pharmacologically very similarly performing cephalotin (iv) and cephalexin (po) were available.
Regarding the protocol, plain X-rays were taken routinely during the controls but MRI was done only on demand. This practice is consistent with a recent study (Courtney et al. 2010). We also had dropouts from our carefully planned follow-up protocol (II, III, IV, V). This said, one should realize that patient care in Finland is virtually free of cost, and children recovering from such a grave disease as OM, OM+SA or SA would almost certainly have sought further treatment, should problems have arisen. Also, there are only a limited number of centers in Finland which treat sequelae from pediatric osteoarticular infections. We find it unlikely that a child with severe sequelae would have been lost from our attention during the study years and thus are confident with our results.

We do realize that unfortunately some sequelae, such as coxa magna, narrow joint space or varus deformity, may remain asymptomatic and only show symptoms such as arthrosis only after decades. Thus practically no study on pediatric OM or SA can claim a 100% certainty that no undetected sequelae occurred. We also had to exclude patients from further analysis, because antimicrobials were not invariably used as recommended. Not all children received the recommended agents, and neither was the treatment always exactly 20 or 30 days in OM and OM+SA or 10 or 30 days in SA. Only 169 of the 265 patients were included in the analysis. These deviations are regrettable, but we believe that the message of the study was not blurred even by this shortcoming.

7.3. Analyses on surgery

The study protocol did not randomize the children in the arthrotomy and non-arthrotomy groups. Even so, for example our 62 patients with hip arthritis were a fairly homogenous group (II). Because of the rarity of septic hip or even septic arthritis in general a randomized trial on surgery of OM or SA may well prove impossible to arrange. It was not feasible in our circumstances. It may prove impossible to follow strict uniform criteria to randomize children to different treatment protocols. It probably would have proved impossible to force individual surgeons in different settings to adhere to such protocols, because they were responsible for the children and, of course, wanted to treat their patients according
to their best knowledge. Even realizing these facts, we have already proven that even a loose protocol of suggesting to avoid surgery may still reduce it by about 80% (II). We find this to be a convincing achievement in its own right.

Since medical advice was sought most often in 2-4 days, we cannot comment whether surgery would have been of greater value had the history been significantly longer. We have found that children presenting early – say under 5 days from the onset of disease – tend to respond faster to treatment (data to be published). Even so, even late presenting cases in our series tended to recover fairly well.

7.4. Problem cases among patients

There were patients referenced in Results 7. who did not recover optimally. How did these cases affect the interpretation of the results?

We find it important to note that most of these patients had been treated with a long course of antimicrobials. In fact, they often underwent significantly longer treatments than average. Patients presented at Results 7.1., 7.2, 7.3, underwent treatments of 28, 80 and 108 days, respectively. We may claim that our protocol was able to identify special cases from the sluggish CRP descent or slow clinical recovery early on, and a prolonged antimicrobial regimen was assigned. Even a prolonged antibiotic regimen did not save all the patients from unfortunate sequelae. These problem cases are just one more challenge for the clinicians to face.

8. From complex treatment to simplified treatment

The incidence of OM, SA and OM + SA is decreasing in many - if not all (Masson et al. 2007) - industrialized countries, patients present early and are treated with effective antimicrobials. Our results bring solid data to support the view that most of these cases can be treated with a simplified treatment course.

The simplified treatment may proceed for example in the following manner: On admission diagnostic joint/bone aspiration or drilling is done and
blood culture is taken (IV, V). No other surgical procedures are done routinely (II). Intravenous antimicrobial is promptly instituted and is switched to oral administration after a few days. The patient is followed up with sequential clinical investigations and CRP monitoring (I, II, IV, V). Both ESR and CRP are measured on arrival (I) but only CRP needs to be measured sequentially (I). Fever and CRP should usually be descending by the second or third day of treatment (II), and intravenous administration can be changed to oral, with large doses *qid*. The antimicrobial is discontinued after 20 days in OM or OM+SA (V) or after 10 days in SA (IV).

Only if the clinical course is complicated by abnormal healing or underlying illnesses prevent normal recovery, the clinician will either resort to invasive surgical procedures, change the antimicrobial, or prolong the administration. Fortunately, according to our data this is seldom required in high income countries (II, III, IV, V).

Even though we can now move to simple, safe, efficient, evidence based (I, II, III, IV, V) treatment protocol of childhood septic osteoarticular infections in high income setting, the real work is still to be done. Osteoarticular infections are rampant in low income countries where the true need for inexpensive treatments is most dire. There is an urgent need to test our approach in a low income setting where a true need for cheap and effective solutions exists.
CONCLUSIONS

Most cases of childhood septic bone and joint infections can be treated in a short, simple and inexpensive manner. For OM and OM+SA, a course of 20 days usually suffices, whereas for SA, a 10-day-course heals most cases. After a short (2-5 days) initial intravenous phase the administration can be changed to oral, but large doses and a qid regimen are likely pivotal. Clindamycin and 1st generation cephalosporins are both time proven and equally effective antimicrobials suitable to be used as first-line treatment, local resistance permitting.

Diagnostic drilling or aspiration discloses the etiology; otherwise, more extensive surgery may be reserved exclusively for complicated cases. Routine arthrotomy should generally be avoided even in hip and shoulder arthritis. Even in most cases of OM + SA extensive surgery is not needed. The prognosis of OM+SA is comparable to that of plain OM.

CRP is an inexpensive aid in diagnostics of OM and SA, and is an excellent tool in monitoring treatment and recognizing cases demanding special attention.

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