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Exclusive oral antibiotic therapy on acute uncomplicated osteomyelitis in children

A multicenter, non-inferiority, randomized, open-labelled, controlled clinical trial

End of term project

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1. ABSTRACT

BACKGROUND: Acute hematogenous osteomyelitis is the most frequently diagnosed type of osteomyelitis (OM) in pediatric patients, being essential optimizing antibiotics to avoid complications as chronic osteomyelitis, sepsis, and impairments in bone development. Long intravenous medication (classical treatment), for 4-6 weeks, transitioning to oral medication when recovery was almost complete was the reference approach to treat the disease until it was demonstrated that an early switch to oral administration (current treatment) has similar cure rates and simplifies the entire treatment process (required hospital stay, bacterial resistance, risk of adverse events and costs). There is no evidence about that OM may be treated with exclusive oral therapy during the whole course of the disease, although it has been demonstrated that children with milder infections without risk factors may have a favorable outcome with only oral antibiotics.

OBJECTIVE: The purpose of the present study is to demonstrate the same or higher proportion of resolution of the disease in children with uncomplicated OM who receive exclusively oral antibiotic therapy compared with patients that receive the standard intravenous plus oral therapy.

DESIGN AND SETTING: A multicenter, non-inferiority, randomized, open-labelled, controlled clinical trial will be performed among four different hospitals of Catalonia.

INTERVENTION AND METHOD: A stratified by age randomized sample will be performed in order to generate two therapy groups (A and B) with participants between >1 to ≤15 years of age. Patients from group A (n=49) will receive intravenous therapy (cefazolin for one week) followed by only oral (cefadroxil during two weeks), while group B patients (n=49) will receive exclusive oral therapy (cefadroxil for two weeks) as a treatment of their acute OM. The duration of the treatment will be three weeks for both groups, taking into account that the group A will require hospitalization during one week, while the other group will take the medication at home. The **main outcome** will be disease resolution, defined as absence of fever at 72h and decrease of the pre-admission maximum CRP value above 30% at 72h in case that the patient presents fever at the moment of the diagnosis, or as a reduction on the severity of the pain >50% at 72h in patients that do not present fever at the moment of diagnosis. Exhaustive controls will be done during the first 72 hours of the treatment, assessing body temperature, CRP, pain severity and possible side-effects due to the treatment. Follow-up visits up at 72h after the onset of the treatment and 1, 2 and 6 months after the end of the treatment will be scheduled for both groups, consisting mainly in clinical examination of body temperature, pain and function of the affected bone.

KEY WORDS: uncomplicated acute osteomyelitis, exclusive oral therapy, children, disease resolution.

2. ABBREVIATIONS

CA-MRSA: community adquired MRSA.

CRP: C-reactive protein.

CT: computed tomography.

DVT: deep vein thrombosis.

ESR: erythrocyte sedimentation rate.

Hib: Haemophylus influenzae type b.

K. kingae: Kingella kingae.

MRI: magnetic resonance imaging.

MRSA: meticillin-resistant-Staphylococcus aureus.

MSSA: methicillin-susceptible S. aureus.

OM: osteomyelitis.

PET/CT: positron emission tomography/computed tomography.

PICC's: inserted central catheters.

PVL: Panton-Valentine leukocidin.

S. aureus: Staphylococcus aureus.

S. pneumoniae: Streptococcus pneumoniae.

US: ultrasound.

3. INTRODUCTION

3.1. OSTEOMYELITIS

Osteomyelitis (OM) is an infection of the bone that may reach the bone directly through traumatic wounds, by spreading from adjacent tissue affected by cellulitis or septic arthritis, or through hematogenous seeding. It is a serious condition, life threatening and related to a high degree of morbidity.

It is important to consider that an adequate and prompt treatment has high rates of clinical cure. The goal of the treatment is to prevent complications such as sepsis, persistent joint damage, growth disturbance or chronic OM. (1,2)

Chronologically, osteomyelitis is classified as acute if the illness duration is bellow 2 weeks, subacute for a duration of 2 weeks to 3 months, and chronic for a longer duration.(1,3)

Acute hematogenous osteomyelitis is the most common type in pediatrics, and is more incident in younger children than in adolescents, due to the rich vascular supply in their growing metaphysis. It should be considered in any patient who presents with fever of unknown origin.(2)

In order to stratify the severity of the process, a **complicated** or **high-risk OM** is considered if:

- It is produced by Salmonella, methicillin-resistant-Staphylococcus aureus (MRSA) or Panton-Valentine leukocidin (PVL)-positive-strains.
- It is developed in young infants or newborns.
- It courses with slow clinical improvement and suppurative complications.

These mentioned cases are more susceptible to receive longer duration of both IV and oral therapy.

In this way, some factors are associated with **more risk of sequelae** as (4,5):

- Late diagnosis (>4 days).
- Inadequate treatment.
- Sickle cell disease.
- Hip involvement.

3.1.1. Epidemiology

In high-income countries, acute osteomyelitis occurs in about 8 per 100.000 children per year, although it is more common in low-income countries. The incidence of the disease is increasing, being interesting to know that its incidence has triplicated over the last 20 years. Moreover, acute osteomyelitis is two times more frequent in boys than girls and half of cases affect children under 5 years of age.(3,5)

3.1.2. Pathogenesis and etiology

The main responsible pathogen depends on the age, comorbidities, socioeconomic, immune and vaccination status. Geographical variations have to be also taken into account to talk about resistances and prevalence of the different bacterial species. Those considerations will be important to decide the appropriate treatment.(6)

Considering the causative agents, *Staphylococcus aureus (S. aureus)* is by far the most common, followed by respiratory pathogens as *Kingella kingae (K. kingae)*, *Streptococcus pyogenes* and *Streptococcus pneumoniae (S. pneumoniae)*.
Infections due to *K. kingae* are increasing, and are more common in children younger than 4 years of age, although historically, *Haemophylus influenzae* type b (Hib) and S. pneumoniae were common pathogens, however, they are now rare thanks to vaccination.
Hib is more likely to affect joints than bones and *Salmonella* species are frequent in developing countries and among patients with sickle cell disease.(1,2)

Most common pathogens by age in acute OM are shown in *table 1*.

Geographically, some important points are a higher incidence of community adquired MRSA (CA-MRSA) in countries as Romania or Greece, or important differences in K. kingae incidence within some countries, being very low in Scandinavia and quite high in Spain, France and United Kingdom.

A recent study of invasive S. aureus disease has shown a prevalence of 8% of MRSA in Europe.(4)

3.1.3. Risk Factors

Minor trauma may be present in around 30% of cases , but up to half of cases have no risk factors at all. There are some specific situations that can be associated to different pathogen(4,6–8):

- Upper respiratory infection (*K. kingae*).
- Preceding trauma.
- Wounds, erosions or varicella infection (*group A Streptococcus*).
- Penetrating wounds. In example, on the sole of the foot (*anaerobes* and *Pseudomonas*).
- Sickle cell disease (*Salmonella spp.*).
- Immunodeficiency:
    - VIH infection (*Streptococcus pneumoniae*).
    - Complement deficit (*Neisseria Meningitidis*).
    - X-linked agammaglobulinemia (*Mycoplasma Pneumoniae*).
    - Chronic granulomatous disease (*S. aureus*, *Serratia marcescens* and *Aspergillus fumigatus*, between others).
- Newborns with complex pathologies, immunodeficiency or prosthetic material (*Coagulase-Negative Staphylococcus)*
- Living conditions, occupation. For example, animal handling and laboratory work in cases of infection caused by *Brucella* and *Coxiella spp*.
- Tuberculosis contact or originate from tuberculosis endemic areas (tuberculosis infection).

Table 1. Most Common Pathogens by Age in Acute OM. Adapted from (4)(5)

Age group	**Pathogen**
Infant **(0-3 months old)**	-*S. aureus* -*Streptococcus agalactiae* -Gram negative enteric bacteria
Young child **(3 months to 4 years old)**	-*S. aureus* -*S. pyogenes* -*K. kingae* -*S. pneumoniae* -*Hib* (exceptional in well-immunized populations)
Older child **(>5 years old)**	-*S. aureus* -*S. pyogenes* -*K. kingae.* -*Neisseria gonorrhoeae* (in sexually active adolescents)

3.1.4. Clinical features

Clinical features may vary greatly depending on the infected site, age of the child and the responsible pathogen.(8)

The "classical presentation" of acute OM is pain (81.1%), limping or inability to walk (50%), fever (61.7%) and focal tenderness, visible redness and swelling (70%), more often seen in inferior extremities.

A specific clinical fact appears in children with MRSA OM, which have high temperature, tachycardia, and a painful limp more than those with MSSA (methicillin-susceptible S. aureus) osteomyelitis.(1,3,5)

Estimated percentages of all cases of acute OM are represented in *figure 1*, in which is demonstrated that although OM may affect any bone, a predilection for long bones and lower extremities is shown.

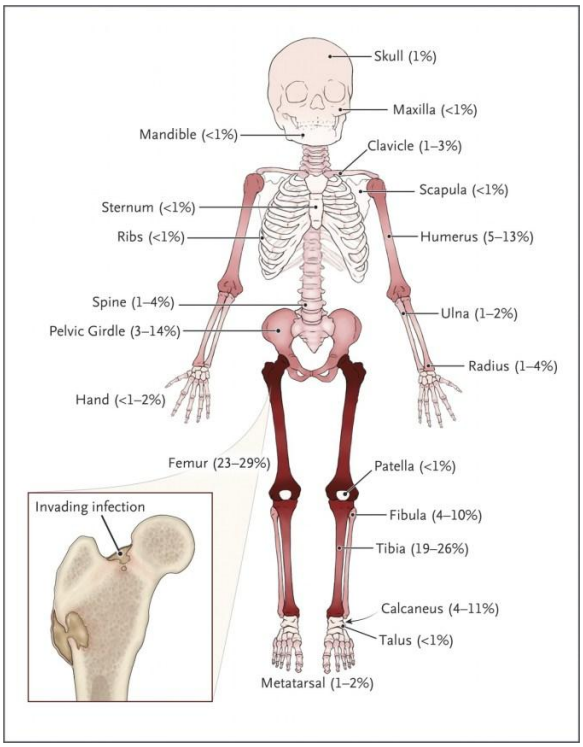


***Figure 1**. Skeletal Distribution of Acute Osteomyelitis in Children*(1)

Considering the age, young children may present tipically with little more than irritability or refusal to use a limb. Neonates, use not to have fever as a main symptom, and the infection may be systemic, particularly if prematures.(8)

All age groups are susceptible to suffer acute OM, but a small incidence peak occurs in prepubertal boys, probably due to high physical activity and microtrauma.(1)

3.1.5. Evaluation

There is no single test that may confirm osteomyelitis. A combination of clinical history, physical exam, laboratory tests, imaging studies and biopsy usually are required to make a definitive diagnosis.(6)

Laboratory studies: blood

Peripheral blood is sent for cell count, erythrocyte sedimentation rate (**ESR**), C-reactive protein (**CRP**), **procalcitonin**, **gram stain**, aerobic and anaerobic **culture**. In children with osteomyelitis, white blood cells (WBC) are elevated in 36% of cases, while the 91% have elevated ESR, and in 81% of patients CRP is elevated.(6)

It has been demonstrated that CRP and procalcitonin levels are sensitive as diagnostic tests and useful in follow-up, but measuraments of the second one are more expensive and do not improve the CRP results, which moreover are easily to determinate and available within 10 minutes.
Decreasing levels of CRP suggest well response to treatment, even if fever is still present. It is important to know that ESR increases rapidly but decreases much more slowly than the CRP level, so it will be less useful to monitor the course of the illness. Another interesting point is that osteomyelitis due to MRSA is associated to greater PCR, ESR, and WBC levels.(1)

Blood cultures are recommended to be performed routinely, even though they identify the causative agent in only 10-20% of the cases, taking into account that the yield of K. kingae can increase by using special culture methods or polymerase-chain-reaction assays.(1)

Imaging studies

Radiographs should be the first imaging study performed. Although they are frequently negative in early OM, repeat imaging shows appearance of osteolytic changes or periosteal elevation often denominated “rat bite” (mostly 10-21 days after onset of symptoms).(1,4,6) So, a normal radiograph on admission to the hospital does not rule out acute OM, but it can be useful in ruling out a bone fracture or detecting Ewing’s sarcoma or another type of malignant condition.(1)

Ultrasound (US) is not very useful in the diagnosis of osteomyelitis, but abscesses and periostal abnormalities may be visualized.
Doppler US may provide an early detection of the infected bone showing a high vascular flow to the affected area.(4,6)

Bone Scintigraphy using technetium radionuclide scan (^{99m}Tc) is sensitive although less specific. It is useful specially when long bone is affected or symptoms are not precisely localized. In this way, it can be helpful to identify multifocal osseous involvement and to document the site of OM if it is localized. Its sensitivity and specificity is lower in neonates.(1,4)

Computed Tomography (CT) is other imaging study that could be useful, but it imply high radiation exposure.(1)

Magnetic Resonance Imaging (MRI) is the most informative imaging modality for OM, because it can detect abnormalities within 48h-3 days of disease onset. Moreover, it is better to show the location and extent of the disease, revealing possible abscesses, sequestra, associated pyomyositis or contiguous venous thrombosis. It is also important to decide the most appropriate surgery plan.(4,6) MRI will not be necessary when the diagnosis is highly suspicious for OM after using other clinical and diagnostic techniques, but it will be indicated in severe clinical conditions or when doubts about the diagnosis exist or complication is suspected. MRI will be required if vertebral or pelvic OM are suspected.(4)
CA-MRSA frecuently affects the growth plate, being this affection frequently missed on standar MRI sequences, so gadolinium enhancement enables identification if these involved areas, being it recommended in suspected cases.(9)
MRI can be also used to differentiate between K. kingae osteoarticular infections and those caused by other pathogens, given that epiphyseal cartilage abscesses were found only in the K. kingae infection group, and soft tissue and bone reaction were significantly less in infection caused by Kingella.(10)

Positron emission tomography/computed tomography (PET/CT) is considered better than MRI in monitoring response to treatment and to differentiate between ongoing infection and reparative activity, but radiation exposure and access to PET/CT may limit its practical use.(6)

Laboratory studies: bone specimen

Osteomyelitis can be diagnosed by means of imaging, but it is essential, whenever possible, to obtain a sample for the antibiogram that may disclose problematic agents such as MRSA.(1)

Representative samples can be obtained mainly percutaneously or through a small incision by drilling, resorting to interventional radiology when osteomyelitis is difficult to localize by clinical examination alone. An alternative is to obtain the sample intraoperatively by a surgeon.(1,4,6)

3.1.6. Differential diagnosis

In a limping child the differential diagnosis should include traumatic, rheumatologic diseases (juvenile arthritis and reactive arthritis), septic arthritis, and neoplasia (osteoid osteoma, leukemia, eosinophilic granuloma, metastasic neuroblastoma, Ewing's sarcoma, osteosarcoma).(5)

In a child with musculoskeletal pain the probability of cancer is 1:10.000 and a pediatric Gait, Arms, Legs, Spine screening (pGALS) examination may be useful to identify red flags that raise concern about infection or malignancy.(11)

3.1.7. Complications

Early diagnosis and appropriate treatment are associated with successful prevention of chronic OM and development of sequestra and fistulae. Even so, acute complications and sequelae can be found.(4,6,7)

Local complications

The most frequent complication, especially in younger children, is spread from the primary focus to adjacent tissues. The following lesions may appear in this context:

- A subperiosteal **abscess**.
- Spread to the joint (**osteoarthritis**).
- Entail muscular involvement (**pyomyositis**).

These complications occur especially in pelvic locations, being more common in case of MRSA. Them must be suspected in case of continued fever, persistently positive blood cultures or sustained high CRP.

Systemic complications

A septic process can appear, requiring admission to an intensive care unit. Pediatric **sepsis** is considered when Systemic Inflammatory Response Syndrome (SRIS) and suspected infection exist. SRIS is determined if at least two of the following four criteria are present(12):

1) Central body temperature > 38.5 °C or <36°C.
2) Cardiac frequency:
    - Tachycardia:
        - Elevation >2 standard deviations (SD) of the mean for the age in the absence of external stimuli, medication or painful stimulus; or
        - Unexplained persistent elevation for 0.5-4 hours.
    - Bradycardia (considered as a criteria if below 1 year of age):
        - Cardiac frequency <10 percentile for the age in absence of vagal stimulation, beta-blocker medication, congnital heart disease; or
        - Unexplained frequency decrease for >0.5h.
3) Respiratory rate >2 SD above the mean for the age or required mechanical ventilation not related to neuromuscular disease or general anesthesia.
4) Elevated or decreased leukocyte count for the age or >10% of immature neutrophils.

It is necessary to look for deep vein thrombosis (**DVT**) in severe *S. aureus* OM and especially in MRSA/PVL+ *S. aureus* infection. In case of DVT, it is recommended to manage the best treatment options with a pediatric hematologist, being low molecular weight heparin started and maintained until DVT is resolved.

An uncommon complication, related with DVT is **septic pulmonary thromboembolism**, with respiratory distress and chest pain, which shows up as nodular images and bilateral cavitations on X-rays.

Sequelae

The consequences of an inadequately treated osteomyelitis can be devastating.

- **Avascular necrosis** of the epiphyses (hip and shoulder): this is the most frequent sequelae.
- Length discrepancy of the extremity (**dismetry**): this is the second most frequent sequelae.
- **Limping**.
- **Growth arrest**.
- **Chronic pain**.
- **Rigidity**.
- **Pathologic fractures**.

3.1.8. Prognosis

The mortality rates are now extremely low compared with the pre-antibiotic era. There are some risk factors for a worse prognosis(8,13)**:**

- **MRSA**, ***S. pneumoniae*** or **PVL+** *S. aureus* as causative agents.
- Concurrent **septic arthritis**, **pyomiositis** and/or **abscess**.
- In relation with the **location**; involvement of the hip is at the highest risk of complications (40%), followed by the ankle (33%) and knee (10%).
- A **positive** culture. It is necessary to take into account that *K. kingae* is a more benign pathogen that is difficult to isolate, being highly associated to negative cultures.
- Increasing **C reactive protein** values for four or more days.
- **Younger age**. This could be due to delays in diagnosis, presentation and treatment, as well as differences in anatomy and immune system.
- **Delay in diagnosis or treatment** (more than three days).

3.1.9. Follow-up

It is recommended a follow-up by orthopedics and pediatricians with musculoskeletal experience at 2 weeks, 4-6 weeks, 3 months and 12 months after hospitalization. Longer follow-up should be consider if there is involvement of the pelvis, vertebrae (spine) and hip, or if the growth plate is affected, especially infants and younger children.

Pain-free normal activity is considered an important end-point before discharge from follow-up.

Check-up should include clinical examination and CRP. An imaging study could be indicated if the evolution is not good, being US or radiography the indicated techniques. In addition, it is essential to provide analgesia as needed.(4)

3.2. OSTEOMYELITIS MANAGEMENT

In order to avoid complications, an early diagnosis and prompt treatment are needed. There are some key factors that should be considered to manage the disease, as the regional prevalence of CA-MRSA and the age of the patient.

Initial management includes adequate drainage of pus, collection of specimens for microbiologic studies and early initiation of empiric antibiotic therapy. The choice of empiric antimicrobial therapy is based on the most likely causative pathogens according to patient age, immunization status, underlying disease, Gram stain and other clinical and epidemiologic considerations, including prevalence of MRSA.(4)

3.2.1. Antibiotic treatment(1,13)

Treatment of acute OM is almost always initiated empirically with intravenous therapy before the causative agent and its resistance pattern are known. In order to identify the causative microorganism, the empirical treatment must be started after the collection of all necessary culture samples to avoid false negative results. Definitive antibiotics will depend on culture and sensitivity results, so the initial antibiotics should be changed or continued accordingly.

In *table 2* is described the initial antibiotic treatment when acute OM is suspected in children, and the specific considerations in function of the causative microorganism.

The best initial antibiotic depends on the age of the patient. Generally, an antistaphylococcal penicillin (cloxacillin, or oxacillin) is used, due to the dominance of MSSA, being cephalosporin the chosen option for unvaccinated children due to the major risk of infection by *H. influenzae* type b, taking into consideration that it should be treated with ampicillin or amoxicillin if the strain is beta-lactamase negative, or with a second- or third generation cephalosporin if the strain is beta-lactamase-positive.

In places where prevalence of MRSA is higher than usually, clindamycin is the elected antibiotic initially, reserving vancomycin for unstable patients or areas where resistance to clindamycin exists, being linezolid used if no response to vancomycin.

To decide the best initial empirical therapy, local up-to-date resistance patterns are required.(4)

Figure 2 shows a summary of the prevalence of the different pathogens in Spain and *table 3* shows the empirical therapy preferences in Spain.

The administered antibiotic must have an acceptable side-effect profile when administered orally and a satisfactory absorption and penetration into the bone tissue. Clindamycin and first-generation cephalosporins fulfill these requirements. Their efficacy as monotherapy has been documented, and large doses usually have an acceptable side-effect profile.(1)

To ensure adequate and mantained blood concentrations of the antibiotic, some studies recommend the measurement of serum concentrations of bactericides, what would be useful to control and reduce complications and readmission rates, although other studies suggest that complications are rare even with the maximum antibiotic oral dose, so any problem should appear. So, to accomplish these therapeutic levels, antibiotics are given in triple doses compared with the recommended dosage to treat other pathologies.

There is no evidence about the use of antibiotic-impregnated cement in paediatric osteomyelitis.(13)

It is basic to mention the importance of the hospitalization in osteomyelitis, since the majority of children are hospitalized at the beginning of diagnosis because intravenous therapy is generally used. This is considerably important in regions with a high rate of MRSA or PVL+, worse clinical severity and in high risk patients such as infants and immunocompromised patients.
When intravenous antibiotic is still needed for specific situations out of the hospital, an alternative approach is the use of a peripheral-inserted central line for daily antibiotic treatment at home. This is the outpatient parenteral antimicrobial therapy.(4)

Table 2. Antibiotic treatment for Acute Osteomyelitis in children. Adapted from (1)				
Conditions	**Antibiotic of election**	**Dose** mg/kg/day	**Maximal Daily Dose**[1]	**Bone penetration**[2] %
Empirical treatment				
Prevalence of MSSA in community >90%.	Antistaphylococcal penicillin	≤200 (4 equal doses).	8-12 g	15-17
	First-generation cephalosporin	≥150 (4 equal doses).[3]	2-4 g	6-7
Prevalence of MRSA in community ≥10%	Clindamycin (if prevalence of clindamycin-resistant S. aureus <10%).	≥40 (4 equal doses).	3 g	65-78
	Vancomycin (if prevalence of clindamycin-resistant S. aureus ≥10%).	≤40 (4 equal doses).	Adjusted with a target of 15 to 20 µg/mL	5-67
	Linezolid (if no response to vancomycin).	30 (3 equal doses).	1.2 g (no >28 days)	40-51
Treatment for specific agents				
Group A β-hemolytic streptococcus (or S. pyogenes)	Ampicillin[4]	150-200 (4 equal doses).	8-12 g	3-31
Hib (β -lactamase-negative strains)				
S. pneumoniae (or pneumococcus)				

[1]The maximal daily dose is not always well defined, but the maximal adult dose should not be exceeded.
[2]Bone penetration is the ratio of the bone concentration to the serum concentration.
[3]Cephalothin and cefazolin are administered intravenously. Cephalexin and cefadroxil are administered orally. Cephradine can be administered by either route. If no parenteral first-generation agent is available, cefuroxime can be used for parenteral administration.
[4]Combination with clindamycin must be considered.

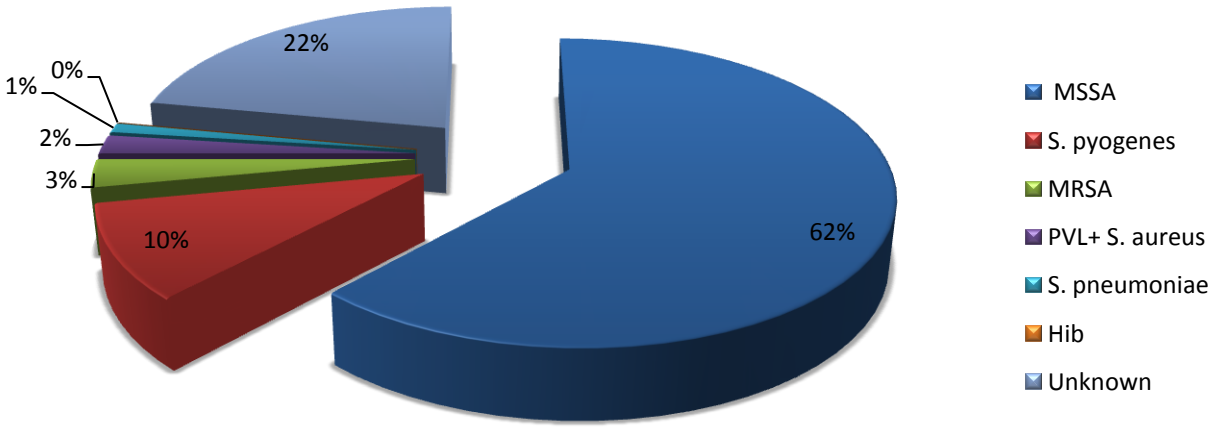


***Figure 2*: Prevalence of pathogens in OM (Spain)**. Adapted from (14)

Table 3. Empirical therapy preferences in Spain. Adapted from (15)

Age group	Antibiotic
Newborn (0-2 months of age)	Cloxacillin + cefotaxime/gentamicin
Children <5 years of age	Cefuroxime or cloxacillin + cefotaxime
Children >5 years of age	Cloxacillin or cefazolin
Sickle cell disease	Cloxacillin + cefotaxime
Preceding trauma	Cloxacillin + ceftazidime
β-lactam allergy	Clindamycin

3.2.2. Switch from intravenous to oral medication(1,13)

The classical approach to treat a child with OM was based on giving long intravenous medication, for 4-6 weeks, transitioning to oral medication when recovery was almost complete. This was understandable due to the high rate of mortality linked to the disease. With the time, it was demonstrated that an early switch to oral administration is not harmful, but there is no agreement as to when the parenteral/oral switch should be instituted nor as to the optimum total treatment duration.

Much of the evidence suggesting longer parenteral treatment comes from a study that reported a complication rate of 19% for patients treated with less than three weeks of intravenous antibiotics, compared with 1% for those treated for longer, but it has been done until three trials (16–18) that have demonstrated the same outcomes when the intravenous phase is shortener than a week. There is also a systematic review that concluded that a short-term parenteral medication is acceptable in uncomplicated cases of osteomyelitis.(13)

In Spain, the initial standard manage for the treatment of acute OM consist on intravenous therapy, switching to oral medication if improvement on inflammation signs or symptoms, disappearance of fever after 48 hours, and decrease of CRP >30%. It is important to consider that the oral therapy will be given at 2 to 3 times superior than pediatric habitual dose to ensure its bioavailability, excluding this consideration for the treatment with clindamycin.(15)

Generally, the standard duration of the treatment in Spain is considered around 3 weeks, doing an empirical short intravenous therapy at first (during 7 days), checking the evolution of the patient, and switching to oral antibiotics for the last 2 weeks if good response to intravenous therapy is seen.(19)

Taking into account this information, it is understood that the treatment of OM has been changing over the years and it is still doing it. So what our study tries to demonstrate is that considering the current management (which is widely spread), consisting in short intravenous therapy followed by oral antibiotics, a new therapy method could be established for uncomplicated cases of OM, that would consist in exclusive oral therapy during the whole course of the disease.

3.2.2.1. Current evidence supporting short intravenous therapy and an early switch to oral administration

There is one prospective randomized study about the subject, in which 131 patients received a short course (two to four days) of intravenous clindamycin or a cephalosporin followed by high-dose oral treatment for 20 to 30 days more. Outcomes were excellent in both groups, with no significant clinical, radiological or haematological differences. According to this study, 20 days duration of the antibiotic treatment is considered enough if the child is improving clinically and CRP returning to normal.(16)

Another important study to consider is one related with a review of 37 patients with acute uncomplicated osteomyelitis, based on improving clinical and haematological parameters, that found that 63% patients needed <4 days of i.v. antibiotics, 89% <6 days and 11% >6 days, followed by three weeks of oral antibiotics. The most relevant parameters on admission to suggest the need for prolonging i.v. antibiotics were fever >38.4°C and CRP >100 for over three and five days, respectively.(17)

A cohort study of 50 patients showed successful results in the treatment with a mean of 4 days i.v. and three weeks oral antibiotics.(20)

All this evidence suggests that in acute uncomplicated OM, a short course of i.v. antibiotics, guided by clinical and haematological parameters and followed by an early switch to oral treatment, is acceptable, but follow-up should be closer and longer.

3.2.2.2. Importance of switching from intravenous to oral medication.

To understand the importance, complications of intravenous therapy must be considered, being the majority related with line problems, such as local infection, phlebitis, thrombosis, bacteremia, sepsis and catheter dysfunction. Around 40% of patients receiving more than two weeks of i.v. therapy suffer complications, being young age and low socioeconomic status risk factors, in almost all cases catheter-related (from both central venous lines and peripherally inserted central catheters (PICC's)), which tend to occur on average by day 21. (4,21)
In this way, although PICC's are effective for delivering high concentrations of antibiotics for serious infections, they increase the risk of developing other infections, thrombotic events, and mechanical complications. It is because of these potential problems why many clinicians have started looking into transitioning to oral antibiotics sooner.(3,22,23)

Shortened regimens of primarily oral antibiotics simplify the entire treatment process in terms of the required hospital stay, antibiotics used and risk of adverse events. It is also associated to a reduced bacterial resistance and it does not seem to be linked with a higher risk of treatment failure. Furthermore, in the majority of cases, oral antibiotics are considerably cheaper than parenteral formulations, so this means that the cost of the treatment is reduced.(1,4)

Other important considerations are the necessity of general anaesthetic for pediatric central lines and often for some peripheral lines, which if not performed at the same time as surgery this requires an extra anaesthetic, and an increased risk of allergenic sensitation to antibiotics with i.v. courses >20 days.(21)

3.2.2.3. Excluded for short intravenous treatment

In situations that are considered of major risk or in cases for which data are lacking in order to make a short-term treatment, it is justified to carry a more conservative and individualized therapy.

A minimum of 4 to 6 weeks of medication is considered for cases due to MRSA, PVL+, patients who present with advanced disease and those coming from areas where osteomyelitis due to salmonella is common.

Although data are lacking on the use of shorter treatments in neonates, immunocompromised or malnourished patients, and patients with sickle cell disease, these patients are likely to need a longer course of medication.

In this way, when acute osteomyelitis is complicated by septic arthritis, the disease is chronic, and the CRP level normalizes slowly, a longer course also make sense.(1)

3.2.3. Other medications

Patients with osteomyelitis may require medication different than antibiotics. So, nonsteroidal antiinflamatory drugs can be used to treat symptoms such as fever or pain.

Anticoagulants may be also needed, being used in case of DVT or septic pulmonary emboli.(1)

3.2.4. Surgery

Studies show that up to 90% of patients with an early OM can be cured with conservative treatment of antibiotics, especially if antibiotics are initiated during the first days of the onset symptoms, so surgery is usually not needed and could in some cases prolong recovery. However, surgery should be considered if the patient has not responded within a few days to antibiotic therapy or a complication is suspected, what also allows collecting samples of tissue and pus, which have a higher chance of giving a bacteriological diagnosis.

A lack of data exists from randomized trials, timing and extent of surgery and the need for surgical intervention remain unanswered, but in the decision process, the following is important(1,4,13):

- Clinical response to antibiotic therapy: for example, persistence of fever >72-96h or its reappearance.
- Surgical drainage may be indicated in patients with a periosteal abscess and persistent fever and CRP elevation.
- Close proximity to a growth plate of the abscess (although even abscesses >3 mm may have good outcome with only antibiotics).
- Sequestration.
- Identification of MRSA or PVL+ *S. aureus* may increase the need for surgery.
- Chronic OM or presence of prosthetic material.

It is important to be aware that blood markers are higher and trigger more to normalise (CRP seven days and ESR 16 days) in surgically treated patients than in those treated medically, but it is not well known if it is due to the operation or because the infection takes longer to resolve.(13)

3.2.5. Physical therapy

Rehabilitation is a very important part in the management of OM, especially after surgery. In this way, it is important to avoid injury to the involved area, trying a prompt mobilisation, which is crucial for the prevention of complications such as rigidity if any articulation is involved.

Depending on the site and severity of the OM, some type of support and/or protection device, such as a soft removable cast, boot case, and instructions to avoid weight bearing for some period, may help prevent the development of a pathologic fracture.

Supportive devices such as corsets may be recommended in case of spondylodiscitis.

4. JUSTIFICATION

Acute osteomyelitis is a potentially devastating or even a fatal disease, with a high morbidity, being among the most common serious bacterial infections of childhood.(1,6,13,24)

The incidence of OM has increased 2.8-fold over the past 20 years.(25)
Acute hematogenous osteomyelitis is the most frequently diagnosed type of osteomyelitis in pediatric patients, being essential optimizing antibiotics to avoid the administration of inappropriate therapy, what can lead to complications as chronic osteomyelitis and impairments in bone growth and development.(2,8,13)

Intravenous therapy may be related with catheter-associated complications (sepsis, DVT, and mechanical complications) and, moreover, oral therapy does not seem to be linked with a higher risk of treatment failure compared with prolonged intravenous therapy in children with OM. (1,3,4,6,21–23)
Intravenous therapy is linked to the necessity of hospitalization, being this related in most cases to different degree of emotional disturbance due to the experience, as may be the separation of the child from his or her familiars during admission. Children from 6 months to 4 years of age are most vulnerable to these emotional upsets (it is important to remember that OM is especially frequent in children <5 years old).(26)

Short intravenous therapy followed by shortened regimens of primarily oral antibiotics (current standard therapy), when compared with continuing long intravenous therapy (previous therapy), appear to have similar cure rates and simplifies the entire treatment process in terms of:

- Require hospital stay
- Emergency department or clinic visits.
- Hospital readmissions.
- Antibiotics used:
    1) Risk of adverse events.
    2) Risk of bacterial resistance.

These complications, as a result, can increase cost burden for the healthcare system, decreasing then the cost-effectiveness.(1,3,4,6)

There is no evidence that OM can be treated with only oral therapy during the whole course of the disease, although children with milder infections without risk factors may have a favorable outcome on oral antibiotics.(4)
So, knowing that the treatment of OM has been changing during long years and it is still doing it, our study is designed to demonstrate that considering the current standard management (short intravenous therapy followed by oral antibiotics), a new therapy method could be established for uncomplicated cases of OM, that would consist in exclusive oral therapy during the whole course of the disease.

5. HYPOTHESIS

5.1. MAIN HYPOTHESIS

Exclusively oral therapy has at least the same clinical efficacy (disease resolution) as the standard management using short intravenous therapy followed by a course of oral therapy in the treatment of acute uncomplicated osteomyelitis in children.

5.2. SECONDARY HYPOTHESIS

Exclusively oral antibiotic treatment in children suffering uncomplicated acute osteomyelitis is related to:

1. Fewer complications linked to the rout of administration.
2. At least the same or more cases of definitive cure of the disease compared to the standard management using intravenous plus oral therapy.
3. At least the same or fewer cases of recurrences of the disease compared to the standard management using intravenous plus oral therapy.
4. At least the same or fewer cases of treatment failure compared to the standard management using intravenous plus oral therapy.

6. OBJECTIVES

6.1. MAIN OBJECTIVE

This study aims to demonstrate the same or higher proportion of resolution of the disease (≥97%) in children with uncomplicated OM who receive exclusively oral antibiotic therapy compared with patients that receive the standard intravenous plus oral therapy.

6.2. SECONDARY OBJECTIVES

To accomplish, in children with uncomplicated OM who receive exclusively oral antibiotic therapy, compared with patients that receive the standard intravenous plus oral therapy:

1. Less complicated cases related with the rout of administration of the antibiotic.
2. The same or higher proportion of cure of the disease (≥95%).
3. The same or less proportion of recurrences of the disease (≤3%).
4. The same or less proportion of treatment failure cases (≤5%).

7. MATERIAL AND METHODS

7.1. STUDY DESIGN

This study is designed as non-inferiority, randomized, open-labelled, parallel group controlled clinical trial.

7.2. STUDY SETTING

This study is designed to be multicenter.

It will be set among the following hospitals of Catalonia:

- *Hospital Universitari de Girona Doctor Josep Trueta*, Girona (146.000 inhabitants as a reference population).
- *Hospital Universitari Vall d'Hebron*, Barcelona (400.000 inhabitants as a reference population).
- *Hospital Sant Joan de Déu*, Barcelona (300.000 inhabitants as a reference population).
- *Hospital Universitari Parc Taulí,* Sabadell (390.000 inhabitants as a reference population).

7.3. STUDY POPULATION

The study population will be all patients with a suspected osteomyelitis (based on the presence of any of the following clinical signs and symptoms; bone pain, fever and restriction of movement) that fulfill the following requirements on admission:

7.3.1. Inclusion criteria

1. **Age** ≥1 and ≤15 years old.
2. Absence of the following **complications** of OM:
    a. Bone abscess.
    b. Septic shock.
    c. DVT.
    d. Septic pulmonary thromboembolism.

7.3.2. Exclusion criteria

1. **Age** <1 year old or >15.
2. **Subacute or chronic** OM.
3. **Complications** of OM (defined in inclusion criteria paragraph).
4. OM requiring **surgical intervention**.
5. **Septic arthritis** or **pyomiositis** without bone involvement.
6. **Hip** or **ankle** involvement.
7. **Hospital-acquired infection**.
8. Underlying **bone diseases, immunodeficiency** or **sickle-cell disease.**
9. Carriers of **prosthetic materials**.
10. Known **allergy** to cephalosporines.
11. Patients **denying informed consent**.

7.3.3. Withdrawal criteria

1. Any severe or life-threatening **adverse event** that could be related to the administrated drug.
2. **Limited clinical response** after 72h of the onset of the treatment: this is understood as the presence of fever (body temperature ≥38°C and/or CRP value >100 mg/L).
3. MRSA, Salmonella or PVL+ *S. aureus* detected on **cultures**.
4. Poor **compliance of the therapy**.
5. Apparition of **sepsis signs** (explained in the *introduction*).

The patients withdrawn from the study will not be replaced and they will be included in the statistical analysis.

7.4. SAMPLE

7.4.1. Sample selection

Our sampling process will be a multi-staged (or conglomerate) sampling consisting in two stages.

The first stage consists on an **intentional or convenience sampling**. In this stage, we will choose the hospitals that will participate in our study by convenience. This type of sampling is chosen because of practical reasons. Although we know that the best system would be choosing the hospitals through a random sampling, it would be methodologically difficult to perform. Then, assuming that the population that is assisted in the different Catalan hospitals is similar in medical terms, we do not think that choosing the hospitals by convenience will generate selection bias.

The second stage consists on a **non-probabilistic consecutive sampling**. In order to choose our patients in all these hospitals, all available subjects suffering a suspected osteomyelitis that are being visited in one of our hospitals, if accomplish the inclusion and exclusion criteria and accept the informed consent, they will be formally included in our study.

7.4.2. Sample size

The free online application Sealed Envelope Ltd. 2012 has been used to calculate the sample size.(27)

Accepting an alpha risk of 0,05 and a beta risk of 0,2 with a non-inferiority limit (also named δ) of 0,05, 49 patients are necessary in first group and 49 patients are necessary in second group (98 patients in total). So, if there is truly no difference between the standard and experimental treatment, then **98 patients** are required to be 80% sure that the upper limit of a one-sided 95% interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the standard group of more than 5%.

7.4.3. Time of recruitment

According to non-published data, the Hospital Universitari de Girona Doctor Josep Trueta (Girona) attends around 15 children suffering acute uncomplicated osteomyelitis per year. So, taking into account the ***potential pediatric population attended in our 4 hospitals***, we estimate that they attend together approximately **95 pediatric patients with acute uncomplicated osteomyelitis per year**.

Of these, we hypothesize that a 20% of patients who accomplish the inclusion and exclusion criteria may not accept to be part of our clinical trial (response rate of 80%), and we estimate a drop-out rate of 10%.

Therefore, we estimate that the time of recruitment will last 18 months.

7.5. VARIABLES AND METHODS OF MEASUREMENT

7.5.1. Main variable or independent variable

The independent variable is the **therapeutical intervention**. Both groups will be treated empirically with a first-generation cephalosporin (due to the high prevalence of MSSA in Spain) once the disease is suspected. One group, which is the control one (**group A**) will receive an intravenous therapy with cefazolin followed by oral therapy with cefadroxil (identified as **therapy A**). The other group, which is the experimental one (**group B**) will receive only oral therapy with cefadroxil (identified as **therapy B**).

This is considered a dichotomus qualitative variable.

7.5.2. Dependent variables

Disease resolution is the **main dependent variable** of our study. It is a dichotomous qualitative variable (Yes/ No). It will be measured as the proportion of responders for each therapy received (therapy A or therapy B). To determine the response to the treatment, we will consider:

- Patients presenting fever at the moment of diagnosis: **absence of fever** and **reduction of the maximum pre-admission CRP value >30%** will be considered as parameters of response. These parameters will be measured 72 hours after the onset of the treatment.
- Patients that do not present fever at the moment of diagnosis: a **reduction on the severity of the pain >50%** in the mean of the indicated pain scale score, from before the treatment to 72 hours after the onset of the treatment will be considered as a parameter of response to treatment. This parameter will be measured 72 hours after the onset of the treatment.

Although many options are available **to measure temperature** in children, the relative ease, speed, accuracy and safety of the infrared tympanic thermometer warrant its use for children in clinical practice, so it will be the employed method to evaluate the body temperature in our study. However, children younger than two years of age will have their temperature taken rectally.

The normal body temperature in children is 37°C, considering fever when is 38°C or greater, measured by a rectal or tympanic thermometer.(28)

The **pain** is scored from less severity to more severity using a punctuation system. To evaluate it, is important to consider the age of the individual. In this way, as our study includes patients aged between 1 to 15 years of age, different methods will be used to evaluate the pain.

For children aged between 1 to 4 years of age, it will be employed the Face, Legs, Activity, Cry and Consolability (FLACC) scale, which incorporates 5 pain behaviours that make up the scale's name: facial, expression, leg movement, activity, cry and consolability. Each behaviour is scored from 0 to 2, with the highest possible cumulative score being 10 (most pain).

On the other hand, for children and adolescents aged between 4 to 12 years of age, several tools can be used to report pain. Thus, in younger children (from 4 to 8 years of age), as developmental capabilities may hinder the use of purely numeric scales, pictorialbased pain scales such as the Faces Pain Scale-Revised is used. In this scale, the child is asked to select 1 of 6 neutral faces that accurately reflect their pain, which is scored from 0 to 10.

For older children (>8 years of age) who are able to understand abstract concepts, the visual analog scale (VAS) can be used. The VAS uses either a vertical or horizontal premeasured line (100 mm) to estimate the pain. The ends of the lines represent the 2 extremes of pain ("no pain" to "worst pain"), and it may include a numerical representation along the line. The child makes a mark on the line to indicate his/her level of pain and the pain score is calculated by measuring the distance from the left end point of the scale to the child's mark.

These pain scales will be provided to the patient or the pertinent tutor in case the patient was not able to compliment the scale, on arrival at the hospital, at 36 and 72h after the start of the treatment, and at follow-up visits in order to detect changes on the severity of the pain associated to the antibiotic therapy, as it is shown in ***Annex 1***.

The **secondary dependent variables** of our study are:

1. Complications related with the rout of administration: It is a dichotomous qualitative variable (Yes/ No). It will be measured as the occurrence of adverse events linked to the intravenous line in the control group or to oral therapy in the experimental group.
   These complications will be measured during the hospital stay by controlling vital signs and checking the punctured area in the case of the intravenous group, and by clinical evaluation focusing on patient and his or her legal tutor opinion during the first week of the treatment.
   If catheter-related thrombosis is suspected, an US must be done.

   The following complications are related with the oral treatment (experimental group): diarrhea, mouth sores and pseudomembranous colitis.
   Complications related with intravenous lines (control group) are mainly:
   - **Catheter-related bloodstream infection**: it is defined as the association of a positive blood culture in a patient with a catheter within 48h prior to the onset of symptoms, and one of the following criteria:
     - A positive culture of either catheter tip or exit site ($\geq 10^3$ CFU/ml) involving the same organism as blood culture.
     - Blood cultures from peripheral venous puncture and intravenous lines positive with the same organism with a quantitative ratio (central sample/ peripheral sample) >5.
     - A differential time to positivity >2h in favor of intravenous line sample.
   - **Catheter-related local infection**: it is defined as a positive culture of the catheter segment ($\geq 10^3$ CFU/ml) with pus emerging from the exit site or a tunnel infection, with local manifestations of infection but no general signs of sepsis and negative blood cultures.

When all these criteria are not present or bacteriological culture not realized, or realized when the patient is under antibiotic therapy, we will classify these suspected infections as “possible infection”. If cultures remain negative (in the absence of antibiotics) or another cause of infection is diagnosed, the case will be classified as “infection not confirmed”.

- **Local inflammation**: it is defined by redness and/or soreness at the catheter exit site.
- **Catheter-related thrombosis**: it is defined as the presence of a mural thrombus that extends from the lumen of the catheter leading to partial or total occlusion of the catheter detected by US.
- **Catheter dysfunctions**:
    - Pre-oclusive event: it is defined as either a significant reduction of infusion flow or an impairment of blood back-flow (aspiration).
    - Lumen occlusion: it is defined as the permanent inability to flush the catheter or to obtain blood back-flow.

2. Definitive cure of the disease: It is a dichotomous qualitative variable (Yes/ No). It is defined as the absence of all the following symptoms and signs two months after the end of the treatment:
    a. Fever.
    b. Any clinical symptom of OM: pain, functional limitation (measured by clinical examination), focal tenderness or redness and swelling around the affected area.

    It will be screened in the follow-up visit by doing a complete physical examination and information collection about possible symptoms manifested by the patient.

3. Disease recurrence: It is a dichotomous qualitative variable (Yes/ No). It will be defined as the presence, within the 30 days after the end of the treatment, of at least one of the following:

    a. Fever.
    b. Any clinical symptom associated to OM: pain, functional limitation (measured by clinical examination), focal tenderness or redness and swelling around the affected area.

   It will be screened in the follow-up visit by doing a complete physical examination and information collection about possible symptoms manifested by the patient.

4. Treatment failure: It is a dichotomous qualitative variable (Yes/ No). It is defined as reappearance during the treatment or within 6 months after the end of the treatment of at least one of the following:

    a. Fever.
    b. Any clinical symptom of OM: pain, functional limitation (measured by clinical examination), focal tenderness or redness and swelling around the affected area.

   It will be screened in the follow-up visit by doing a complete physical examination and information collection about possible symptoms manifested by the patient.

7.5.3. Covariates

We will take into account the following covariates, as they may act as confounding factors:

1. Age: It is a continuous quantitative variable.
   It will be calculated through the date of birth obtained from the patient's ID card or other valid document.
   It will be expressed in years.

2. Gender: It is a dichotomous qualitative variable (Male/ Female). It will be collected from the patient's ID or other valid document during the admission.
   It will be expressed as a proportion**.**

3. Ethnicity: It is a nominal qualitative variable. It will be collected by asking the patient for him or her nationality.
   It will be expressed as White or Caucasic/ African/ Hispanic or Latino/ Other.

4. Time from the beginning of symptoms until the diagnosis of OM: It is a continuous quantitative variable. It will be collected by clinical evaluation and consulting the clinical history of the patient.
   It will be expressed in hours.

5. Time from the diagnosis of OM until the onset of the treatment: It is a continuous quantitative variable. It will be determined by asking the patient and taking into account the patient information from the clinical history.
   It will be expressed in hours.

Table 4. Variables of the study			
Variable	**Type**	**Categories or values**	**Measure instument**
Independent			
Therapeutical intervention	Dichotomous qualitative	Group A / Group B	
Dependent			
Disease resolution (main dependent)	Dichotomous qualitative	Yes / No	Clinical evaluation (body temperature measuring and pain scales) and CRP blood marker
Complications related with the rout of administration	Dichotomous qualitative	Yes / No	Vital signs, catheter area observation, clinical evaluation and US
Definitive cure of the disease	Dichotomous qualitative	Yes / No	Clinical evaluation: body temperature measuring, pain scales and physical examination
Disease recurrences	Dichotomous qualitative	Yes / No	Clinical evaluation: body temperature measuring, pain scales and physical examination
Treatment failure	Dichotomous qualitative	Yes / No	Clinical evaluation: body temperature measuring, pain scales and physical examination
Covariates			
Age	Continuous quantitative	Number of years	Clinical examination
Gender	Dichotomous qualitative	Male / Female	Clinical examination
Ethnicity	Nominal qualitative	White or Caucasic/ African/ Hispanic or Latino/ Other	Clinical examination
Time from the beginning of symptoms until the diagnosis of OM	Continuous quantitative	Number of hours	Clinical examination
Time from the diagnosis of OM until the onset of the treatment	Continuous quantitative	Number of hours	Clinical examination

7.6. STUDY INTERVENTIONS

7.6.1. Randomization and masking technique

The patients enrolled in this clinical trial will be randomly distributed in two groups:

- **Group A** (control group): this group will receive intravenous therapy with cefazolin followed by oral therapy with cefadroxil (identified as **therapy A**).
- **Group B** (experimental group): this group will receive oral therapy with cefadroxil (identified as **therapy B**).

A stratified random-sample will be done, so the population will be split in two groups according to age:

- 1 to 5 years of age.
- 5 to 15 years of age.

By stratifying by age, we will avoid differences in efficacy of response to treatment due to the different causative agent depending on the age, expecting treatment groups to be comparables.

The members from each group of treatment will be chosen randomly by a computer-generated randomization, so investigators will not intervene in this process. When a new patient is enrolled in the study, the computerized information will show to the investigator the age group and the treatment group where the patient belongs to (A or B) and, then, therapy will have to receive (A or B). In this way, we are guaranteeing that members from each group will be represented in the sample.

Our study will be open-labelled, so the researchers will know which treatment is being given to each study subject. In the same way, each study subject will know what treatment is receiving.

We will make an open-label study due to logical reasons. The rout of administration of the antibiotic is different in function of the therapy group. One group is treated orally, and the other is treated intravenously plus orally, so it is not possible to mask because they are different formulations.

7.6.2. Study interventions

The following paragraphs will show the steps of our study interventions depending on the randomly assigned group from which the patient will be part:

Group A (control group): this group will receive intravenous therapy with cefazolin followed by oral therapy with cefadroxil (identified as **therapy A**). The administrated dose of cefazolin will be 150 mg/kg/day in 4 equal dosis. The maximum dose that can be given is 4g/day.

If cefazolin resolve the OM (absence of fever at 72h and decrease of the pre-admission maximum CRP value above 30% at 72h in case that the patient presents fever at the moment of the diagnosis, or a reduction on the severity of the pain >50% at 72h in patients that do not present fever at the moment of diagnosis), oral therapy with cefadroxil (90 mg/kg/day in 3 equal dosis) will be started once 7 days of intravenous treatment are completed, until complete 2 more weeks with exclusive oral therapy.

On the contrary, if cefazolin does not resolve the OM, the patient will be closely followed, employing more specialized diagnosis techniques and an alternative therapy will be given to him or her.

The cefazolin will be administered by an experimented nurse (supervised by an experimented pediatrician) as a direct bolus in 3-5 minutes at a maximum concentration of 150 mg/ml. A PICC will be use as a venous access to administrate the drug, taking into account that before and after the infusion of the antibiotic, a sterile saline solution will be administrated through the catheter to prevent inflammation of the vain.

The cefadroxil pills will be taken by the patient at home.

Group B (experimental group): this group will receive oral therapy with cefadroxil (identified as **therapy B**). The administrated dose will be 90 mg/kg/day in 3 equal dosis. The maximum dose that can be given is 4g/day.
If this drug resolve the OM (absence of fever at 72h and decrease of the pre-admission maximum CRP value above 30% at 72h in case that the patient presents fever at the moment of the diagnosis, or a reduction on the severity of the pain >50% at 72h in patients that do not present fever at the moment of diagnosis), the same therapeutic regimen will be maintained until complete 3 weeks of treatment. On the contrary, if this drug does not resolve the OM, the patient will be considered as a non-responder, changing him or her treatment for the standard therapy (described in group A).

We need to know the patient weight in both groups of our study to calculate the necessary dose of the antibiotic used. So, the weight will be obtained by a nurse measuring the patient weight at the time of arrival to the hospital.

A document containing essential information about the administered antibiotics has been elaborated in order to be aware of the possible consequences for the patient related with their use ***(Annex 2: Relevant information about the drugs used in our study).***

7.7. METHOD OF DATA COLLECTION

All the information that should be recorded appear in the "Data collection sheet" ***(Annex 3).***

Those aspects will be considered:

At the emergency room, any attended case of suspected OM will be considered a potential patient to be included in our study. If the patient accomplishes the inclusion and exclusion criteria and the informed consent is obtained, he or she will be formally enrolled in our study.

To rule out complications in each of our patients in order to know if accomplishes the inclusion and exclusion criteria, we will indicate:

- An **urgent MRI** (to rule out local complications, DVT and pulmonary thromboembolism), establishing previously an agreement with the radiology department in order to ensure that our patients will be studied urgently.
- To **rule out** a systemic **sepsis**: vital signs (cardiac frequency, respiratory rate and central body temperature) and the general state of the patient will be evaluated to confirm or discard the sepsis.

Once we consider that the patient accomplishes all the inclusion and exclusion criteria, as soon as possible, the investigators will try to treat the fever and the possible pain. At the same time, they will begin the treatment of the OM with one of our drugs of study according to the therapy group (A or B) that the patient will have been randomly assigned.

The treatment of the fever and pain will be intravenously in the group A, and orally in the group B.

If the patient form part of the **group A** (standard therapy), he or she will be moved to the general hospitalization area. The patient will stay in this area until the finish of the intravenous therapy (7 days).

If the patient form part of the **group B** (oral therapy), he or she will receive the first dosage of cefadroxil at the emergency room. The tolerance will be controlled during six hours at hospital in order to increase our safety about the compliance of the therapy. If the drug is well-tolerated, the patient will be discharged and continuing the therapy at home. If the drug is non-well tolerated, the patient will be considered as a non-responder, changing him or her treatment for the standard therapy.

While the antibiotic treatment persists, hemogram and CRP will be done each 10 days to control the evolution of the infection and possible adverse effects related to the drugs. These evaluations are included in the standard management of OM. They will be done by the laboratory staff and an experienced nurse, who will call the patient tutor to program a visit in case of alteration in any parameter.

In order to evaluate our main dependent variable (disease resolution), body temperature, CRP and the severity of the pain will be measured before and after 36 and 72 hours of the onset of the treatment in each child from both groups. Body temperature will be also measured each 4 hours within first 24 hours after the onset of the treatment.
In this way, to screen other dependent variables as definitive resolution of the disease, disease recurrence and treatment failure, the following actuations must be done:

- Measurement of body temperature: it will be done before the onset of the treatment, during the treatment (each 4 hours within the first day and at 36 hours), and 72h, 1 month, 2 months and 6 months after the end of the treatment.
- Clinical evaluation: it will consist in an exhaustive clinical examination, evaluating any possible symptom or complication associated to OM.
  Here, pain scales described in ***Annex 1*** will be used in order to evaluate the pain.
  If any doubt of the existence of any reappearance or persistence of the disease exists, complementary techniques of diagnosis will be carried out.
  It will be done before the onset of the treatment and 1 month, 2 months and 6 months after.

- Drug compliance control: It will be checked in both groups of treatment during the follow-up visits by requesting the patient to bring the blister pack in order to ensure that pills are being taken correctly. In addition, in those follow-up visits, the responsible pediatrician will talk with the patient or him/her legal tutor about compliance problems and possible adverse drug events, which is the most important factor for the adherence.

  Moreover, after proving that the drug is well tolerated by the patient at the emergency room, training will be performed by the nurse staff to the patient and him or her parents at the emergency room in order to increase the compliance.

  In this way, the informed consent will contain a section in which it appears that the patient agrees to accomplish the treatment as it is established in our protocol.

The follow-up will last six months for both groups:

1) First visit: 72 hours after the onset of the treatment.

2) Second visit: one month after the end of the treatment.

3) Third visit: two months after the end of the treatment.

4) Fourth visit: six months after the end of the treatment.

These actuations will be carried out by a pediatric infectious disease specialist.

8. STATISTICAL ANALYSIS

The statistical analysis will be done using the Statistical Package for the Social Sciences (SPSS Windows®) and the responsible statistician who will do it will be blinded to the study groups. The statistical analysis method used will be double, using both the intention to treat analysis and per protocol analysis.

8.1. UNIVARIANT ANALYSIS

The result of our variables in each group of study will be expressed according to if they are qualitative or quantitative:

- Qualitative variables:
    1) Therapeutical intervention: group A (cefazolin plus cefadroxil) or group B (cefadroxil).
    2) Disease resolution.
    3) Complications related with the rout of administration.
    4) Definitive cure of the disease.
    5) Disease recurrence.
    6) Treatment failure.
    7) Gender.
    8) Ethnicity.

  These variables will be expressed as a proportion (percentage). A table of frequencies and a sector diagram will be used to represent these proportions.

- Quantitative variables:
    1) Age.
    2) Time from the beginning of symptoms until the diagnosis of OM.
    3) Time from the diagnosis of OM until the onset of the treatment.

  Results for variables with a normal distribution will be expressed as a mean and standard deviation (SD), and those for variables without a normal distribution will be expressed as median, estimating also quartiles.

8.2. BIVARIATE ANALYSIS

Different tests will be used to analyze the association between the independent variable with the dependent variables. The test used to evaluate the association between our independent variable (therapeutical intervention), which is dichotomous qualitative variable, with a dependent variable will be chi-square (x^2) test for dependent qualitative variables, taking into account that all our dependent variables are qualitative.

Results will be considered as statistically significant at a value of $p < 0.05$ defining a confidence interval of 95%.

8.3. MULTIVARIATE ANALYSIS

Although a stratified by age random sample will be done and because of this it is not expected to find confounding, a multivariate analysis will be performed in order to detect possible confounding produced by the covariates.

The analysis of our main dependent variable (disease resolution), which is a qualitative variable, and our secondary dependent variables, which are also qualitative variables, between both therapy groups (A: cefazolin plus cefadroxil, and B: only cefadroxil) will be performed using a Multiple Logistic Regression model.

A per-protocol analysis and an intention-to-treat analysis analysis will both be performed. Therefore, two groups of analysis will be elaborated.

The per-protocol analysis will only include those patients who have fulfilled the requirements of the protocol and/or have completed the study.

By the other hand, as an intention-to-treat analysis will be done, all patients who have been selected and in the group in which they were randomly assigned (even if they have not completed the study or have changed their group) will be included in the analysis.

9. ETHICAL CONSIDERATIONS

This clinical trial will respect the medical ethics principles of human experimentation, according to the *World Medical Association Declaration of Helsinki* (1964) about the Ethical Principles for Medical Research Involving Humans Subjects.

Once this protocol will be finished, it will be sent to the Clinical Research Ethics Committee (CEIC) of the *Hospital Universitari de Girona Doctor Josep Trueta,* Girona. The validation by this committee is mandatory to start the clinical research, as it is registered in the *"Real Decreto 1090/2015, de 24 de diciembre, ensayos clínicos con medicamentos"*.
In this way, permission will also be solicited to the direction of each of our hospitals and the protocol will be sent to the *Asociación Española de Medicamentos y Productos Sanitarios* (AEMPS) to receive its authorization. After the approval, the last step will be submitting the protocol to the *European Clinical Trials Database* (EudraCT).

Our study will include pediatric subjects. For this reason, in agreement to the *"Real Decreto 1090/2015, de 24 de diciembre, ensayos clínicos con medicamentos"* and the European legislation *"Reglamento (UE) N° 536/2014 del parlamento Europeo y consejo de 16 de abril de 2014"*, the parents or legal representatives of our patients will receive information about our study ***(Annex 4. Information sheet)***, giving to us their informed consent if they agree ***(Annex 5. Informed consent document)*** to enroll the child in the study. About this legislation, it is also important to consider the obligation of an economical compensation to the patients if they suffer injuries due to the clinical trial, being needed an insurance to face with these situations.

Knowing that our clinical trial could be considered as invasive and pending on what CEIC establishes, we will accomplish the considerations from "*Ley 14/2007, de 3 de julio, de investigación biomédica*".

According to the Spanish legislation, *"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales"*, all the information obtained from the patient will be confidential and anonymous, being used just for the purpose of the research. Data will only be accessible for the responsible researchers of the project.

Taking into account the ethical principles, we decided not using placebo in our study because osteomyelitis is an urgent disease that needs to be treated as prompt as it could to ensure a good prognosis for the patients. In addition, osteomyelitis is a potentially life-threatening disease that could be fatal. In agree with this, we could not administer placebo to any of our patients while different medicines with demonstrated effectiveness are available.

We have to consider the possible ethical conflict linked to the use of oral therapy during the whole course of acute OM, because that therapeutic regimen is not considered for such indication. However, the history of the treatment of acute OM has shown that the increasing reduction of intravenous treatment has not been detrimental to the results. This suggests that oral treatment can show the same effectiveness.

10. STUDY LIMITATIONS

OM is a low incidence disease, so the recruitment time would be long. For this reason, we tried to minimize this circumstance by doing a multicentric trial.
As a multicentric study could create variability in the procedures done in each hospital, we have collected some considerations about a suspected OM that are widely accepted to start the diagnosis and treatment process. Although OM can be confounded with other entities, we have established really specific inclusion criteria to avoid this situation.

Although our clinical trial could be thought as expensive, we consider that a randomized clinical trial is the best design to reach our study objectives. In addition, it is important to know that it is a future investment, because the exclusive oral treatment would suppose the absence of hospitalization of the patients, what would greatly reduce treatment costs.

The fact of being a prospective study has the risk that patients can leave it due to adverse drug effects or to lack of compliance. However, an estimated drop-out rate has been taken into account in our study sample, so this should not be a problem.

Regarding our masking technique, we decided to carry out an open-labelled clinical trial because it would not be feasible to blind neither patients nor investigators because different formulations of the drug will be used.

Our main dependent variable (disease resolution) includes fever and pain as parameters of measurement. In this way, acute OM may require concomitant treatment different than antibiotics, as could be nonsteroidal antiinflammatory drugs, which may reduce fever and pain as a therapeutic effect. This could be thought as a confounding factor, but it is consider that these both parameters do not disappear unless if it is treated with antibiotics.

We assume that the presence of a very effective standard therapy could difficult the acceptation of exclusive oral antibiotic therapy as the reference protocol treatment. Despite this, we consider exclusive oral therapy a better alternative to avoid catheter-related complications and absence of hospitalization, what could cause emotional disturbances in patients and familiars due to the experience.

Both therapy groups of our study will have to take medication at home, so the therapeutic compliance must be strictly controlled. To deal with this circumstance, some evaluations will be established:

- Informed consent (see ***Annex 5***): it will contain a section in where the patient agrees to accomplish the treatment as it is established in our protocol.
- At the emergency room: after proving that the drug is well tolerated by the patient at the emergency room, training will be done by the nurse staff to the patient and him or her parents in order to increase the compliance.
- During the follow-up visits: the patient will be requested in each visit to bring the blister pack in order to ensure that pills are being taken correctly, by making a count of the pills that have been consumed. In addition, in those follow-up visits, the responsible pediatrician will talk with the patient or him/her legal tutor about compliance problems and possible adverse drug events, which is the most important factor for de adherence.

11. WORK PLAN

The research team will develop the tasks of coordination, interpretation and presentation of the results. The **"principal investigators"** of our study will be the pediatric infectious disease team of each hospital, being one coordinator from each team, who will meet twice a year with the other coordinators.

The study will be multidisciplinary, considering as **"co-investigators"** the following team:

- A pharmacist staff from each hospital.
- A radiologist staff from each hospital.
- A nursing staff from each hospital.
- One statistic to analyze the results.

The sequence of the activities will be developed in the following order:

- **Stage 0**: Study design, coordination and training (December 2018 – February 2019).
    1) Bibliographic research and protocol elaboration (objectives, hypothesis, variables and methodology).
    2) First meeting of research team in order to choose who will be the principal investigators of each hospital center included in our study. The organization of tasks and discussion of how to teach to fill the data information sheet will be also included.
    3) Multidisciplinary team meetings and instructions to fill the data information sheet and sequence of data transference.
    4) Training: the pediatricians who will participate in the study will receive information about the study protocol (collecting and registering data, giving information to patients and diagnosing and treating OM) in order to avoid differences when diagnosing and treating. That will ensure the homogeneity required to obtain representative conclusions.

Investigators and co-investigators will be the main responsible.

- **Stage 1**: Ethical evaluation of the protocol (February 2019).
    1) Presentation and evaluation of the protocol by the Clinical Research Ethics Committee of the *Hospital Universitari de Girona Doctor Josep Trueta,* Girona.
    2) Contracting an insurance.

  Investigators will be the main responsible

- **Stage 2**: Sample collection, data collection and follow-up visits (March 2019 – September 2021).
    1) Patient recruitment: by a consecutive sampling, patients will be enrolled in our study if they accomplish the inclusion and exclusion criteria and if they accept the informed consent.

       Patients will be randomly distributed in two groups by stratifying by age (control and experimental). The relevant therapy will be administrated to each group according to the established plan.
    2) Follow-up visits: during the treatment, patients will be controlled after 72 hours of the onset of the treatment and each 10 days to evaluate possible adverse events and response to treatment. The follow up will last 6 months, with visits at the month, at the second month and at the sixth month after the end of the treatment.
    3) Data collection: each pediatrician will record the information collected in every visit in our database by using the data collection sheet ***(Annex 3: Data collection sheet)***. The database will be revised constantly to guarantee its functioning.
    4) Coordinators of each hospital will meet twice a year to evaluate if the protocol is being well fulfilled. If something do not work, they will take the necessary decisions.

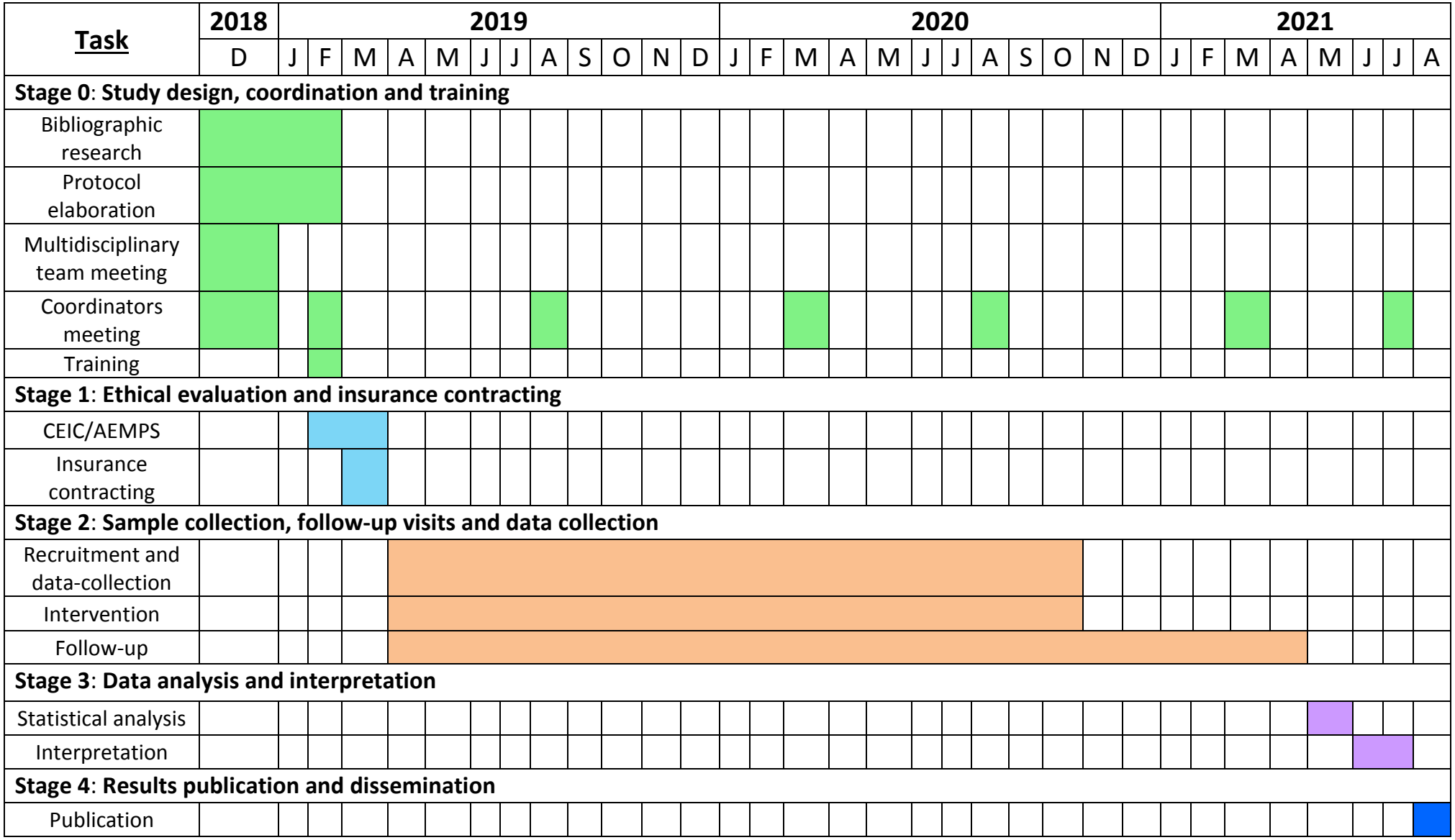
  Investigators and co-investigators will be the main responsible.

- **Stage 3**. Data analysis and interpretation (October 2021 – November 2021).
    1) Statistical analysis: performed by an experienced statistical. All the information collected will be analyzed by him or her according to the variables of our trial.
    2) Interpretation of results: the principal investigators are the responsible. After this step, the discussion and conclusion will be elaborated.

  Coordinators and the statistic are the main responsible.

- **Stage 4**. Publication of results (November 2021 – December 2021).
    1) Principal investigators will generate a paper to show the study results and conclusions. It will be sent to the principal pediatrics journals and to the *Pediatric Spanish Association* (AEPED).

  Coordinators are the main responsible.


Task
2018
2019
2020
2021
D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A
Stage 0: Study design, coordination and training
Bibliographic research
Protocol elaboration
Multidisciplinary team meeting
Coordinators meeting
Training
Stage 1: Ethical evaluation and insurance contracting
CEIC/AEMPS
Insurance contracting
Stage 2: Sample collection, follow-up visits and data collection
Recruitment and data-collection
Intervention
Follow-up
Stage 3: Data analysis and interpretation
Statistical analysis
Interpretation
Stage 4: Results publication and dissemination
Publication

12. BUDGET

Personnel recruitment

A qualified statistician will be hire for data managing and statistical analysis and a monitoring and data collection assistant will be hire to ensure data validity.

Insurance policy

As our study is an open-labelled clinical trial, an insurance will be contracted.

Material needed

The material for treatment administration must be taken into account. We have to take into account that only the experimental group will take these pills. Costs are estimated only for the first week of the treatment, because the following two weeks are included in the current standard therapy. As the maximum dose that can be administrated is 4g/day (each pill contains 500 mg), we consider this quantity per patient to calculate the cost.

In addition, to control our main dependent variable, CRP blood marker will be measured at 36 and 72 hours after the onset of the treatment, being this not included in the standard management of OM.

A magnetic resonance imaging will be done to all patients in order to discard complications and then consider if they accomplish the inclusion criteria. So, as this technique is not included in the systematic management of OM unless diagnosis doubts exist, we have to consider it in our budget.

Results publication, dissemination and travel

There will be seven meetings during all our study to coordinate the four different participant hospitals. The coordinator (principal investigator) of each hospital will be the responsible of attending to the meetings. An estimated cost of 60€ is established per person in order to pay diets and displacement.

The assistance to two different conferences to show the results of the study has been considered.

In the following table is estimated the needed budget to complete our study:

Item	Quantity	Cost	Subtotal
Staff expenses			
Pediatrics **Nursing staff** **Pharmacists** **Radiologists**		0€/h	0€
Subcontracted professional services			
Qualified statistic	8h/day x 3 days/week x 4 weeks.	20€/h	1.920€
Monitoring and data collection assistant	4h/day x 1 day/week x 18 months	15€/h	4.320€
Insurance policy			
Trial policy	1	20.000€/trial	20.000€
Material			
Cefadroxil	4 boxes of 28 pills (500 mg/pill)	8.96€/box	1.756€
MRI	98	160€/patient	15.680€
CRP value	196	9€/CRP	1.764€
Publication and travels			
Revision and publication fees	1	1.000€/protocol	1.000€
Coordination meetings	7 meetings (4 coordinators)	60€ per meeting per coordinator	2.040€
National congress	1	500€	500€
International congress	1	1.000€	1.000€
TOTAL			49.980€

13. IMPACT ON THE NATIONAL HEALTH SYSTEM

OM is an important infectious disease in terms of incidence and life-threatening. For this reason, numerous important studies have been carried out worldwide to achieve an adequate management of the disease. In this sense, our study would help to establish a new therapeutic alternative that considers exclusive oral therapy as a factor to be taken into account to avoid emotional and behavioral problems, given that with standard therapy hospitalization is always required, even if they have not complications.
Thus, the implementation of our protocol would suppose an important improvement in quality of life and emotional balance of the affected patients.

Based on our hypothesis, in the absence of complications of the disease, patients would avoid hospitalization, as well as risks associated with, as the possibility of acquiring nosocomial infections or complications arising from the use of intravenous catheter, what would condition the necessity of complementary techniques and more intensive and invasive treatments in order to manage these situations. This would be translated in more costs coming from the health system and an increased risk for the apparition of antibiotic resistances.

From an administrative point of view, the incorporation of our protocol into the health system would mean saving 600€ per patient as a result of the absence of expenses derived from hospitalization, according to data obtained from management of the *Universitary Hospital Doctor Josep Trueta*.

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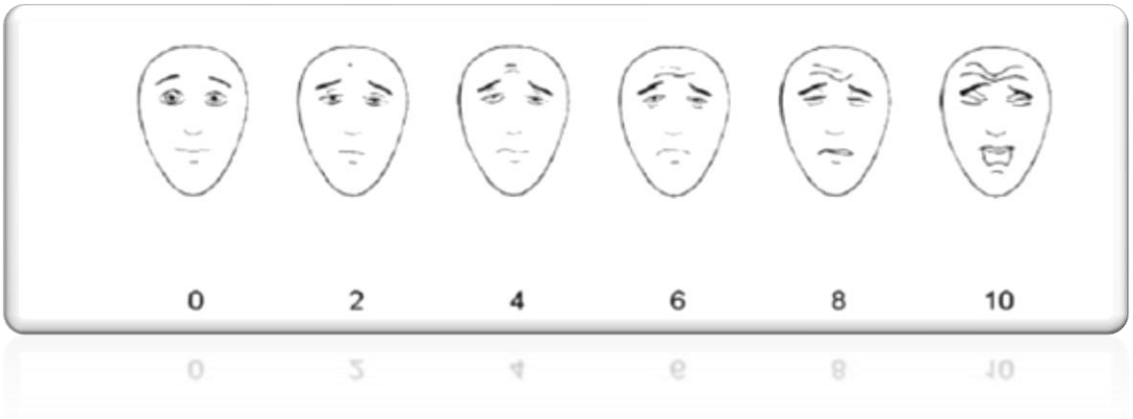
15. ANNEXES

Annex 1. Scales to evaluate the severity of the pain depending on the age of the patient(29)

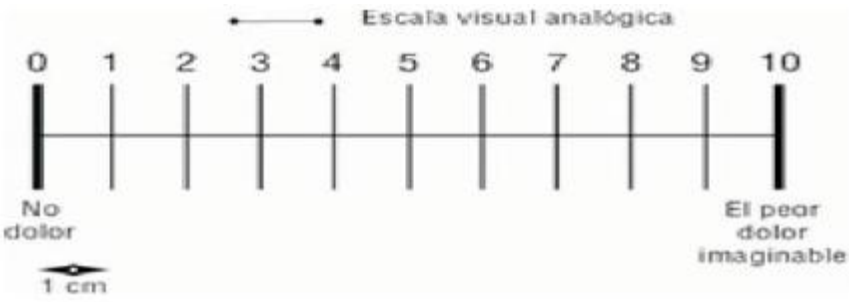
FLACC scale *(for patients between 1-4 years of age)*

Categoría	Puntaje 0	Puntaje 1	Puntaje 2
Expresión facial (Face)	Ninguna expresión especial o sonrisa	Ocasionalmente muecas o ceño fruncido; retraído, desinteresado	Frecuente o constante temblor del mentón. Mandíbula encajada
Piernas (Legs)	Posición normal, relajadas	Inquietas, rígidas, tensas	Pataleo o piernas alzadas
Actividad (Activity)	Tranquilo, posición normal, movimiento fácil	Retorcido, giros de acá para allá, tenso	Arqueado, rígido con sacudidas
Llanto (Cry)	No llora (despierto o dormido)	Gemido o lloriqueo quejido ocasional	Llanto continuo
Consuelo (Consolability)	Contento, relajado (dormido o despierto)	Tranquilo por caricias o abrazos ocacionales, o al hablarle para distraerlo	Dificultad para controlarlo o confortarlo

Faces Pain Scale – Revised *(for patients between 4-12 years of age)*



Visual Analog Scale *(for pacients >8 years of age that are able to understand abstract concepts)*



Annex 2. Relevant information about drugs used in our study(30)(31)

	Relevant information about drugs of our clinical trial	
	Cefazolin (intravenously)	**Cefadroxil** (orally)
Contraindications	Hypersensitivity to cephalosporins or inmediate hypersensitivity to penicillins.	Hypersensitivity to cephalosporins or inmediate hypersensivity to penicillins
Precautions	-If anaphilaxis -If hypersensitivity to penicillins or decreased renal function -A prolonged administration could result in bacterial or fungical infection -It should not be administered intrathecally -High blood levels can increase the risk of seizures in epileptic patints with low threshold	-If hypersensitivity to penicillins or decreased renal function - A prolonged administration could result in bacterial or fungical infection
Adverse effects No specific data exists in children. The data are those found in adult population. They are generally transitory and mild	-Nausea and vomiting -Transaminases and alkaline phosphatase elevation -Leukopenia, neutropenia, thrombocytopenia and + Coombs direct and indirect. -INR alterations -Related with the intravenous administration	-Frequent: diarrhea -Rare: abdominal pain, nausea, vomiting, cholestasis, transaminases elevation, pseudomembranous colitis, agranulocytosis, anaphylaxis, skin reactions
Pharmacological interactions	-Other antibiotics that have a mechanism of bacteriostatic action (tetracyclines, sulfonamides and erythroomicin). -Concomitant use of nephrotoxics (polymixin, vancomycin and aminoglycosides).	-Bacillus-Calmette-Guérin vaccine (decrease of its therapeutic effect if administered simultaneously). - Typhoid fever vaccine (decrease of its therapeutic effect). Do not administer this vaccine until 24h after the suspension of cefadroxil
Renal insuficiency*	-For a $CrCl^2$ of 40-70 mL/min: 60% of the normal daily dosage divided every 12h. -For a CrCl of 20-40 mL/min: 25% divided every 12 hours. -For a CrCl of 5-20 mL/min: 10%	-For a CrCl of 10-25 mL/min: administration each 24h -If CrCl <10 mL/min: administration each 36h

*Creatinine clearance.

Annex 3. Data collection sheet

Hoja de recogida de datos	**Proyecto**
Osteomielitis aguda no complicada pediátrica	Exclusive oral antibiotic therapy on acute uncomplicated osteomyelitis in children

Instrucciones:

Para la participación del paciente en el proyecto, es fundamental que el paciente cumpla **todos** los criterios de inclusión y **ningún** criterio de exclusión.

Criterios de inclusión	
Edad entre 1 y 15 años	
Ausencia de **complicaciones** de OM: absceso óseo, shock séptico, DVT, tromboembolismo pulmonar séptico	

Criterios de exclusión	
Edad <1 año ó >15	
OM **subaguda** o **crónica**	
Complicaciones de OM	
OM que requiere **cirugía**	
Piomiositis o **artiris séptica** sin afectación ósea	
Afectación de **tobillo** o **cadera**	
OM **adquirida** en el **hospital**	
Enfermedades de base: óseas, inmunodeficiencia o drepanocitosis	
Portador de **material protésico**	
Alergia a **cefalosporinas**	
Rechazo del **consentimiento**	

Datos generales		
Nombre y apellido		
Fecha de nacimiento	/ /	Género: Hombre ☐ Mujer ☐
Fecha de consulta	/ /	
Edad		
Hospital		
Etnia		

Historia clínica		
Alergias		
Tratamiento concomitante		
Antecedentes patológicos		
Antecedentes quirúrgicos		
Evaluación clínica osteoarticular		
Constantes vitales	Frecuencia cardíaca	
	Frecuencia respiratoria	
	Tensión arterial	
	Temperatura	
	$SatO_2$	
Peso y talla		/

INFORMACIÓN RELEVANTE PARA EL ENSAYO CLÍNICO EN URGENCIAS	
Medicación previa en relación a la OM	
Tiempo transcurrido desde la aparición de sintomatología en relación a la OM	
Tiempo transcurrido desde el diagnóstico hasta el inicio del tratamiento antibiótico	
Puntuación según escala de dolor	
Valor PCR	
Informe RM	
Tolerancia al antibiótico administrado (post-inclusión al ensayo clínico)	

	PARÁMETROS A CONSIDERAR DURANTE EL TRATAMIENTO				
	Primeras 24h	A las 36h	A las 72h	A los 10 días	A los 20 días
Tª corporal					
Valor PCR					
Puntuación escala dolor					
Complicaciones asociadas al fármaco					

	INFORMACIÓN RELEVANTE PARA EL ENSAYO CLÍNICO EN LAS VISITAS DE SEGUIMIENTO			
	1ª visita	**2º visita**	**3ª visita**	**4ª visita**
Tª corporal				
Exploración clínica				
Adherencia terapéutica				

Annex 4. Information sheet

HOJA DE INFORMACIÓN SOBRE EL ENSAYO CLÍNICO

Centro asistencial:
Investigador principal:

Introducción

Nos dirigimos a usted para informarle acerca de un estudio de investigación en el cual se invita a su hijo/a o representado/a a participar. Dicho estudio ha sido aprobado por el Comité de Ética de Investigación Clínica de este hospital y por la Agencia Española del Medicamento y Productos Sanitarios, de acuerdo a lo establecido en la legislación vigente, *Real Decreto 1090/2015, del 24 de diciembre,* por el cual se regulan los ensayos clínicos con medicamentos.

Nuestra intención es que usted reciba la información adecuada y suficiente para que pueda evaluar y juzgar por sí mismo si desea o no que su hijo/a o representado/a participe en este estudio. Por ello, le rogamos lea esta hoja informativa con atención y consulte con nosotros cualquier duda que le pueda surgir.

Participación

Debe saber que la participación de su hijo/a o representado/a en este estudio es voluntaria y que puede decidir no participar o cambiar de decisión retirando el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzcan prejuicios en su tratamiento.

Descripción del estudio

La osteomielitis aguda es una infección ósea que puede suponer una amenaza para la vida y que está relacionada con un alto porcentaje de complicaciones y secuelas. Es una enfermedad que, a pesar de ser poco frecuente (8 de cada 100.000 niños), su incidencia está aumentando considerablemente en estos últimos años. La osteomielitis puede aparecer a cualquier edad, aunque es más frecuente en menores de cinco años.

En la actualidad, el tratamiento de esta enfermedad muestra una eficacia muy elevada, siendo asimismo destacable la gran cantidad de pacientes que presentan complicaciones asociadas a la forma de administración del medicamento, que es cercana al 40%. Además, dicha forma de administración requiere de una hospitalización media del niño/a de aproximadamente 5 días, lo cual supone un impacto psicosocial considerable con sus respectivas consecuencias emotivo-conductuales en el futuro. Es para evitar todo esto el motivo principal por el que hemos desarrollado un nuevo protocolo de tratamiento, consistente en tratamiento exclusivo por vía oral, de manera que se podría llevar a cabo en el propio domicilio del paciente.

Metodología e intervención

Nuestro estudio incluirá a niños y niñas de entre 1 y 15 años de edad con osteomielitis no complicada.

Una vez que el consentimiento informado se ha formalizado, se le realizará una resonancia magnética a cada paciente, que en caso de no presentar complicaciones, pasará a formar parte de nuestro ensayo clínico. Los pacientes de este estudio serán distribuidos aleatoriamente en dos grupos de tratamiento (**A** y **B**) estratificados por edad (uno de 1-5 años y otro de 5-15 años). Cada grupo recibirá un medicamento antibiótico diferente, administrado por diferente vía, de manera que el **grupo A** recibirá cefazolina intravenosa y el **grupo B** cefadroxilo oral. Tras 72 horas del inicio del tratamiento, se valorará si la enfermedad a resuelto determinando la severidad del dolor, la temperatura corporal y los niveles de proteína C-reactiva en sangre en ambos grupos de tratamiento.

En el **grupo A**, si se considera que la enfermedad ha resuelto, se continuará infundiendo intravenosamente el fármaco hasta completar 5 días de terapia intrahospitalaria, dando de alta posteriormente al paciente para que continúe el tratamiento en su domicilio mediante cefadroxilo por vía oral (2 semanas más). Si por el contrario, la enfermedad a las 72 horas no ha resuelto, se realizarán nuevas pruebas diagnósticas y se manejará la enfermedad de manera más minuciosa.

En el **grupo B**, si se considera que la enfermedad ha resuelto, se continuará con la terapia oral domiciliaria hasta completar 3 semanas de duración. Si por el contrario, la enfermedad a las 72 horas se considera no resuelta, el paciente pasará a realizar la pauta de tratamiento estándar.

Cabe destacar que en ambos grupos de tratamiento se harán las evaluaciones clínicas establecidas dentro del manejo estándar de la enfermedad a las 72 horas tras el inicio del tratamiento y a los 30 días, 2 meses y 6 meses post-tratamiento.

Objetivo

El principal objetivo es determinar que la proporción de resolución de la enfermedad es al menos la misma en los pacientes que reciben tratamiento exclusivo oral comparado con los que reciben tratamiento intravenoso asociado a oral. Además, se analizarán las complicaciones asociadas al tratamiento intravenoso, así como la proporción de curación definitiva de la enfermedad, de recurrencias de la misma, de fallo terapéutico y la necesidad de estancia hospitalaria comparando ambos grupos de tratamiento.

Beneficios y riesgos asociados a la participación en el estudio

Los dos fármacos estudiados en este ensayo clínico (cefazolina y cefadroxilo) están comercializados y se utilizan en el tratamiento de la osteomielitis, si bien es cierto que el cefadroxilo se utiliza actualmente tras una pauta de 5 días de cefazolina.

A pesar de esto, se vienen haciendo muchos estudios que cada vez tienden a reducir más la duración del tratamiento intravenoso (algunos llegan a los 2-3 días), de manera que no resulta desproporcionado esperar la resolución de la enfermedad utilizando exclusivamente cefadroxilo. En cualquier caso, debido a que es un fármaco que no está estandarizado para el

tratamiento de la osteomielitis durante todo su curso, decidimos realizar esta pauta terapéutica siguiendo unos criterios de inclusión y exclusión a nuestro estudio muy definidos y estrictos, de manera que solo aquellos casos que sean claramente no complicados y que, por tanto, tienden a resolver más fácilmente, son los que se incluyen en el ensayo clínico. Además, para evitar riesgos asociados, se informará adecuadamente al niño/a o representante legal del mismo en referencia a los posibles signos y síntomas indicativos de empeoramiento de la enfermedad, teniendo en cuenta que además se realiza un control muy estrecho, siguiendo visita a las 72 horas y controlando cada 10 días la PCR sanguínea durante la terapia para asegurar un buen control de la enfermedad. En caso de que existiera alguna duda acerca de una posible no respuesta al tratamiento, ese paciente pasaría inmediatamente a recibir el tratamiento estándar.

Póliza de seguro

El promotor del estudio dispone de una póliza de seguro que se ajusta a la legislación vigente y que le proporcionará la compensación e indemnización correspondiente en caso de detrimento de la salud de su hijo/a o representado/a que pueda aparecer como consecuencia de participar en el ensayo clínico.

Protección de datos

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ajustará a la *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*. De acuerdo a ésta ley, usted podrá ejercer los derechos de acceso, modificación, oposición y cancelación de estos datos.
Los datos recogidos para el estudio estarán identificados mediante un código y solo los investigadores podrán relacionar estos datos con su hijo/a o representado/a. El nombre de su hijo/a o representado/a, en ningún caso aparecerá en la publicación de los resultados.
El acceso a la información personal de su hijo/a o representado/a quedará restringido a los investigadores, autoridades sanitarias y al Comité de Ética de Investigación Clínica, manteniendo siempre la confidencialidad.

Compensación económica

Los investigadores no obtendrán beneficio económico alguno procedente de este estudio. Además, ni usted, ni su hijo/a o representado/a recibirán remuneración por el hecho de participar en el mismo, teniendo en cuenta que tampoco les supondrá ningún gasto. Además, los medicamentos del ensayo clínico no tendrán que ser pagados por usted.

Información adicional

Si usted decidiese en algún momento del proceso retirar el consentimiento para que su hijo/a o representado/a participe en el ensayo clínico, ningún dato será añadido a la base de datos, pudiendo usted exigir la destrucción de todas las muestras identificables.
Además, debe conocer la posibilidad de que su hijo/a o representado/a pueda ser excluido del estudio si los investigadores lo consideran necesario.

Annex 5. Informed consent document

DOCUMENTO DE CONSENTIMIENTO INFORMADO PARA PARTICIPAR EN EL ENSAYO CLÍNICO

Yo, _____ , con DNI _____ , como padre, madre o representante legal del niño/niña _____ declaro:

- Haber leído y comprendido la hoja informativa sobre el estudio que se me ha entregado.
- Haber podido realizar todas las cuestiones necesarias respecto al estudio.
- Haber sido informado/a de las implicaciones y objetivos del estudio.
- Entender que la participación de mi hijo/a o representado/a en el estudio es voluntaria y no remunerada.
- Entender que se respetará la confidencialidad de los datos de mi hijo/a o representado/a.
- Entender que puedo revocar el consentimiento sin necesidad de justificación y sin que conlleve modificación alguna en mi asistencia sanitaria.
- Haber comprendido los posibles riesgos asociados a la participación de de mi hijo/a o representado/a en este estudio.
- Comprometerme a cumplir con la adherencia al tratamiento oral pautado en mi domicilio tal y como se establece en el protocolo.

Deseo recibir información vía telefónica o por correo electrónico sobre los futuros resultados del estudio:

SÍ ☐ NO ☐

	Dirección de correo electrónico	Número de teléfono
Medios de contacto:	.....	.....

Por todo ello, otorgo mi consentimiento para participar en este estudio y estoy de acuerdo en que la información obtenida en este ensayo clínico pueda ser utilizada en investigaciones futuras sobre el manejo de la osteomyelitis aguda no complicada en el niño.

Firma del padre/ madre/ representante legal Firma del investigador

Fecha: ..... de ..... de 20...