Cefpodoxime proxetil as a therapeutic option in switching therapy for infective endocarditis in children – case reports and literature review

Nina Krajcar[1], Lorna Stemberger Marić[1,2], Dalibor Šarić[3], Neven Milić[4], Goran Tešović[1,5]

[1]*University Hospital for Infectious Diseases „Dr. Fran Mihaljević“, Zagreb, Croatia*

[2]*School of Dental Medicine, University of Zagreb, Zagreb, Croatia*

[3]*University Hospital Centre Zagreb, Zagreb, Croatia*

[4]*General Hospital Zadar, Zadar, Croatia*

[5]*School of Medicine, University of Zagreb, Croatia*

Corresponding author:

Nina Krajcar, MD

e-mail: ninakrajcar@gmail.com

+385 91 4012 618

ORCID iD: 0000-0003-3816-8100

Notes on contributors:

Nina Krajcar, MD, works at the Pediatric Infectious Disease Department, University Hospital for Infectious Diseases „Dr. Fran Mihaljević“ in Zagreb, Croatia. She conceived the paper and wrote the article.

Lorna Stemberger Marić, MD, PhD, works at the Pediatric Infectious Disease Department, University Hospital for Infectious Diseases „Dr. Fran Mihaljević“ in Zagreb, Croatia. She wrote the article in part and revised the article.

Dalibor Šarić, MD, works as a pediatric cardiologist at the University Hospital Centre Zagreb, Croatia, and he revised the article.

Neven Milić, MD, is a pediatric cardiologist at the General Hospital Zadar, Croatia and he revised the article.

Goran Tešović, MD, PhD, is a specialist in Adult and Pediatric Infectious Diseases and Assistant Professor of Infectious Diseases at the University of Zagreb Medical School. He is also Head of the Pediatric Infectious Diseases Department at the University Hospital for Infectious Diseases „Dr. Fran Mihaljević“ in Zagreb, Croatia. He conceived the paper, wrote the article in part and revised the article.

Abstract

Infective endocarditis (IE) is uncommon in children, affecting predominantly subjects with congenital heart disease (CHD) and patients with indwelling central lines. The principles of antibiotic treatment in pediatric population are similar to those in adults. Prolonged intravenous administration of bactericidal rather than bacteriostatic agents is preferred. Outpatient intravenous therapy after initial treatment in the hospital may be considered only in selected patients. Partial oral treatment has been described in cases of left-sided, uncomplicated IE caused by common pathogens in adult patients. There are no guidelines or trials in pediatric population regarding switching therapy from intravenous to oral route. We present two cases of IE in children caused by uncommon pathogenic bacteria (*Abiotrophia defectiva* and *Haemophilus parainfluenzae*) successfully treated with oral third-generation cephalosporin - cefpodoxime proxetil after initial intravenous therapy. This paper provides observations on different therapeutic approach for IE in children as well as another potential use of cefpodoxime proxetil.

Keywords: cefpodoxime proxetil, infective endocarditis, oral therapy, children, *Abiotrophia defectiva*, *Haemophilus parainfluenzae*

Introduction

In the last two decades, congenital heart disease (CHD) has been the predominant underlying condition for IE in children older than two years of age residing in developed countries. Children with central venous catheters, especially newborns, are at higher risk for developing IE as well [1]. The incidence of IE in this time period has remained unchanged, but a slight shift towards community acquired IE has been noticed [2]. Interestingly, in up to 10% of all cases of IE diagnosed in children, there are no structural cardiac disease or identifiable risk factors present [1]. Among children with underlying CHD, *Streptococcus* and *Staphylococcus* spp are equally and the most frequently isolated pathogens, while in patients with structurally normal heart, *Staphylococcus aureus* causes approximately 50% of cases [3]. The isolation of the causative microorganism accompanied by susceptibility testing is crucial for appropriate antimicrobial treatment. Although dosage and, in some cases, the choice of antibiotics for children differs from those in adults, general therapeutic principles and duration of antibiotic treatment remain similar for all age groups. The recommendations for the duration of antimicrobial treatment are mainly based on the characteristics of the infecting organism and usually last for 4-8 weeks. General consensus is that the antibiotic should be given intravenously and the outpatient intravenous treatment can be considered only in selected patients after initial treatment in the hospital. Oral antibiotics can be the convenient alternative in adults with limited options for effective intravenous therapy (resistant bacteria or patients with multiple allergies) or when prolonged intravenous access is not possible or is undesirable (intravenous drug users). However, the role of oral therapy in treating IE is not well established and reports about switching therapy from intravenous (IV) to oral during treatment are still lacking,

especially in pediatric population.

This paper gives observations on two children with IE caused by unusual bacteria treated with oral third-generation cephalosporin after initial IV therapy. Additionally, these cases give further information about the efficacy and safety of cefpodoxime proxetil as the treatment option for pediatric IE.

Case presentation

Case 1

A previously healthy 5.5-year-old girl was admitted to the Pediatric Department at the University Hospital for Infectious Diseases (UHID) in Zagreb, Croatia, following a 46-day history of low-grade fever and fatigue. Her past medical history was unremarkable. Empirical treatment with oral cefixime was started early in the course of illness. During treatment her symptoms resolved, but soon after discontinuation of therapy the fever relapsed. Diagnostic tests obtained in a local hospital where she was first examined, revealed positive IgM and negative IgG antibody to cytomegalovirus (CMV). Laboratory findings showed slightly elevated liver enzymes and she was discharged with the diagnosis of a recent CMV infection. As her symptoms persisted for the next 3 weeks, she presented to our pediatric emergency department. On physical examination, she was well-appearing with normal vital signs and low-grade fever (37.5ºC). Cardiovascular examination demonstrated systolic murmur grade II/VI along the left sternal border. The liver and spleen were both palpable for 3 cm below the costal margins. The initial laboratory investigations revealed slightly elevated C-reactive protein (14.2 mg/L), mild anemia (hemoglobin 9.9 g/dL; hematocrit 30.2%) with normal erythrocyte sedimentation rate (10 mm/hour), WBC count (5200 cells⁄microL,

ANC 3614 /microL) and platelet count (240 000 /microL). Liver and renal function tests were within normal ranges. Repeated serological test for CMV gave completely negative results. Chest radiography revealed cardiac enlargement and abdominal ultrasound confirmed hepatosplenomegaly. Culture of blood drawn on the first visit to UHID yielded *Abiotrophia defectiva* and intravenous ampicillin (300 mg/kg/day divided q6h) and gentamicin (7 mg/kg/day divided q8h) were initiated. The patient became afebrile following the 1st day of treatment and her fatigue resolved within a week. Although vegetations or abscesses were not detected, transthoracic echocardiogram (TTE) showed previously undiagnosed small patent ductus arteriosus. Based on this echocardiographic finding, the isolation of *A. defectiva* from 5 sets of blood cultures and clinical presentation, subacute endocarditis was diagnosed. On the 5th day of treatment, *A. defectiva* isolate was found to be sensitive to cephalosporins and ampicillin was changed to ceftriaxone (100 mg/kg/day divided q12h). After 18 days of combined IV therapy, the treatment was switched to oral cefpodoxime proxetil (10 mg/kg/day divided q12 h) for 6 weeks in total. All blood cultures drawn after the initiation of treatment with ceftriaxone remained sterile. The treatment with cefpodoxime proxetil was well tolerated and there were no adverse events related to drug therapy. Transcatheter closure of PDA was done 3 months after treatment completion. The patient recovered completely and at the cardiology follow-up visit after another 2 months no sequelae or relapses of the disease were found.

Case 2

A 6.5–year-old male child was admitted to the UHID on the 26th day of febrile illness. The patient had a history of congenital heart disese and underwent surgical conduit replacement after total correction of the truncus arteriosus communis (type I according

to Collett and Edwards) by Rastelli procedure 5 years prior to current illness. On the 1st day of acute onset of a high-grade fever up to 40 ºC, a 14-day course of oral amoxicillin/clavulanate therapy was started. Other symptoms included headache, sore throat, abdominal pain and vomiting. After three days of therapy the fever resolved, but on the 12th day of disease, fever increased up to 39 ºC accompanied with night sweats and chills. The treatment was switched to oral cefuroxime axetil but without any clinical effect. On the 21st day of illness, the patient was hospitalised in a local hospital in Coastal Croatia with presumptive diagnosis of infective endocarditis and empiric intravenous therapy with vancomycin and meropenem was initiated. The patient became afebrile the following day but diagnostic tests didn´t confirm the diagnosis of endocarditis therefore he was transferred to the UHID. On admission, the patient was well-appearing, afebrile and with normal vital signs. Physical examination revealed a pansystolic murmur best heard over the 3rd and the 4th left intercostal spaces. The patient's WBC count was 7000 /microL and his C-reactive protein level was 20.6 mg/L. In the next 3 days the antibiotic therapy was discontinued and several blood cultures were obtained which were all negative. On the 4th day of hospitalization, the patient became febrile again, up to 39.1 ºC.The laboratory findings showed elevated C-reactive protein (234.3 mg/L) and erythrocyte sedimentation rate (85 mm/hour). Furthermore, mild anemia (RBC 3.78 x10^6/microL; hemoglobin 9.4 g/dL; hematocrit 28.6%) and thrombocytopenia (127 000 /microL) were registered. After blood cultures were collected, the treatment with vancomycin (45 mg/kg/day divided q8h) and ceftriaxone (80 mg/kg/day in one daily dose) was initiated. The patient`s clinical condition improved rapidly and he became afebrile within 48 hours. Despite the fact that TTE as well as heart MR imaging didn`t reveal vegetations, infective endocarditis could not have been eliminated due to dysplastic aortic valve and degenerated conduit. PCR

analysis of blood, using primers targeting the 16S rDNA sequence, was negative as well as the results of serologic examinations for Q fever and *Brucella*. However, one blood culture taken during febrile episode came positive for *Haemophilus parainfluenzae*. Since the organism was sensitive to third-generation cephalosporins, 9 days after the initiation vancomycin was discontinued and ceftriaxone monotherapy was administered for the next 6 days. Intravenous treatment was followed by oral cefpodoxime proxetil (10 mg/kg/day divided q12 h) for 6 weeks in total. Blood cultures drawn during and after IV therapy remained negative and the patient was discharged with full recovery. In the following two years after hospital discharge, the patient was in good condition, afebrile, without complaints and relapses of IE.

Discussion

Long-term parenteral treatment of IE represents a significant practical problem (risk of catheter-related infections, prolonged hospital stay) resulting with discomfort and anxiety in pediatric patients. Intravenous antibiotics are considered principal in the treatment of IE because they achieve rapid therapeutic concentrations in blood and perfused tissues and they are generally regarded as more potent and reliable than their oral equivalents. Although IV treatment remains the first choice for IE, few studies have showed that in uncomplicated cases of IE oral treatment could be effective and safe.

Oral combination of ciprofloxacin and rimfapicin has showed efficacy in the right-sided *S. aureus* IE in adults in one randomized trial and one observational study [4,5]. This therapeutic strategy was associated with a favorable clinical outcome even in complicated left-sided endocarditis, but generally in a limited number of cases [6,7]. In a recently published retrospective study conducted in France from 2002-2012, researchers evaluated the outcomes in 426 patients (of whom 3 children) treated for IE

with oral antibiotics after IV induction therapy [8]. The most common oral regimens were amoxicillin monotherapy or a combination of amoxicillin with clindamycin, a fluoroquinolone or rifampicin. The results showed that switching to peroral therapy was not associated with attributable risk for relapse or reinfection. However, patients in the oral group received on average 3 weeks of IV treatment and they were less severely ill. Furthermore, another trial performed at cardiac centers in Denmark from 2011 to 2017 demonstrated similar results [9]. The study included 400 adults in stable condition with left-sided IE caused by streptococci, *Enterococcus faecalis*, *Staphylococcuss aureus* or coagulase-negative staphylococci. In all patients the antibiotic treatment was administered intravenously for at least 10 days. After a median of 17 days of IV therapy, 50% of all patients were treated orally for the next 19 days (range from 14 to 25 days). Results showed that changing to oral antibiotic treatment was noninferior to continuous intravenous antibiotic therapy.

To the best of our knowledge, no study has ever been published on IV/oral therapy switch for endocarditis in pediatric population, except the report of 14 episodes of subacute bacterial endocarditis in children treated in the 1960-1975 period [10]. All children reported were successfully treated, without relapses. No significant complications during treatment were recorded either. In 42% of cases the treatment was entirely oral and in other cases antibiotics were given parenterally just for the first 2 or 3 days. Contrary to our cases, there were no unusual bacteria isolated from blood and in all cases the causative pathogens were streptococci, staphylococci and enterococci. The most frequently used antibiotic was ampicillin, while in some patients different penicillin derivatives (cloxacillin, flucloxacillin, penicillin V) and erythromycin were given. Other studies in which oral ampicillin and amoxicillin were used for treating mainly streptococcal IE, reported high response rates [11,12].

Opposite to previously mentioned studies where cases of orally treated IE were caused by usual bacteria (*Streptococcus viridans*, *Enterococcus faecalis*, *Staphylococcuss aureus* or coagulase-negative staphylococci), in our patients uncommon microorganisms, *Abiotrophia defectiva* and *Haemophilus parainflunezae,* were isolated. Because of low bacterial virulence of these pathogens, we estimated that partial oral antibiotic treatment in reported cases was even more reasonable. *Abiotrophia defectiva*, formerly known as nutritionally variant streptococci (NVS) is a fastidious bacteria responsible for higher rates of complications than IE caused by other streptococci. Because of limited clinical data and reported high rates of resistance to penicillin, the American Heart Association (AHA) guidelines suggest treating NVS IE as enterococcal IE [1]. On the other hand, the European Society of Cardiology (ESC) guidelines differ slightly, as they recommend 6 weeks of benzylpenicillin, ceftriaxone or vancomycin, combined with an aminoglycoside for at least the first 2 weeks [13]. Additionally, the recommendations for the treatment of *Haemophilus parainflunezae* IE are similar to NVS IE and a 4-week course of ceftriaxone or another parenteral third-generation cephalosporin alone are recommended.

According to these guidelines, our patients were treated for the first 2 weeks with ceftriaxone combined with gentamicin or vancomycin. After a satisfactory clinical and laboratory response, the treatment was changed to oral cefpodoxime proxetil for another 4 weeks. This treatment option resulted in a complete recovery in both patients, without relapses of IE.

Cefpodoxime proxetil is an oral, third-generation cephalosporin, widely used for the treatment of upper (pharyngitis/tonsillitis, otitis media) and lower (pneumonia, bronchitis) respiratory tract infections (usually administered 8 to 10 mg/kg/day in 2 divided doses). It is a prodrug that is rapidly de-esterified in its active metabolite

cefpodoxime during absorption. Clinical studies have demonstrated extensive distribution of cefpodoxime trough tonsils, bronchial mucosa, lung parenchyma, pleural and interstitial inflammatory fluid [14]. Due to significant distribution of the drug in urine, periodontal (gingival tissue, alveolar bone) structures and skin, cefpodoxime proxetil can be an adequate therapeutic option for urinary tract, skin and soft tissue infections as well [14]. One clinical study conducted on piglets showed low (about 5%) penetration of cefpodoxime into cerebrospinal fluid (CSF), but the concentration of the drug in CSF exceeded MIC_{90} values for the majority of bacteria that are usually susceptible to this drug [15]. There are no reports regarding cefpodoxime distribution in endocardial vegetations nor possible use of this antibiotic in the setting of IE. Although oral bioavailability of the drug is about 50%, cefpodoxime shows low plasma protein binding (ranging from 18-23%) and the plasma concentration of the antibiotic remains above 0.5 mg/L for at least 8 hours after oral administration [14,16]. In children, peak plasma concentrations (range from 3.7 to 5.5 mg/L) are achieved approximately 2 hours after a single oral dose of cefpodoxime proxetil (6 mg/kg) [14]. In comparison, typical doses of oral amoxicillin (1g, q8h), which has excellent bioavailability (>90%) and low binding to serum proteins (17%), produce peak and 6-hour serum concentrations of 16 mg/L and 1.1 mg/L, respectively [7]. Because of favourable pharmacokinetic profiles in conjunction with the previously reported clinical efficacy, oral amoxicillin and penicillin V are considered a plausible alternative for the treatment of IE caused by susceptible bacteria, mainly streptococci. On the other hand, cefpodoxime has a broad bactericidal activity against a wide range of gram-positive and gram-negative pathogens, including *Streptococcus pneumoniae,* other streptococci (but not enterococci), *Haemophilus* spp. (including β-lactamase-producing strains) and *Moraxella catarrhalis*. Furthermore, pharmacodynamic/pharmacokinetic analyses

demonstrated that, compared to other cephalosporins (cefuroxime axetil, cefixime, ceftibuten), only cefpodoxime proxetil exceeds 90% of time above MIC_{90} values for susceptible pathogens (*Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus* spp.) [17]. Although streptococci continue to be the leading pathogens of IE, recent changes of attributable risk factors and causative, previously uncommon, pathogens for pediatric IE, have made cefpodoxime proxetil a reasonable alternative for oral treatment of IE.

In conclusion, our clinical experience provides evidence for successful therapy of uncomplicated IE with cefpodoxime proxetil in pediatric population and emphasize the need for further investigation of this therapeutic approach.

Funding:

The authors received no specific funding for this work.

Disclosure of interest:

The authors declare that they have no conflict of interest.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all parents of participants included in the study.

References

1.Baltimore, Gewitz M, Baddour LM, Beerman LB, Jackson MA, Lockhart PB, et al. Infective Endocarditis in Childhood: 2015 Update A Scientific Statement From the American Heart Association. Circulation. 2015;132:1487-515.

2. Kelchtermans J, Grossar L, Eyskens B, Cools B, Roggen M, Boshoff D, et al. Clinical Characteristics of Infective Endocarditis in Children. Pediatr Infect Dis J. 2018. Oct 30; doi:10.1097/INF.0000000000002212

3. Gupta S, Sakhuja A, McGrath E, Asmar B. Trends, microbiology, and outcomes of infective endocarditis in children during 2000-2010 in the United States. Congenit Heart Dis. 2017;12:196-201.

4. Heldman AW, Hartert TV, Ray SC, Daoud EG, Kowalski TE, Pompili VJ, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med. 1996;101:68-76.

5. Dworkin RJ, Lee BL, Sande MA, Chambers HF. Treatment of right-sided Staphylococcus aureus endocarditis in intravenous drug users with ciprofloxacin and rifampicin. Lancet. 1989;2:1071-3.

6. Demonchy E, Dellamonica P, Roger PM, Bernard E, Cua E, Pulcini C. Audit of antibiotic therapy used in 66 cases of endocarditis. Med Mal Infect. 2011;41:602-7.

7. Al-Omari A, Cameron DW, Lee C, Corrales-Medina VF. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. BMC Infect Dis. 2014;14:140.

8. Mzabi A, Kernéis S, Richaud C, Podglajen I,Fernandez-Gerlinger MP, Mainardi JL. Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non-severely ill patients. Clin Microbiol Infect. 2016;22:607-12.

9. Iversen K, Ihlemann N, Gill SU, Madsen T, Elming H, Jensen KT, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. N Engl J Med. 2018 Aug 28. doi: 10.1056/NEJMoa1808312.

10. Phillips B, Watson GH. Oral treatment of subacute bacterial endocarditis in children. Arch Dis Child. 1977; 52: 235-7.
11. Gray IR, Tai AR, Wallace JG, Calder JH. Oral Treatment of Bacterial Endocarditis with Penicillins. Lancet. 1964;2:110-14.
12. Chetty S, Mitha AS. High-dose oral amoxycillin in the treatment of infective endocarditis. S Afr Med J. 1988;73:709-10.
13. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Eur Heart J. 2009;30:2369-413.
14. Fulton B, Perry CM. Cefpodoxime proxetil: a review of its use in the management of bacterial infections in paediatric patients. Paediatr Drugs. 2001;3:137-58.
15. Abdel-Rahman SM, Maxson S, Teo C, Hubbard AE, Kearns GL. Cerebrospinal fluid pharmacokinetics of cefpodoxime proxetil in piglets. J Clin Pharmacol. 2000;40:290-5.
16. Tremblay D, Dupront A, Ho C, Coussediere D, Lenfant B. Pharmacokinetics of cefpodoxime in young and elderly volunteers after single doses. J Antimicrob Chemother. 1990;26:21-8.
17. Stoeckel K, Hayton WL, Edwards DJ. Clinical pharmacokinetics of oral cephalosporins. Antibiot Chemother. 1995;47:34-71.