Authors: Jason Webb, Michael Kheir, Randi Silibovsky

QUESTION 8: Can ceftriaxone be utilized as an alternative to cefazolin in the treatment of orthopaedic infections caused by methicillin-sensitive Staphylococcus aureus (MSSA)? If so, what dosing is recommended?

RECOMMENDATION: There is minimal data in the literature evaluating the use of ceftriaxone and its appropriate dosage to treat orthopaedic infections caused by MSSA. International guidelines state that there is no consensus on the use of ceftriaxone in the treatment of prosthetic joint infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

MSSA is a potent pathogen and a leading cause of orthopaedic infections including prosthetic joint infections (PJIs) [1]. The antibiotic standard of care therapy (SOCT) for MSSA infections includespenicillinase-resistant penicillins (nafcillin/oxacillin/flucloxacillin) with the first-generation cephalosporin, cefazolin, as an alternative [1–4]. For penicillin-allergic patients, the use of third- or fourth-generation cephalosporin or cephalosporins (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin, carries a negligible risk of cross-allergy and may be used in this specific instance for MSSA infections [5–7].

Cephalosporins are broad-spectrum antibiotics with structures based on the beta-lactam ring [8]. They are divided into generations. The first generation, which includes cefazolin (CFZ), are predominantly active against gram-positive bacteria. The third generation of cephalosporins, which includes ceftriaxone, have better activity against gram-negative organisms, but *reduced* activity against gram-positives. Ceftriaxone (CTX) is characterized by a prolonged half-life (eight hours) compared to other cephalosporins and this allows a once-daily dosing regimen [9]. This has proved convenient for certain medical indications including outpatient antibiotic therapy services [10–12]. One potential benefit of cephalosporins over penicillins is lower reported rates of adverse drug reactions for the former group of drugs in clinical studies [13,14] Weiland et al. [15] compared ceftriaxone versus oxacillin for MSSA osteoarticular infections in 124 patients and found no difference in treatment success at three to six months (83 vs. 86%, p = 0.7) and at > six months (77 vs. 81%, p = 0.6) following the completion of intravenous antibiotics. Furthermore, patients receiving oxacillin were more likely to have it discontinued due to toxicity.

The literature regarding the use of CTX as an alternative to CFZ in the treatment of MSSA infections is sparse, with only seven published studies providing direct comparison. These include five retrospective cohort descriptive studies and two prospective, double blinded, randomized controlled trials (RCTs). Of these, three are industry-funded by the manufacturer of CTX (Roche™, Basel, Switzerland) including one of the RCTs (which will be discussed first).

Mandell et al. [16] compared the efficacy of CTX vs. CFZ against various organisms, including gram-negatives, and showed no significant difference in clinical outcomes. Gugliemo et al. [17], in a retrospective cohort study of 31 patients, compared CTX against CFZ in various dosing regimens and found no significant difference in outcomes. Tice et al. [18] reported on the outcome of treating osteomyelitis with various antibiotic regimens in another retrospective cohort study of 454 patients. Despite there being no significant differences found in any of the treatment groups (potentially due to the lack of power in the study), they concluded that the outcome supported the use of CTX.

The independent studies similarly did not show any significant difference in treatment, perhaps due to their design and lack of statistical power. Winans et al. [12], in a well-performed retrospective study comparing the efficacy of CTX against CFZ in MSSA infections, showed no differences between the groups and advised the need for a large RCT. Grayson et al. [19], in an RCT studying the outcome of treating cellulitis with either CFZ combined with probenecid to allow once daily dosing against CTX, showed no significant differences in outcome. However, this study was underpowered. Paul et al. [20] showed a higher 30-day mortality rate in patients with MSSA bacteremia treated with CTX compared to CFZ or oxacillin but again the study lacked power.

In conclusion, there are no robustly-designed or suitably-powered clinical studies to answer the null hypothesis that CTX is as effective as CFZ in treating MSSA infections.

A few experimental and animal studies, however, provide useful additional information. Cephalosporins are known to be protein bound in serum and this is thought to mediate the inoculum effect that increases their minimum inhibitory concentration (MIC). This is described by the developers of CTX based on their in vitro and in vivo data [9] and corroborated by Tawara et al. [21] in their animal study that shows that CTX has higher protein binding than CFZ and this may explain the consistently recorded MICs that CTX has over CFZ against MSSA species.

This leads onto dosing considerations. Due to the protein binding of CTX, numerous authors have suggested that higher dosing regimens are required with experimental data in support [4,21–23]. CTX is licensed at doses of 1 to 2 gm per day, but the studies above suggest that doubling this dose to 2 gm twice a day may be necessary to overcome the protein binding effect [22–24]. Nguyen et al. [25] argues that 2 gm per day is the appropriate dosing, given that the US Food and Drug Administration recommends a ceftriaxone dosage for MSSA of 2 to 4 gm per day based on pharmacodynamic analysis.

In summary, there is no robust data to support the use of ceftriaxone instead of cefazolin in the management of orthopaedic MSSA infections. Infectious diseases leaders also hold this opinion worldwide [1,25,26]. There is a need for multi-center RCTs to answer this question definitively.

Search Methodology: A comprehensive literature review was performed to identify all studies on the use of ceftriaxone in the treatment of orthopaedic infections caused by MSSA. The Medical Subject Headings (MeSH) search strategy included the following terms: (“ceftriaxone*”AND/OR “cefazolin*”) AND (“MSSA*” OR “*Staphylococcus aureus**” OR “orthopaedic infections*”) in various combinations and with different Boolean operators. The search engines used were: Cochrane, Embase, PubMed, Medline, Google Scholar and Web of Science. The search was conducted for studies through February 2018. Inclusion criteria for our systematic review were all English studies (level I to IV evidence) that reported on ceftriaxone use in treating orthopaedic infections caused by MSSA. Exclusion criteria were non-English language articles, studies > ten years old, nonhuman studies,

retracted papers, case reports, review papers, studies with less than ten patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search results in excess of 1,000 papers. After removal of duplicates and screening of titles and abstracts, 69 full reports were assessed and reviewed.

REFERENCES

[1] Darley ESR, MacGowan AP. Antibiotic treatment of gram–positive bone and joint infections. J Antimicrob Chemother. 2004;53:928–935. doi:10.1093/jac/dkh191.

[2] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1–25. doi:10.1093/cid/cis803.

[3] Meehan J, Jamali AA, Nguyen H. Prophylactic antibiotics in hip and knee arthroplasty. J Bone Joint Surg Am. 2009;91:2480–2490. doi:10.2106/JBJS.H.01219.

[4] Sharff KA, Graber CJ, Spindel SJ, Nguyen HM. Ceftriaxone for methicillin–sensitive staphylococcus aureus osteoarticular infections: A survey of infectious disease physicians' attitudes and review of the literature. Infect Dis Clin Pract. 2014;22:132–140. doi:10.1097/IPC.0000000000000109.

[5] Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin–allergic patients: a literature review. J Emerg Med. 2012;42:612–620. doi:10.1016/j.jemermed.2011.05.035.

[6] Pichichero ME. Use of selected cephalosporins in penicillin–allergic patients: a paradigm shift. Diagn Microbiol Infect Dis. 2007;57:13S–18S. doi:10.1016/j.diagmicrobio.2006.12.004.

[7] Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin–allergic patients: a meta–analysis. Otolaryngol Head Neck Surg. 2007;136:340–347. doi:10.1016/j.otohns.2006.10.007.

[8] Bryan JP. Cephalosporins and carbapenems. Curr Opin Infect Dis. 1991;4:727.

[9] Angehrn P, Probst PJ, Reiner R, Then RL. Ro 13–9904, a long–acting broad–spectrum cephalosporin: in vitro and in vivo studies. Antimicrob Agents Chemother. 1980;18:913–921.

[10] Patel UC, McKissic EL, Kasper D, Lentino JR, Pachucki CT, Lee T, et al. Outcomes of ceftriaxone use compared to standard of therapy in methicillin susceptible staphylococcal aureus (MSSA) bloodstream infections. Int J Clin Pharm. 2014;36:1282–1289. doi:10.1007/s11096–014–9999–5.

[11] Seaton RA, Sharp E, Bezlyak V, Weir CJ. Factors associated with outcome and duration of therapy in outpatient parenteral antibiotic therapy (OPAT) patients with skin and soft–tissue infections. Int J Antimicrob Agents. 2011;38:243–248. doi:10.1016/j.ijantimicag.2011.05.008.

[12] Winans SA, Luce AM, Hasbun R. Outpatient parenteral antimicrobial therapy for the treatment of methicillin–susceptible Staphylococcus aureus: a comparison of cefazolin and ceftriaxone. Infection. 2013;41:769–774. doi:10.1007/s15010–013–0477–0.

[13] Wynn M, Dalovisio JR, Tice AD, Jiang X. Evaluation of the efficacy and safety of outpatient parenteral antimicrobial therapy for infections with methicillin–sensitive staphylococcus aureus. South Med J. 2005;98:590–595. doi:10.1097/01.SMJ.0000145300.28736.BB.

[14] Duncan CJA, Barr DA, Seaton RA. Outpatient parenteral antimicrobial therapy with ceftriaxone, a review. Int J Clin Pharm. 2012;34:410–417. doi:10.1007/s11096–012–9637–z.

[15] Wieland BW, Marcantoni JR, Bommarito KM, Warren DK, Marschall J. A retrospective comparison of ceftriaxone versus oxacillin for osteoarticular infections due to methicillin–susceptible staphylococcus aureus. Clin Infect Dis. 2012;54:585–590. doi:10.1093/cid/cir857.

[16] Mandell LA, Bergeron MG, Ronald AR, Vega C, Harding G, Saginur R, et al. Once–daily therapy with ceftriaxone compared with daily multiple–dose therapy with cefotaxime for serious bacterial infections: a randomized, double–blind study. J Infect Dis. 1989;160:433–441.

[17] Guglielmo BJ, Luber AD, Paletta D, Jacobs RA. Ceftriaxone therapy for staphylococcal osteomyelitis: a review. Clin Infect Dis. 2000;30:205–207. doi:10.1086/313620.

[18] Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. J Antimicrob Chemother. 2003;51:1261–1268. doi:10.1093/jac/dkg186.

[19] Grayson ML, McDonald M, Gibson K, Athan E, Munckhof WJ, Paull P, et al. Once–daily intravenous cefazolin plus oral probenecid is equivalent to once–daily intravenous ceftriaxone plus oral placebo for the treatment of moderate–to–severe cellulitis in adults. Clin Infect Dis. 2002;34:1440–1448. doi:10.1086/340056.

[20] Paul M, Zemer–Wassercug N, Talker O, Lishtzinsky Y, Lev B, Samra Z, et al. Are all beta–lactams similarly effective in the treatment of methicillin–sensitive staphylococcus aureus bacteraemia? Clin Microbiol Infect. 2011;17:1581–1586. doi:10.1111/j.1469–0691.2010.03425.x.

[21] Tawara S, Matsumoto S, Kamimura T, Goto S. Effect of protein binding in serum on therapeutic efficacy of cephem antibiotics. Antimicrob Agents Chemother. 1992;36:17–24.

[22] Kang N, Housman ST, Nicolau DP. Assessing the surrogate susceptibility of oxacillin and cefoxitin for commonly utilized parenteral agents against methicillin–susceptible staphylococcus aureus: focus on ceftriaxone discordance between predictive susceptibility and in vivo exposures. Pathogens. 2015;4:599–605. doi:10.3390/pathogens4030599.

[23] Housman ST, Sutherland CA, Nicolau DP. Pharmacodynamic profile of commonly utilised parenteral therapies against meticillin–susceptible and meticillin–resistant staphylococcus aureus collected from US hospitals. Int J Antimicrob Agents. 2014;44:235–241. doi:10.1016/j.ijantimicag.2014.05.012.

[24] Coiffier G, Albert JD. Is ceftriaxone 2 g once daily a valid treatment option for osteoarticular infections due to staphylococcus spp., streptococcus spp., and gram–negative rods? Joint Bone Spine. 2014;81:200–202. doi:10.1016/j.jbspin.2014.02.004.

[25] Nguyen HM, Jones RN. Treatment of methicillin–susceptible staphylococcus aureus osteoarticular and prosthetic joint infections: using the oxacillin minimum inhibitory concentration to guide appropriate ceftriaxone use. Clin Infect Dis. 2013;57:161–162. doi:10.1093/cid/cit188.

[26] Marschall J, Lane MA, Beekmann SE, Polgreen PM, Babcock HM. Current management of prosthetic joint infections in adults: results of an Emerging Infections Network survey. Int J Antimicrob Agents. 2013;41:272–277. doi:10.1016/j.ijantimicag.2012.10.023.