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Pharmacodynamics of Ceftriaxone versus Cefazolin and Alternatives as Out–Patient Parenteral Antimicrobial Therapy for Methicillin-Susceptible *Staphylococcus aureus* Infections

Sheryl Zelenitsky[1,2], Nathan Beahm[3,4], Rob Ariano[1,2], Harris Iacovides[1,2], George Zhanel[1]

[1]University of Manitoba, Winnipeg, MB, Canada, [2]St. Boniface Hospital, Winnipeg, MB, Canada,
[3]University of Alberta, Edmonton, AB, Canada, [4]Yorkton Regional Health Centre, Yorkton, SK, Canada

Dr. Sheryl Zelenitsky
Professor, College of Pharmacy
Rady Faculty of Health Science
University of Manitoba, Winnipeg, Canada
zelenits@umanitoba.ca

BACKGROUND

- Due to convenient dosing, ceftriaxone is often used as OPAT even when broad–spectrum therapy is not required [eg, methicillin–susceptible *S. aureus* (MSSA) infections]. Once–daily dosing along with high "susceptibility" rates may even lead to the selection of ceftriaxone for treating presumed or actual MSSA infections in hospitalized patients.
- Since antimicrobial pharmacodynamics (PDs) are dependent on actual MIC distributions, the activity of ceftriaxone may be compromised compared with other options such as cefazolin. As OPAT, however, cefazolin presents less convenient, thrice–daily dosing.
- **GOAL:** To use an integrated pharmacokinetic (PK)–PD analysis to evaluate ceftriaxone and alternatives as OPAT for MSSA infections.

METHODS

- Monte Carlo simulations (MCSs) were used to create cohorts of 5,000 study subjects using SYSTAT® (v12). Ceftriaxone[1] and cefazolin,[2-4] and if contraindicated, alternatives including vancomycin,[5] daptomycin[6] and linezolid[7] were tested using published PK models to simulate free (f) plasma concentration profiles in a relevant patient population (75 ± 10 kg, Cl_{cr} 50–100 mL/min/72 kg).
- Robust MIC distributions were based on data from 6,490 MSSA isolates collected from patients in13 Canadian hospitals from 2007 to 2015.
- PD targets for ceftriaxone and cefazolin were >50%$fT_{>MIC}$ (bacteriostatic), >75%$fT_{>MIC}$ (1–2 log kill), and 100%$fT_{>MIC}$ (bactericidal) based on literature values and previous *in vitro* PD modeling studies.[8]
- PD targets for vancomycin, daptomycin and linezolid were an $AUC_{T(total)}$/MIC >400, >800 and >80, respectively.
- Predicted target attainment (TA) for each MIC was calculated as the fraction of 5,000 simulated subjects achieving target. Cumulative target attainment (CTA) was determined by multiplying the PTA at each MIC by the fraction of isolates at that MIC, and then adding the values.
- CTA was considered optimal when the PD target was achieved in at least 90% of simulated subjects.

RESULTS

- The subject body weights and PK parameters generated by MCS are detailed in **Figure 1** and **Table 1**, respectively. The MIC distribution of MSSA isolates is described in **Table 2**.
- Ceftriaxone 2 g q24h attained PD targets for bacteriostatic, 1–2 log kill and bactericidal activity in 86%, 46%, and 17% of cases, respectively. **[Figure 2]** Ceftriaxone 1 g q12h reached these targets in 92%, 78%, and 57%, respectively. **[Figure 3]** As such, ceftriaxone 2 g once–daily did not even achieve optimal target attainment for bacteriostatic therapy. Although ceftriaxone 1 g twice–daily reached optimal target attainment for bacteriostasis, it was still inadequate for bacterial kill.
- Cefazolin 2 g q24h attained PD targets for bacteriostatic, 1–2 log kill and bactericidal activity in 96%, 50%, and 15% of cases, respectively. **[Figure 2]** Cefazolin 2 g q12h reached these targets in 100%, 100%, and 97%, respectively. **[Figure 3]** Hence cefazolin 2 g once–daily achieved optimal target attainment for bacteriostasis, and cefazolin 2 g twice–daily was optimal for bactericidal therapy.
- The influence of renal function on the PDs of ceftriaxone and cefazolin is depicted in **Figure 4**.
- Of the alternatives, vancomycin 1 g q12h (2 g/day) and 1 g q8h (3 g/day) attained AUC_T/MICs >400 in 81% and 100% of simulated subjects, respectively. Daptomycin 4 and 6 mg/kg q24h achieved AUC_T/MICs >800 in 96% and 100% of cases, respectively, whereas linezolid 600 mg q12h reached AUC_T/MICs >80 in 77%.

Table 1: PK parameters (n = 5,000, Cl_{cr} 50–100)

	Vd (L)	$t_{1/2}$ (h)	free (%)	CL (L/h)
Ceftriaxone	12.8 ± 2.6	9.2 ± 1.6	7.5 ± 0.26	–
Cefazolin	11.3 ± 2.3	3.2 ± 1.8	18.0 ± 0.61	–
Vancomycin	–	–	–	4.5 ± 0.97
Daptomycin	–	–	–	0.8 ± 0.12
Linezolid	–	–	–	6.8 ± 1.03

Table 2: MSSA MICs (mg/L, n = 6, 490)

	MIC_{50}, MIC_{90} (range)
Ceftriaxone	4, 4 (1-8)
Cefazolin	0.5, 1 (0.5-1)
Vancomycin	1, 1 (0.25-1)
Daptomycin	0.25, 0.25 (0.06-0.5)
Linezolid	2, 2 (0.5-4)

Fig 1: Body weight (n = 5,000)

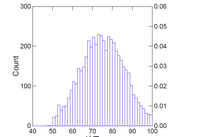


Figure 2: Cumulative target attainment (CTA) of once–daily ceftriaxone and cefazolin (Cl_{cr} 50–100 mL/min/72 kg)

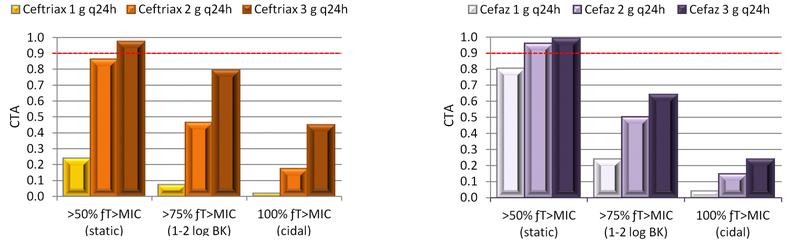


Figure 3: Cumulative target attainment (CTA) of twice–daily ceftriaxone and cefazolin (Cl_{cr} 50–100 mL/min/72 kg)

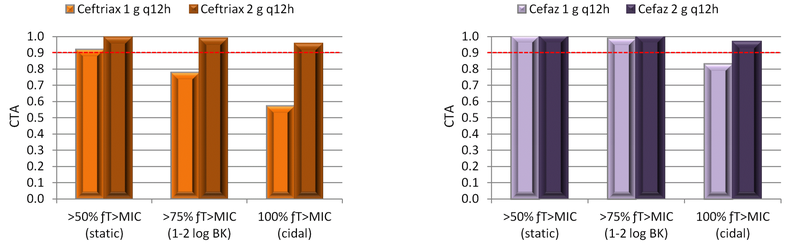
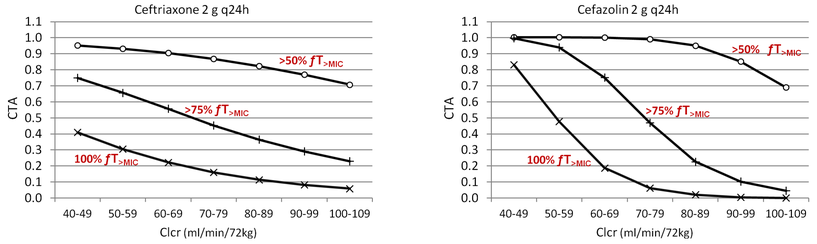


Figure 4: Effects of renal function on cumulative target attainment (CTA) of once–daily ceftriaxone and cefazolin



CONCLUSIONS

- ✓ Although convenient, once-daily ceftriaxone has poor PD activity against MSSA and exposes patients to unnecessary broad–spectrum antibiotic therapy.
- ✓ Once–daily ceftriaxone was inadequate even for bacteriostasis, and was actually inferior to once–daily cefazolin. [Fig 2]
- ✓ Twice–daily cefazolin achieved optimal PD targets even for bactericidal therapy, offering a more convenient option than the traditional thrice–daily dosing. [Fig 3]
- ✓ Since renal function influences the PD activity of cefazolin, [Fig 4] Cl_{cr} should be considered in selecting appropriate dosing (eg, once–daily or twice–daily) or if strategies such as adding probenecid would be beneficial.
- ✓ Of the alternatives, optimal PD targets could be achieved with vancomycin and daptomycin but not with linezolid.

REFERENCES:

[1] So *et al.* Infect Dis Ther 2014, [2] Sharma *et al.* AAPS Pham Sci Tech 2015, [3] Lavillaureix *et al.* Infect 1975, [4] Bhalodi *et al.* AAC 2013, [5] Rodvold *et al.* AAC 1998, [6] Dvorchik *et al.* AAC 2004, [7] Meager *et al.* AAC 2003, [8] Iacovides *et al.* 52nd ICAAC 2012