In vitro Activity of Ceftaroline and 11 Comparators against Pediatric *Staphylococcus aureus* and Pneumococcal isolates from 2007-2013, Focusing on Invasive and Antibiotic Resistant Strains

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SUBMITTED ABSTRACT

Background: Ceftaroline (CPT) is a parenteral cephalosporin FDA approved for adult use. It has bactericidal activity against *Staphylococcus aureus* (SA), both methicillin resistant (MRSA) and methicillin susceptible (MSSA), and pneumococci (SPN), including multi-drug resistant (MDR) 19A strains. To expand data on pediatric isolates, we assayed *in vitro* MICs of CPT for pediatric MSSA, MRSA and SPN.

Methods: From a repository with 1240 non-duplicate consecutive SA and SPN strains isolated at Children's Mercy Hospitals from pediatric patients during 2007-2013, 416 isolates have been tested to date. Susceptibility was assayed by CLSI broth microdilution testing against CPT and 11 comparators specific for each species. All SPN were serotyped by the Quellung method.

Results: Clindamycin resistant SA made up nearly 20% of both MSSA and MRSA, with most clindamycin resistant MSSA being D test positive. Among tested SA, CPT had MIC50/90 of 0.25/1 µg/mL. MRSA CPT MIC50/90values were higher than for MSSA (0.5/1 µg/mL vs. 0.25/0.5 µg/ml). For 230 invasive SA (59% MSSA), all were susceptible to vancomycin and linezolid; and 95% were susceptible to trimethoprim/sulfa. Among all SA (52% MRSA), MIC50/90 for linezolid was 1/2 µg/mL, for levofloxacin 0.25/4 µg/mL and for tetracycline 0.5/1 µg/mL.

Among SPN, 34% had penicillin MIC ≥2 µg/mL and 19% had penicillin MIC ≥0.1 but <2.0 µg/mL; 22% were ceftriaxone-nonsusceptible. All were vancomycin susceptible. For 186 SPN overall, CPT had MIC50/90 of ≤0.06/0.25 µg/mL. CPT MIC50/90 values were ≤0.06/0.125 µg/mL for clindamycin resistant and 0.25/0.5 µg/mL for ceftriaxone non-susceptible strains. Against penicillin-resistant SPN (≥2 µg/mL), MIC50/90 for CPT was 0.25/0.5 µg/mL, compared to 2/4 µg/mL for ceftriaxone, 4/8 µg/mL for cefuroxime, and 8/16 µg/mL for amoxicillin. Among the 69 serogroup-19 strains, MIC50/90 for CPT were 0.125/0.25 µg/mL

Conclusions: Against pediatric invasive SA isolates, CPT has potent *in vitro* activity vs. MRSA and MSSA, including isolates resistant to clindamycin, tetracycline or levofloxacin. CPT also has consistent activity vs. pediatric SPN including MDR serotype 19A strains.

BACKGROUND

S. pneumoniae (SPN) & *Staphylococcus aureus* (SA) are common pediatric pathogens with increased antibiotic resistance in the past 20 years.

Pneumococcal conjugate vaccines (PCV7, PCV13) were released in 2000 and 2010, respectively.

After PCV7 vaccine (type 4, 6B, 9V, 14, 18C, 19F, and 23F), serotype substitution caused emergence of multidrug-resistant (MDR) strains (mostly type 19A) prompting release of PCV13 (PCV7 serotypes plus 1, 3, 5, 6A, 7F, and 19A).

SA, methicillin-resistant (MRSA) and –susceptible (MSSA) is a frequent cause of invasive or soft tissue/bone infections.

Ceftaroline is active against MDR SPN and MSSA plus nearly all MRSA. Due to this and adult clinical data, the FDA approved ceftaroline fosamil for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infection in adults.

We report here results of *in vitro* testing of SPN and SA isolates from 2007 – 2013 in children from a Midwest freestanding children's hospital.

METHODS

- SPN or SA from children in Kansas City region up to 21YO
- From repository at Children's Mercy Hospital 2007-2013
- Assayed by standard CLSI broth microdilution method using frozen 96 well antibiotic testing plates
- SA: Mueller-Hinton broth (Remel, Lenexa KS)
- SPN: MHB with 5% lysed horse blood (Remel, Lenexa KS)
- Breakpoints for MIC interpretation from FDA or CLSI
- QC strains recommended by CLSI
  - SPN - ATCC 49619, SA - ATCC 29213
- Selected isolates confirmed by E-test (BioMerieux, Durham NC)

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Antibiotics and Concentrations in Assays:

ANTIBIOTIC	PATHOGEN	RANGE (µg/ml)
Ceftaroline (CPT)	SPN and SA	0.06 - 8
Amoxicillin	SPN	0.03 – 16
Amoxicillin-clavulanate	SA	0.03 – 16
Ceftriaxone	SPN and SA	0.06 – 8
Cefuroxime	SPN and SA	0.06 – 8
Cefdinir	SPN and SA	0.06 - 8
Azithromycin	SPN and SA	0.06 - 8
Clindamycin	SPN and SA	0.06 - 8
Trimethoprim - sulfamethoxazole	SPN and SA	0.125 – 16 Tmp in 1:19 ratio to sulfamethoxazole
Tetracycline	SA	0.125 – 4.0
Vancomycin	SPN and SA	0.25 – 8
Linezolid	SPN and SA	0.25 – 8
Levofloxacin	SPN and SA	0.25 – 8

RESULTS:

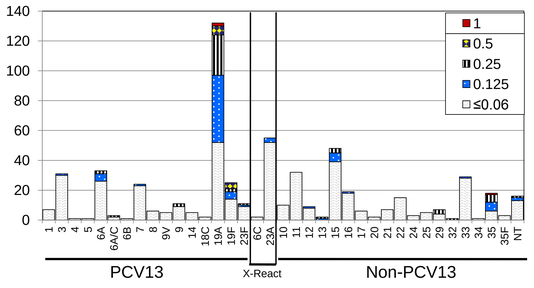
***Streptococcus pneumoniae* (SPN)**

- Patient mean age 42.5 months (0.1 – 184), 59% male
- 38% invasive, 44% noninvasive, 18% colonizing
- Of invasive: CSF=10%, blood=55%, empyema=19%, mastoid=14%, abscesses 10%
- 100% susceptible: vancomycin, linezolid, levofloxacin
- Ceftaroline was most active β-lactam
  - Table 1 shows all SPN, N-588
  - Table 2 shows the 132 type 19A subset of total 588
  - Figure 1 shows MICs by serotype
- Penicillin resistant (N=137): 72% were type 19A or 19F
  - CPT MIC50 = 0.125, MIC90 = 0.25µg/ml
  - Ceftriaxone MIC50 =1.0, MIC90 = 4.0 µg/ml
  - Amoxicillin MIC50 = 4.0, MIC90 = 8.0 µg/ml
- Ceftriaxone resistant (N=61): 90% type 19A or 19F
  - CPT MIC50 = 0.125, MIC90 = 0.5 µg/ml
- Clinda resistant (N=104): 83% were type 19A or 19F
  - Ceftriaxone MIC50 = 1.0 , MIC90 = 4.0 µg/ml
  - CPT MIC50 = 0.125,MIC90 = 0.25 µg/ml
  - Type 15 comprised 10% of clinda resistant strains

TABLE 1. All SPN N=588	% Resistant (criterion)	MIC50	MIC90
Ceftaroline	0.3 (>0.5)$	≤0.06	0.25
Penicillin	22.1 (≥2.0)	≤0.06	4.0
Amoxicillin	14.7 (>2.0)	≤0.06	4.0
Imipenem	9.9 (≥1.0)	≤0.06	0.5
Ceftriaxone	6.8 (≥2.0)	≤0.06	2.0
Cefuroxime	26.7 (≥2.0)	≤0.06	8.0
Cefdinir	38.6 (≥2/0)	≤0.06	>8.0
Azithromycin	41.8 (≥2.0)	0.5	8.0
Tmp/Smx	31.0 (≥4/76)	0.5/9.5	16/304
Clindamycin	22.1 (>0.25)	≤0.06	>8.0

TABLE 2. 19A SPN N=132	% Resistant (criterion)	MIC50	MIC90
Ceftaroline	2.2 (>0.5) $	0.125	0.25
Penicillin	63.5 (≥2.0)	≤0.06	4.0
Amoxicillin	17.4 (>2.0)	≤0.06	4.0
Imipenem	23.3 (≥1.0)	≤0.06	2.0
Ceftriaxone	17.9 (≥2.0)	1.0	4.0
Cefuroxime	67.4 (≥2.0)	4.0	>8.0
Cefdinir	74.2 (≥2.0)	4.0	>8.0
Azithromycin	75.6 (≥2.0)	4.0	>8.0
Tmp/Smx	74.2 (≥4/76)	4/76	16/304
Clindamycin	56.1 (>0.25)	>8.0	>8.0

$ SPN value for CPT is % nonsusceptible in Table 1 and 2



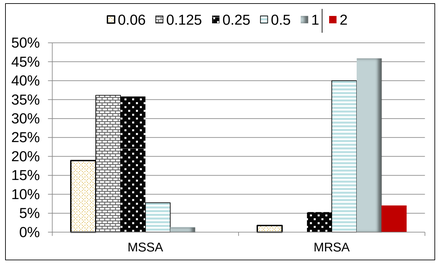
CPT FDA Susceptibility Breakpoint ≤0.5 mcg/mL

Figure 1. CPT MICs for SPN in mcg/mL by Serotype

RESULTS (continued):

***Staphyloccoccus aureus* (SA) (N=491)**

- Pt. mn age 73.8 months (0.3 – 228), 51% male
- 48.6% invasive, 49.2% noninvasive, 2% colonizing
- Of invasive: blood =91%, empyema = 4%, deep abscess = 3%, joint/bone 2%
- Noninvasive : >90% pyoderma, abscess or furuncle
- Overall SA Susceptibility:
  - 100% S to vancomycin, linezolid
  - 97% S to Tmp/Smx and 95% to tetracycline
- Ceftaroline was the most active β-lactam (Fig 2)
  - MIC50/90 = 0.25/1.0 µg/ml
- MSSA (N=291) Susceptibility - Table 3
  - 100% Susceptible to Amox/clav, cefuroxime, cefdinir, ceftaroline
  - D-test results added 55 isolates to clindamycin resistant group
- MRSA (N=200) Susceptibility - Table 4
  - 94% susceptible to ceftaroline
  - D-test results added 10 isolates to clindamycin resistant group
- Clindamycin Resistant MSSA + MRSA Strains
  - N=108
  - CPT MIC50/90 = 0.5/1.0 µg/m



CPT FDA Susceptibility Breakpoint ≤1.0 mcg/mL

Figure 2. CPT MICs for SA in mcg/mL by MecA

TABLE 3. MSSA, N=291	% Resistant (criterion)	MIC50	MIC90
Ceftaroline	0 (>1.0)	0.125	.25
Cefuroxime	0 (≥4.0)	0.5	1.0
Levofloxacin	12.1 (≥2/0)	0.25	4.0
Azithromycin	31.5 (≥8.0)	0.25	8.0
Clindamycin	22.0* (≥4.0)	0.12	0.12

TABLE 4. MRSA, N=200	% Resistant (criterion)	MIC50	MIC90
Ceftaroline	6.1 (>1.0)	0.25	1.0
Levofloxacin	69.6 (≥2.0)	4.0	4.0
Azithromycin	81.3 (≥8.0)	8.0	>8.0
Clindamycin	25.2* (≥4.0)	0.12	>8.0

* Includes D-test positives with MICs that initially suggested susceptibility to clindamycin (N=55 MSSA, 10 MRSA)

Discussion:

- Empiric antimicrobials for very ill or toxic pediatric patients often requires coverage for MRSA, MSSA and SPN.
- Currently, vancomycin or linezolid are FDA approved drugs for children with such coverage
- Ceftaroline fosamil is approved for adults for CAP and skin/soft tissue infections.
- Our data reveal similar patterns of susceptibility in pediatric SPN and SA pathogens as previously noted in adults and mixed age populations (1,2)
- 99.7 of all and 97.8% of MDR SPN S to CPT
- 100% of MSSA and 94% of MRSA S to CPT
- We noted >20% clindamycin resistance among both MSSA and MRSA

Speculation:

- As further pediatric safety/efficacy data accrue, FDA approval of CPT for children would add a useful choice for clinical presentations that require parenteral treatment of MDR SPN plus MRSA and clindamycin resistant MSSA.

References:

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2. Jacobs MR, Good CE, Windau AR et al. Activity of Ceftaroline against Recent Emerging Serotypes of Streptococcus pneumoniae in the United States . Antimicrob Agents Chemother. 2010 June; 54(6): 2716–2719