K-1277

Clinical Presentation, Etiology and Outcome of Infective Endocarditis in University Hospital of Toulouse, France, 2010-2012

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ABSTRACT

Background
Some studies have showed that the profile of infective endocarditis (IE) significantly changed over the past decades. A large multicenter study conducted in France in 2008 showed that *Staphylococcus aureus* was the leading cause of IE. Here the objective was to describe the population in our center for 2010-2012 period in order to improve the diagnosis of IE.

Methods
A retrospective observational study was conducted. Results of blood cultures and of culture of implantable cardiac devices and prosthetic valves send by Cardiology and Cardiovascular Surgery units were analyzed. After selection of patients with IE diagnosis, the following information was collected: sex, age, history of heart disease, comorbidities, risk factors and symptoms of IE, medical and surgical treatment.

Results
Ninety three patients were included in this study. The mean age of the patients was 63±16.6 years (range 14-90). The incidence was highest in men aged 70-79 years. Eight patients were drug addicted. Fifty six (60%) had native valve endocarditis and 37 (40%) had prosthetic valve endocarditis. Twenty two patients (23.7%) possessed implantable cardiac devices. The aortic (58.6%), the mitral (20%), or the both (12%) were infected most commonly. *S. aureus* was the most common pathogen (40%). Other causal agents were coagulase negative staphylococci (32%), *Streptococcus* (11%), *Enterococcus* (9%), *Enterobacteriaceae* (6%). Two uncommon pathogens were found in our study: *Tropheryma whipplei* and *Ureaplasma parvum*. Mortality remains relatively high (14%). Surgical and medical treatments were conducted following the European Society of Cardiology guidelines.

Conclusions
In our population, IE occurred more often on native valve, with a high rate of *S. aureus* infections. Mortality is still high, especially on prosthetic valve with *S. aureus* infection. Some atypical pathogens were found. Because of the retrospective and observational character of this study, many limits exist. So a prospective study is actually in progress, with systematic realization of the serology for the IE cases with negative blood cultures, and of PCR diagnosis on cardiac valves and devices.

METHODS

- **Retrospective study**: 2010 to 2012
- **93 patients included** (positive blood cultures or positive culture for cardiac valve/implantable cardiac devices) (Table 1)
  - *Cardiology and Cardiovascular Surgery units, University Hospital of Toulouse*
  - Age: 63 ± 16.6 years
  - Sex ratio: 2.8 M/F
- **Evaluation criteria**: patients with Infective Endocarditis (IE) diagnosis
- **Data collected**: sex, date of birth, history of heart disease, comorbidities (diabetes, cancer, dialysis, immunosuppressive therapy...), risks factors for IE, symptoms of IE, type of IE (aortic, mitral, tricuspid) with or without implantable devices, microbiological data, medical and surgical treatment, outcome.
- **Microbiological data**:
  - Total number of positive blood cultures
  - Results of valve/implantable devices culture
  - Results of serological tests and/or PCR
  - Causative microorganism identified

INTRODUCTION

In industrialized countries, the profile of infective endocarditis (IE) has been changing significantly over the past decades (higher frequency of comorbidities, increase of patients with prosthetic valves)[1]. We observed a shift in causative microorganisms with staphylococci surpassing streptococci as the most common causative bacteria in IE[2]. A recent Nationwide Study made in USA for the 1998-2009 period showed (i) an incidence of 12.7/100 000 in 2009 ; (ii) 13.2% - 15.9% of patients possessed intracardiac devices ; (iii) the mortality rate was 14.6% and (iv) *S. aureus* was the most common pathogen (37.6%)[3]. Similar data were obtained in a large epidemiological study in France[4,5]: (i) an incidence of 3.2 / 100 000 in 2008 ; (ii) 13.2% of patients had intracardiac devices ; (iii) the mortality rate was 22.7% and (iv) *S. aureus* was also the first pathogen responsible of IE, especially in IV drug-users and in patients with prosthetic valve or intracardiac devices. The aim of our study was to evaluate the epidemiology in our University Hospital, in Toulouse, in the South-West region of France.

RESULTS

Table 1. Main Characteristics of Patients with IE

	All patients		Patients with prosthetic valve	
	93		38 (40.9%)	
	N	%	N	%
Age (years ; mean ± SD)	63.3 ± 16.6		64.4 ± 17.8	
Age ≥ 70 years	38	40.1	20	52.6
Male Sex	69	74.2	30	78.9
Intracardiac devices (PM or ICD)	22	23.7	4	10.5
Injection drug users	8	8.6	1	2.6
Embolic complications	10	10.8	4	10.8
Mortality	13	14	6	15.7

PM: pacemaker ; ICD: implantable cardioverter defibrillator

Figure 1. Evolution of number of IE cases in the study population by age, between 2010-2012.

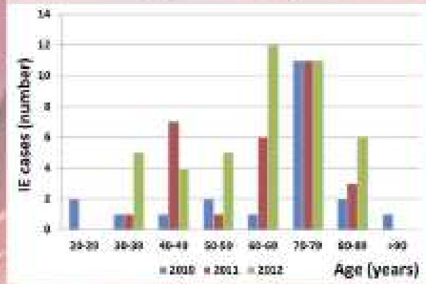


Table 2. Bacteria responsible for IE in function of location of IE, presence of intracardiac device and in case of IV drug use ; mortality (2010-2012).

Bacteria	IE on native valve N=37 (39.8%)		IE on prosthetic valve	Intracardiac devices	Mortality	Total
	No IV drug use	IV drug users	N=38 (40.9%)	N=18 (19.4%)	N=13 (14%)	N=93
	N=31 (83.8%)	N=6 (16.2%)				
S. aureus	12 (38.7%)	5 (83%)	12 (31.6%)	9 (50%)	10 (76.9%)	38 (40.9%)
CoNS	7 (22.6%)	0	15 (39.5%)	7 (38.9%)	1 (7.7%)	29 (31.1%)
Enterococcus	3 (9.7%)	1 (17%)	4 (10.5%)	0	0	8 (8.6%)
Oral Streptococci	2 (6.5%)	0	0	0	0	2 (2.2%)
Gr D Streptococci	3 (9.7%)	0	3 (7.9%)	0	1 (7.7%)	6 (6.5%)
Others*	4 (12.8%)	0	4 (10.5%)	2 (11.1%)	1 (7.7%)	10 (10.7%)

	Our data 2010-2012	France[4] 2008	USA[3] 1998-2009
Population characteristics			
Mean age	63.3 ± 16.6 years	62.3 ± 15.9 years	59.7 years
Age > 70 ans	40.1%	38.0%	36.4%
Male predominance	74.2%	74.2%	57.7%
Injection drug use	8.6%	5.8%	7.8%
Intracardiac devices	23.7%	13.3%	15.5%
Location of IE			
Aortic	58.6%	30.8%	
Mitral	20%	34.6%	
Aortic + mitral	12%	12.1%	
Major pathogens			
S. aureus	40.9%	26.6%	44.2%
CoNS	31.1%	9.7%	10.3%
Enterococcus spp.	8.6%	10.5%	9.8%
Group D Streptococci	6.5%	12.5%	
Oral Streptococci	2.2%	18.7%	

Figure 2. Type of infections : prosthetic or native valves, or on intracardiac devices, 2010-2012.

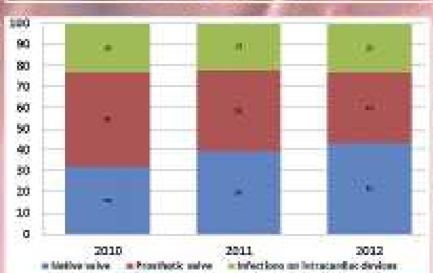


Figure 3. IE location: aortic, mitral, tricuspid or pulmonar (all cases, 2010-2012).

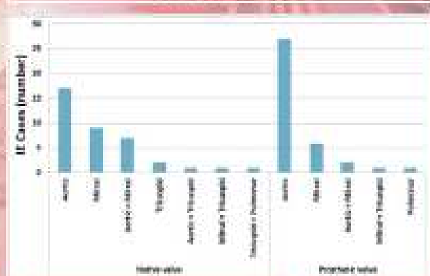


Figure 4. Distribution of causative microorganisms (all cases, 2010-2012).

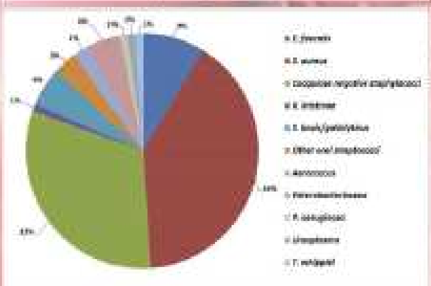
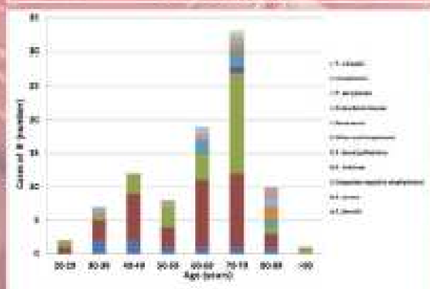


Figure 5. Distribution of microorganisms by age (all cases, 2010-2012).



DISCUSSION

In this study, we have observed similar data than other multicenter studies in France[4,5] or in USA[3]. Interestingly, *S. aureus* has become the predominant species among causative bacteria, with decrease of Streptococci/Enterococci infection cases. CoNS are responsible of IE on prosthetic valves and on IDC essentially. Some atypical microorganisms have been observed: *T. whipplei* and *Ureaplasma*. However, this is only an observational retrospective study. Actually, we conduct a prospective study to obtain more complete data, including IE with negative blood cultures.

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No significant differences between generics Vancomycin (VAN) Products from Europe and America in the Treatment of Methicillin-Resistant Staphylococcus aureus (MRSA) Experimental Endocarditis in Rabbits: a confirmatory study

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Background / Objectives

- Concerns have recently emerged about the potency and the quality of generic vancomycin (VAN) products approved for use in humans, based on experiments in a neutropenic mouse thigh infection model.
- We previously found no statistically significant differences between 6 generic VAN products from Europe and America, in the model of MRSA aortic valve endocarditis in rabbits. However, due to limited sample sizes per generic (n=10), and multiple comparisons, these experiments may have been underpowered to detect clinically significant differences.
- To confirm these results, we performed a face-to-face comparison of the two VAN generics that demonstrated the highest and the lowest bactericidal effect in our previous study, with additional experiments and increased sample sizes.

Methods

- **Bacterial strain**. *S. aureus* strain COL is a homogeneous, highly methicillin-resistant isolate (VAN MIC 1.5 µg/ml)
- **Antibacterial agents**. VAN generics were bought from local drug purchases companies and prepared following label instructions
- **Rabbit endocarditis model**.

-The protocol was in keeping with French legislation on animal experimentation and was approved by the local Animal Use Committee

- To establish endocarditis, a polyethylene catheter was positioned across the aortic valve, and 24 hours later, 1 ml of 0.9% saline containing ~ 8×10^7 CFU of COL was injected intravenously

- 20 rabbits in each group were treated with i.m. VAN generics from APP (USA), or Hospira (Spain), 60 mg/kg bid during 4 days. Rabbits were euthanized 12 h after the last VAN dose. Aortic valve vegetations and spleens were removed.

Data analysis. Bacterial titers were expressed as $\log^{10}$ CFU per gram of tissue. Cultures yielding no growth were scored as sterile, and assigned a value of 1.7 $\log^{10}$ CFU. The two groups were compared using chi2 test for sterility rates, and non-parametric Wilcoxon tests for titers of residual organisms in vegetations and spleens, with Bonferroni correction methods to estimate adjusted P-values.

In addition, we compared the rate of emergence of VAN-resistant sub-populations in rabbits treated with the 6 VAN generics previously tested, as previously reported (Rodriguez et al.). Briefly, the area under the VAN concentration versus the $\log_{10}$ CFU/ml curve (AUC) was calculated, and the resistance frequency at each concentration was determined by dividing the number of CFU that grew in antibiotic-containing agar by the total population in antibiotic-free plates.
The intensity of the effect (*IE*) was calculated as the difference between the AUCs of the control and treated groups by the following formula: ***IE*** = $AUC_{control} - AUC_{treated}$.

Results

Comparison of the VAN generics who had the lowest, and the highest bactericidal activity in the previous study (20 rabbits/group)

	Controls (n=10)	Hospira (n=20)	APP (n=20)	P
	Median [q1, q3] (% sterile)			
Vegetations	9.4 [8.6, 9.8] (0%)	2.4 [2.3, 3] (70%)	3.2 [2.2, 4.9] (50%)	ns
Spleen	5.4 [4.5, 6.5] (0%)	1.7 [1.6, 1.7] (100%)	1.6 [1.5-1.7] (100%)	ns

- **No significant differences between the VAN generics with the highest (Hospira), and the lowest (APP) bactericidal activity, even after increasing the sample sizes**, in terms of:
  - organism titers in vegetations, and in spleens
  - proportions of spleen and vegetations sterilized

- **No significant differences in terms of resistance selection under treatment between 6 VAN generics approved for use in Europe and America** (Akron, APP, Hospira, Mylan, Sandoz and Téva).
- **This holds true even for generics who were found sub-optimal in the neutropenic mice model**

Resistant sub-populations of MRSA after VAN generics exposure

AUC (area under the VAN serum concentration vs. the $\log_{10}$ CFU/ml curve)	Mean ± sd	Median [q1, q3]*	min, max
Total (n=42)	25.1 ± 2	24.6 [23.9, 25.6]	21, 31
Akron (n=6)	25.2 ± 1	25.1 [24.7, 25.4]	23.9, 26.8
App (n=7)	23.4 ± 1.4	24 [22.8, 24.2]	21, 24.9
Hospira (n=3)	26.1 ± 1.9	25.9 [25.1, 27]	24.4, 28.1
Mylan (n=4)	27.4 ± 3.3	27.4 [25.1, 29.7]	23.8, 31
Sandoz (n=5)	26.9 ± 1.9	27.1 [25, 28.6]	24.7, 28.9
Untreated (n=10)	24.5 ± 1.6	24.5 [23.6, 25.4]	21.8, 27.1
Teva (n=7)	24.3 ± 1	24.4 [23.5, 25.1]	23.2, 25.6
Intensity of the effect **			
	Mean ± sd	**Median [q1, q3]***	**min, max**
Total (n=42)	-0.6 ± 2	-0.1 [-1.1, 0.6]	-6.5, 3.5
Akron (n=6)	-0.7 ± 1	-0.6 [-0.9, -0.2]	-2.3, 0.6
App (n=7)	1.1 ± 1.4	0.5 [0.3, 1.7]	-0.4, 3.5
Hospira (n=3)	-1.6 ± 1.9	-1.4 [-2.5, -0.6]	-3.6, 0.1
Mylan (n=4)	-2.9 ± 3.3	-2.9 [-5.2, -0.6]	-6.5, 0.7
Sandoz (n=5)	-2.3 ± 1.9	-2.6 [-4.1, -0.5]	-4.3, -0.2
Untreated (n=10)	0 ± 1.6	0 [-0.8, 0.9]	-2.6, 2.7
Teva (n=7)	0.2 ± 1	0.1 [-0.6, 1]	-1.1, 1.3

** q1 = 25th percentile, median =50th percentile, q3 = 75th percentile.*
*** The intensity of the effect (IE) = $AUC_{control} - AUC_{treated}$*

Pairwise comparisons using Wilcoxon rank sum test

	Akron	APP	Hospira	Mylan	Sandoz
APP	0.475				
Hospira	1	0.604			
Mylan	1	1	1		
Sandoz	1	0.14	1	1	
Teva	1	1	1	1	0.512

P value adjustment method for multiplicity testing: Bonferroni

Comments

- **In this stringent MRSA endocarditis model, additional investigations found no significant differences in the *in vivo* bactericidal activity of generic VAN products currently used in Europe and America** even after increasing sample sizes, and testing for resistance selection after VAN generics exposure.
- **Limitations:**

i) **we could not compare generic VAN products with the innovator**, as Eli-Lilly halted its production in 2005

ii) these are **not non-inferiority studies** (sample sizes required not realistic)

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Multicenter Experience of the Effectiveness and Safety with Ceftaroline Fosamil (CPT) Therapy

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ICAAC 2013
K-192

Abstract (Updated)

Background: The US Food & Drug Administration (FDA) approved CPT for acute bacterial skin & skin structure infections (ABSSSI) & community-acquired bacterial pneumonia (CABP). CPT is indicated for ABSSSI caused by *S. aureus* (SA) including methicillin-susceptible (MSSA) & resistant (MRSA) strains. Limited clinical data exists for use outside these indications. Objective of this study is to describe the outcomes of patients (pts) treated with CPT for various infections.
Methods: Retrospective cohort analysis in pts receiving ≥ 72 hrs of CPT at 5 different hospitals from 2011 to 2013. Clinical & microbiological outcomes were analyzed. Clinical cure (CC) was defined as infection resolved at the end of CPT & no additional therapy needed.
Results: 527 pts receiving CPT were included and 33% were within the FDA labeling, see Figure 1 for types of infections. Median APACHE II was 11 (6-16). Most pts (80%) were initiated on CPT after receipt of alternative therapy, with 49% citing disease progression as a reason for switching. A total of 327 (62) were culture positive, 83% of which were SA (241 MRSA, 30 MSSA). Median CPT MIC for SA was 0.5 mg/L (0.5- 0.75). For patients with SA bacteremia (SAB): 112 MRSA, 10 MSSA, & 11 daptomycin-nonsusceptible *S. aureus*. Remaining cultures were 21% (68) other Gram-positive & 20% (67) Gram-negative bacteria. Of the SA infections, 21% (58/271) were polymicrobial with another bacteria. Clinically, 426/484 (88%) achieved CC at the end of CPT therapy. Median duration of CPT was 6 days (4-9) and the most common CPT dose was 600mg q12h. 29% were given another antibiotic with CPT. Median length of stay was 13 days (7-24). For SAB, median time to bacterial clearance was 3 days (1-4). In hospital mortality was seen in 20 (5%) pts. 37 (9%) experienced an adverse event while on CPT and 21 (7%) were re-admitted within 30 days after discharge, with 8 (9%) for the same infection.
Conclusions: The majority of pts treated with CPT for off-label infections had favorable outcomes. Further research is necessary to clarify its clinical role in these infection types outside its FDA approved label.

Introduction

- Ceftaroline fosamil (CPT), is an advanced generation cephalosporin with bactericidal activity against Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).
- US Food and Drug Administration (FDA) approved CPT for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in October 2010.
- The objective of this study was to evaluate characteristics and outcomes of patients with an infection treated with CPT including use with off-label indications and dosing.

Methods

- A multicenter, retrospective cohort study was conducted at participating academic and community hospital systems. The cohort included consecutive adult patients from January 2011 to June 2013 treated with CPT for ≥ 72 hours during hospitalization.
- Data collected from medical records included:
  - Patient demographics, comorbid conditions, indication for CPT, CPT dose, duration and concomitant therapy, and microbiology. CPT minimum inhibitory concentrations (MICs) were recorded when available, determined by Etest according to each institutions' clinical laboratory.
  - Outcomes were assessed in evaluable patients at the end of CPT therapy:
    - Clinical cure: resolution of all signs and symptoms of infection with no further need of antibiotic treatment while on CPT determined by the prescriber.
    - Microbiological cure: In patients with follow up cultures defined as eradication of the infecting organism while on CPT.
  - Patients were also assessed for adverse reactions, 30-day readmission, and all-cause mortality.
- Analysis: Descriptive statistics performed using SPSS, version 21.0 (IBM SPSS Inc., Chicago, IL).

Disclosures: No financial support was received for the conduct of this study. The authors acknowledge the following potential conflicts of interest: AMC, VOB, KPK, KEB, LMS: (nothing to disclose); SLD Forest, Durata, Cubist, Pfeizer (consulting or research support);DAG Merck, Cubist, Forest, Rempex (advisory board, speaker, or research support); RPM Cubist (speaker); KSK Forest (speaker, consultant, and research support); JMP Forest, Pfizer, Cubist (speaker or consultant); MJR Cubist, Forest, Novartis, Durata, Tiba, Cephalo, Theravance, Cerexa (speaker, consultant, or research support)

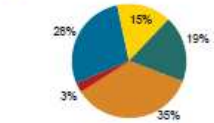
Results

Patient and Infection Characteristics

Over the 2.5-year evaluation, 527 patients received CPT for a minimum of 72 hrs: 352 (66.8%) off-label indications and 175 (33.2%) US FDA approved labeled indications.

Baseline Characteristics	Median (IQR) or n (%) (n = 527)
Age (years)	60 (49-72)
APACHE II Score	11 (6-16)
Charlson Comorbidity Score	2 (1-4)
Prior hospitalization (1 year)	314 (59.6)
Male Gender	304 (57.7)
ICU admission	170 (32.3)
Diabetes	212 (40.2)
Heart Disease	177 (33.6)
Chronic Kidney Disease	118 (22.4)
Hemodialysis	43 (8.2)
COPD	67 (12.7)
Previous antibiotics (3 months)	158 (30)

Classification of Infection



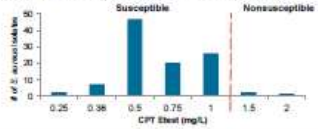
Microbiology

327 (62%) patients had positive cultures
73/327 (22.3%) were polymicrobial

Pathogens	n
S. aureus	271
Methicillin-Resistant *S. aureus*	241 (88.9%)
Streptococcus spp.	31
Coagulase-Neg *Staphylococcus spp.*	20
Other Gram-positives	17
K. pneumoniae	22
E. coli	19
Proteus spp.	10
K. oxytoca	4
Other Gram-negatives	12

7 Enterobacteriaceae isolates were tested for CPT susceptibility a median CPT MIC of 0.19 mg/L (IQR 0.12-0.25)

105 *S. aureus* isolates were tested for CPT susceptibility



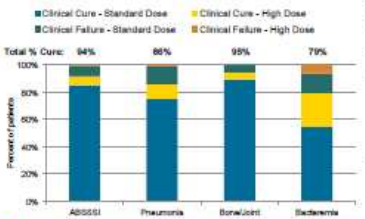
Antimicrobial Therapy

Rationale for CPT vs Other Agents as documented by prescribers

- 422 (80.1%) were given another antimicrobial prior to the start of CPT
- Median time to switch to CPT was 3 days (IQR 1-6)
- Median duration of CPT in hospital was 6 days (IQR 4-9)
- CPT dose and frequency
  - 452 (85.8%) were given 600 mg IV Q12h (standard dose) or equivalent renal adjustment
  - 75 (14.2%) were given 600 mg IV Q8h (higher dose) or equivalent renal adjustment
- 154 (29.2%) were given another antimicrobial in combination with CPT

Clinical Outcomes

Clinical Outcome: Indication and Dosing



Outcomes at Discharge and Follow-Up

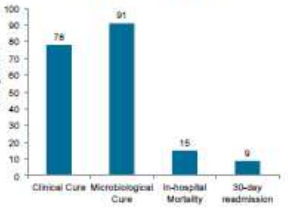
- In-hospital mortality was 7.6% (40/527)
- Median length of stay was 12 days (IQR 7-21)
- Median ICU LOS was 8 days (IQR 4-17)
- 41 (7.8%) experienced an adverse reaction
  - The most commonly reported adverse effects were: GI (9), renal (6), rash (7), infection with a resistant organism (5) and *C. difficile* (3)
  - 30 (5.7%) discontinued CPT therapy
- 30 day follow up was available in 307 (58.3%)
  - 30-day readmission rate was 9.1% (28/307)
  - 30-day all cause mortality was 15.5% (47/307)

Subset Analysis: *S. aureus* Bloodstream Infection

133 patients with *S. aureus* bloodstream infection were evaluated in an *a priori* subset. 123 (93%) were MRSA; 11 (8%) were daptomycin non-susceptible.

Characteristics	Median (IQR) or n (%) (n = 133)
Concomitant Infection Sites	
Infective Endocarditis	35 (26.3%)
Bone or Joint Infection	31 (23.3%)
Pneumonia	30 (22.6%)
ABSSSI	10 (7.5%)
IV Catheter Related	10 (7.5%)
Prosthetic Device Related	7 (5.3%)
Deep Abscess (e.g. Spinal)	6 (4.5%)
Unknown source	4 (3%)
Antimicrobial Therapy	
Duration of prior therapy (days)	6 (3-11)
Off-label dosing (i.e. q8h)	44 (33.1%)
Duration of CPT (days)	9 (4-16)
Outcomes	
Duration of SAB (days)	6 (3-9)
Length of stay (days)	21 (13-29)

Clinical Outcomes of CPT for *S. aureus* Bacteremia



Summary

- The majority of patients were treated with CPT had favorable outcomes including *S. aureus* bacteremia.
- CPT was mostly used as alternative therapy for off-label indications including bone and joint infections, MRSA pneumonia and MRSA bloodstream infection.
- In conclusion, further research is necessary to better describe the clinical role of CPT in these complicated infections outside of the FDA approved labels.

Characterization of Patients with Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infective Endocarditis (IE)

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ICAAC 2013
K-1285

Introduction

- Infective endocarditis (IE) is among the most complicated and serious infection types.
- Methicillin-resistant *Staphylococcus aureus* (MRSA) accounts for up to 1/3 of all patients with IE.
- Vancomycin (VAN) has been the preferred treatment of MRSA IE.
- Recent MRSA guidelines have provided a road map in management for MRSA IE.
- Changes in total burden of disease have not been accurately quantified.
- The objective of this study was to describe whether incidences remain stable or have changed in patient with MRSA IE treated with VAN over an 8 year period.

Methods

Study Design:

- A retrospective cohort study was conducted at the Detroit Medical Center.
- Consecutive adult patients treated for MRSA IE with VAN for >/= 72h inpatient were collected from 2005-2012.
- Medical records were reviewed for demographics, comorbidities, antimicrobial therapy, microbiologic cultures, clinical outcomes, and vancomycin pharmacokinetic/pharmacodynamic variables.

Outcome Assessment:

- VAN treatment failure: persistent bacteremia (>/= 7 days on VAN) or death by MRSA within 30 days of first positive blood culture
- Length of hospital stay (LOS)
- Days of bacteremia (time from 1st positive blood culture to first day of 48 hours of negative blood cultures)

Microbiological Assessment:

- VAN minimum inhibitory concentration (MIC) were determined by broth microdilution (BMD) and Etest per Clinical Laboratory Standards Institute and manufacturer guidelines, respectively.
- VAN population analysis profiles (PAP) were determined at an inoculum adjusted to a 10^8 CFU/mL density, and spiral plated (Don Whitley Scientific Limited, West Yorkshire, England) on to BHI agar (Difco, Detroit, MI) plates containing 0, 0.5, 1, 1.5, 2, 3, 4, 8 and 16 mg/L VAN.
- PCR strategy for subtyping SCC*mec* and *agr* genotype were performed for each isolate.

Statistical Analysis:

- SPSS Statistics, version 21.0 (IBM SPSS Inc., Chicago, IL) was used to perform descriptive statistical analyses including data frequencies and distributions.

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Results

Study Population

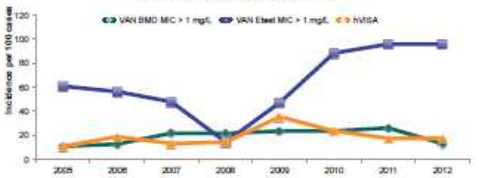
Characteristics median (IQR) or n (%)	2005 n = 28	2006 n =16	2007 n = 23	2008 n = 14	2009 n = 17	2010 n = 17	2011 n =23	2012 n = 23
Age (years) (IQR)	49 (46-65)	52 (44-66)	49 (43-57)	52 (49-66)	54 (52-58)	51 (46-58)	60 (55-66)	55 (44-63)
APACHE II score (IQR)	8 (7-15)	14 (8-18)	5 (5-12)	10 (7-18)	11 (5-14)	12 (9-18)	13 (11-18)	13 (10-17)
Admission to ICU, n (%)	14 (50%)	7 (44%)	7 (30%)	9 (64%)	8 (47%)	6 (35%)	10 (43%)	10 (43%)
Left-sided IE, n (%)	13 (46%)	6 (38%)	3 (13%)	4 (29%)	4 (24%)	0 (0%)	1 (4%)	11 (48%)
Injection Drug User, n (%)	18 (64%)	10 (63%)	20 (87%)	6 (43%)	10 (59%)	9 (53%)	4 (17%)	10 (43%)
Hemodialysis, n (%)	7 (25%)	3 (19%)	5 (22%)	1 (7%)	5 (29%)	4 (24%)	8 (35%)	10 (43%)
Chronic Kidney Disease, n (%)	5 (18%)	4 (25%)	1 (4%)	2 (14%)	5 (29%)	4 (24%)	17 (74%)	8 (35%)

Microbiological Trends

Characteristics of MRSA isolate per year

	2005 n = 28	2006 n =16	2007 n = 23	2008 n = 14	2009 n = 17	2010 n = 17	2011 n =23	2012 n = 23
SCC*mec* Type IV	19 (68%)	10 (63%)	19 (83%)	9 (64%)	13 (76%)	15 (88%)	16 (70%)	14 (61%)
agr genotype 1	16 (57%)	8 (50%)	18 (78%)	8 (57%)	11 (65%)	14 (82%)	14 (61%)	13 (57%)

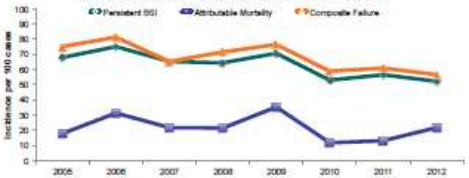
Characteristics of MRSA isolate per year



Clinical Outcomes

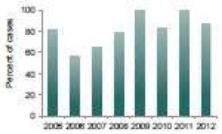
- Overall composite VAN failure was experienced in 109 (67.7%) patients
  - 101 (62.7%) patients had persistent bacteremia
  - 34 (21.1%) patients had 30-day attributable mortality
- Throughout the years after 2009, persistent failure starts to decline
- Attributable mortality remained consistent during the timeframe

Clinical Outcomes of Patients with MRSA Infective Endocarditis

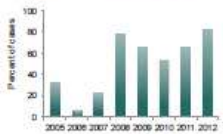


Management of MRSA IE

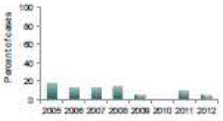
Infectious Disease Consultation



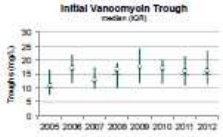
Switched to Alternative Therapy



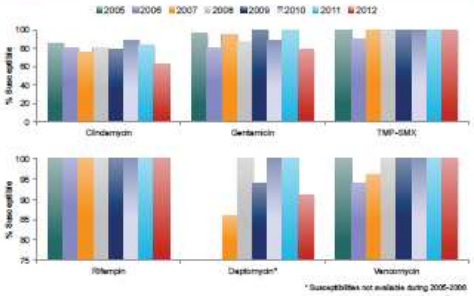
Surgical Intervention



Initial Vancomycin Trough
median (IQR)



Antimicrobial Susceptibilities



* Susceptibilities not available during 2005-2006

Conclusions

- MRSA IE treated with VAN is associated with high treatment failure.
- The number of MRSA IE cases have been consistent in incidence per year.
- There seems to be a change in trends during 2009 with an increase in infectious diseases consult and less surgery/valve replacement interventions.
- Admission to ICU and injection drug users were common throughout the years.
- hVISA frequencies ranged from 10-35% and was consistently 17% of the population.
- VAN Etest values > 1 mg/L continue to increase after 2007.
- After 2007, median initial VAN trough levels were consistent at the 15-20 mg/L range having a higher range that may indicate a more aggressive vancomycin dosing.
- The number of VAN treatment failure have decreased after the year 2009.
- Frequencies in switching to another antimicrobial for MRSA IE treatment doubled after the year 2007.
- Further research is necessary to identify factors that may affect the role of MRSA IE management.

K-1273

Staphylococcus aureus bacteremia: factors associated with infective endocarditis

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Abstract

Background: *Staphylococcus aureus* is the first cause of infective endocarditis (IE) in France. We aimed to identify the factors associated with IE in case of *S. aureus* bacteremia (SAB).
Methods: VIRSTA is a prospective cohort study that enrolled all SAB observed in 8 University Hospitals in France between 2009 and 2011. Factors associated with definite IE according to Duke-Li criteria in cases of SAB who were not referred for IE were analyzed using logistic regression.
Results: 2008 cases of SAB were included (male: 65%, median age: 70 years). SAB was nosocomial in 56%, non-nosocomial health-care related in 18% and community-acquired in 27% of cases. Presumed portal of entry was unknown in 20% and the most frequent one was a vascular access (28%). *S. aureus* was methicillin-resistant in 19%. An echocardiography was performed in 60% of pts. A definite IE was diagnosed in 11% of SAB enrolled. The proportion of IE was 20% in community-acquired SAB, 12% in non nosocomial health-care related SAB and 7% in nosocomial SAB. It was 7% in pts without known cardiac predisposing disease. In-hospital mortality was 28% in the whole population and 25% in pts with IE (p = 0.063). Factors significantly associated with IE were injecting drug use (IE: 38%, adjusted odds-ratio: [aOR] = 5.7), absence of diabetes mellitus (IE:12%, aOR = 1.8), community acquired SAB (aOR = 3.6), non-nosocomial health-care related (aOR = 2.4), presence of a prosthetic valve (IE: 33%, aOR = 9.8) or of a native valvular disease (IE: 25%, aOR = 4.3), time > 24 hrs between first symptoms of SAB and performance of blood culture (IE: 15%; aOR = 1.8) and C-reactive protein > 190 mg/L (IE: 15%, aOR = 2.2).
Conclusions: IE is a severe complication of SAB. Its frequency is high, even in case of nosocomial infection and in the absence of known predisposing factor.

Background/ Objectives

During the last decade, *Staphylococcus aureus* has become the leading cause of infective endocarditis (IE) in Western Europe and Northern America.

Large and prospective epidemiological studies of *Staphylococcus aureus* bacteremia (SAB) are rare since 2000 (Khatib, Rasmussen, Forsblom, Finkelstein).

Objective: to identify factors associated with infective endocarditis in patients presenting with *S. aureus* bacteremia.

Methods

All adult patients in whom a SAB was observed between April 2009 and October 2011 in the 8 French University hospitals participating to the study were prospectively enrolled.

- SAB was defined as at least one blood culture yielding *S. aureus*. Patients having catheter colonisation were excluded.
- Transesophageal echocardiography was encouraged but was not mandatory.
- Cases were classified as definite, possible or excluded IE according to the Duke-Li classification by a college of clinicians in each participating hospital.
- Factors associated with definite IE in patients who were not transferred for IE were analysed using multivariate logistic regression.

The VIRSTA Study Group:
Clinical centres: Besançon: Catherine Chirouze, Elodie Curlier, Cécile Descottes-Genon, Bruno Hoen, Isabelle Patry, Lucie Vettoretti. **Dijon:** Pascal Chavanet, Jean-Christophe Eicher, Marie-Christine Greusard, Catherine Neuwirth, André Péchinot, Lionel Piroth. **Lyon:** Marie Célard, Catherine Cornu, François Delahaye, Malika Hadid, Pascale Rausch. **Montpellier:** Audrey Corne, Florence Galtier, Philippe Géraud, Hélène Jean-Pierre, Vincent Le Moing, Catherine Spontouch, Jacques Reynes. **Nancy:** Nejla Assia, Thanh Doco-Lecompte, François Goehringer, Nathalie Kell, Lorraine Letranchant, Aalin Lozniewski, Hecher Maiela, Thierry May, Christine Selton-Suty. **Nîmes:** Nathalie Bedos, Jean-Philippe Lavigne, Catherine Lechiche, Albert Sotto. **Paris:** Xavier Duval, Emila Ilic Habensus, Bernard Iung, Catherine Leport, Pascale Longuet, Raymond Rulmy. **Rennes:** Eric Bellissant, Audrey Brenner, Pierre-Yves Donnio, Fabienne Le Gac, Christian Michelet, Caroline Piau, Matthieu Revest, Pierre Tattevin, Elise Thebault.
Coordination and statistical analyses: François Alla, Pierre Braquet, Marie-Line Erpelding, Laetitia Minary.
Centre National de Référence des staphylocoques: Michèle Bès, Jérôme Etienne, Anne Tristan, François Vandenesch.
Erasmus University Rotterdam: Alex Van Belkum, Willem Vanwamel.
Sponsor CHU de Montpellier: Sandrine Barbas, Christine Delonca, Virginie Bussmuth, Anne Verchère.
This study has been financed by the Programme Hospitalier de Recherche Clinique, Ministère des Affaires Sociales et de la Santé, France.

Results

- A total of 2091 patients were enrolled. After exclusion of the 77 patients refered in the participating hospital for management of IE, 2008 were available for the present analysis.
- Description of outcome of the patients is displayed on poster K-1275

Description of the 2008 patients analysed

Men n (%)	1295 (65)
Median age (yrs) (IQR)	70 (58-81
McCabe score n (%):	
• No disease or non fatal disease	977 (49)
• Ultimately fatal disease	751 (38)
• Rapidly fatal disease	368 (18)
Diabetes mellitus n (%)	567 (28)
Cancer n(%)	593 (30)
Immunodepression n (%)	738 (37)
Previously known heart disease predisposing to IE n (%)	
• Prosthetic valve	140 (7)
• Other	350 (18)
Intravascular device n (%)	217 (11)
Chronic hemodialysis n (%)	211 (11)
Time between onset of symptoms and performance of blood culture n (%)	
• Unknown	80 (4)
• < 1 day	945 (47)
• 1-7 days	809 (40)
• > 7 days	174 (9)
Presumed portal of entry	
• None identified	409 (20)
• Injecting drug use	35 (2)
• Other intravascular access	566 (28)
• Surgery	297 (15)
• Skin	375 (19)
• Other	326 (16)
Presumed source of acquisition	
• Unknown	58 (3)
• Community	528 (27)
• Nosocomial	1074 (53)
• Healthcare nomosocomial	348 (17)
Median baseline C-Reactive Protein (mg/L) (IQR)	189 (113-281)
Methicillin-resistance	380 (19)

Factors associated with IE: final multivariate model

1200 pts (60%) had an echocardiography ammong whom 602 (30%) had a transesophageal echocardiography

Definite IE according to Duke-Li was diagnosed in **222 patients (11%)**:

- pathologic criteria 25,
- clinical criteria: 197 (2 major; 138; 1 major 3 minor: 57; 5 minor: 2)

Among the 723 patients with nosocomial SAB and no predisposing factor for IE, 23 (3.2%) had an IE.

Factor	% IE	Adjusted odds-ratio [95% IC]
Diabetes mellitus:		
Yes	7.8	0.57 [0.39-0.83]
No	12.4	1
Injecting drug use		
Yes	38.1	5.71 [3.10-10.5]
No	10.2	1
Predisposing heart disease		
None	7.1	1
Prosthetic valve	32.9	9.77 [6.19-15.4]
Other	19.7	4.34 [3.03-6.21]
Presumed source of acquisition		
Community	20.3	3.77 [2.62-5.44]
Healthcare-related non nosocomial	12.1	2.37 [1.53-3.67]
Nosocomial	6.5	1
Unknown	5.2	1.13 [0.33-3.86]
Time between onset of symptoms and blood culture		
< 1 day	7.8	1
≥ 1 day	13.9	1.53 [1.09-2.14]
C-Reactive Protein (mg/L)		
< 190	7.6	1
> 190	15.3	2.21 [1.59-3.08]
Missing value	6.3	0.75 [0. 3-1.89]

Other factors studied not associated with IE in multivariate model: age, sex, immunodepression, other portal of entry, McCabe score, sensitivity of *S. aureus* to penicillin and methicillin, urine culture yielding *S. aureus*

Discussion/ Conclusions

IE is a severe complication of SAB. Its frequency is high, even in case of nosocomial infection and in the absence of known predisposing condition.

- Echocardiography should be performed in most cases of SAB in order to detect IE as early as possible and thus improve its prognosis.
- Except well-known predisposing conditions, we did not find any clinical or epidemiological factor that may explain why IE occurs in some cases of SAB. Genetic analyses in both the human host and the causative agent are under way.
- Most SAB are healthcare-related in tertiary hospitals in France. Every effort should be made to prevent this dreadful complication of medical progress.

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ICAAC 2013

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Four Cases of Ceftaroline Salvage Therapy for Complicated Methicillin- Resistant *Staphylococcus aureus* Infections

UK HealthCare

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Abstract

Background: Treatment of serious MRSA infections with decreased susceptibility to daptomycin (DAP) and vancomycin (VAN) represents a significant challenge to clinicians today. Little data exists to date supporting the use of ceftaroline (CPT) for the treatment of these infections. We report four such patient cases of complicated MRSA infections treated with CPT at an academic medical center. **Methods:** Data pertaining to four patients with MRSA infections with decreased susceptibility to DAP and VAN encountered by the infectious disease consult service were collected from the medical record and evaluated for clinical and microbiological outcomes. **Results:** Minimum inhibitory concentrations (MIC) were determined by Phoenix automated susceptibility system or Etest. All patients had MRSA isolates that demonstrated elevations in VAN and DAP MIC while undergoing treatment. Three isolates were found to be DAP non-susceptible, one of which also having intermediate susceptibility to VAN. The remaining isolate had a VAN MIC of 2ug/mL, which has been previously associated with clinical failure of VAN. CPT was used both as monotherapy and in combination with VAN, DAP, linezolid (LZD), trimethoprim- sulfamethoxazole (TXS), or rifampin (RIF). Three patients have achieved microbiological and clinical cure to date. All continue to be monitored closely for signs of recurrence. No adverse drug reactions were observed with CPT. **Conclusions:** The cases presented demonstrate treatment success associated with CPT use for MRSA infections with decreased susceptibility to first line agents. Due to the favorable pharmacokinetic and safety profile observed thus far, CPT represents an attractive treatment option for clinicians faced with emerging multi-drug resistant organisms.

Background

- The National Hospital Safety Network surveillance of antimicrobial-resistant pathogens associated with healthcare acquired infections reports *Staphylococcus aureus* as the most frequently isolated organism, representing 15.6% of all nosocomial pathogens.[1]
- An increasing proportion of *Staphylococcus aureus* are now resistant to first- line therapies such as beta-lactams and the glycopeptide vancomycin.[2,3]
- Ceftaroline is an advanced generation cephalosporin with activity against MRSA which has been successfully employed in the treatment of a variety of serious infections in isolated cases.[4]
- Ceftaroline has also been shown to synergistically enhance the activity of both vancomycin and daptomycin against staphylococci with reduced susceptibilities to either agent.[5,6]

Methods

- Data pertaining to four patients with MRSA infections with decreased susceptibility to DAP and VAN encountered by the infectious disease consult service were collected from the medical record and evaluated for clinical and microbiological outcomes.

Results

Patient 1

- A 36- year- old female with a past medical history of polyglandular autoimmune syndrome was approaching completion of 6 weeks of outpatient DAP 7mg/kg as treatment for cervical discitis when found to be bacteremic with MRSA. She was admitted and started empirically on VAN for 2 days before the new isolate was identified as a DAP non-susceptible, vancomycin-intermediate *S. aureus*, and therapy was changed to LZD. After being bacteremic for 3 days on LZD therapy, trimethoprim-sulfamethoxazole (SXT) was added at 12mg/kg/day. Approximately 36 hours later, SXT was changed to ceftaroline (CPT) 600mg every 12 hours. Soon after the initiation of CPT, the patient underwent a C5-C6 anterior cervical discectomy and fusion with plate and structural allograft. Tissue culture from disc grew MRSA. Blood cultures cleared within 36 hours of CPT initiation and remained negative. The patient was discharged on 6 weeks of LZD and CPT. Over the course of treatment DAP MICs varied greatly from 6-16 mg/L. Vancomycin was reported as susceptible by BD Phoenix® automated system, and later corrected to intermediate when E-tests performed.

Patient 2

- A 23- year- old male with a past medical history of cerebral palsy and ventriculo- peritoneal shunt requiring multiple revisions presented four days after endoscopic third ventriculostomy with fever of 40 C and leakage of clear fluid from the surgical wound. Upon admission a previously placed Rickham reservoir was surgically removed, samples of purulent drainage and cerebrospinal fluid (CSF) cultured, and the patient was started on VAN, cefepime, and metronidazole. Cultures from both CSF and the Rickham reservoir grew MRSA. When Etest revealed the VAN MIC to be 2mg/L, the patient was started on adjunctive CPT 400mg Q8hr while cefepime and metronidazole were discontinued. Heteroresistance testing via Macro Etest method yielded negative results. RIF 300mg orally Q8hr was subsequently added for anti- biofilm activity while awaiting removal of remaining ventriculo-peritoneal shunt components four days later. Treatment with VAN and CPT combination therapy continued for a total of 14 days following shunt removal. Cultures following the removal of the Rickham reservoir remained negative and the patient was discharged home.

Patient 3

- A 61- year- old male with a past medical history of non-ischemic cardiomyopathy, placement of biventricular implantable cardioverter-defibrillator (ICD) and left ventricular assist device (LVAD), presented with recurrent MRSA bacteremia. The patient was approaching completion of four weeks of VAN therapy for MRSA bacteremia and presumed infective endocarditis. DAP 8mg/kg was empirically initiated upon admission. The recurrent MRSA isolate was initially reported via BD Phoenix® as VAN MIC <1mg/L, though subsequent testing via Etest revealed the VAN MIC to be 3mg/L. The initial DAP MIC via Etest was 0.5mg/L. While on DAP therapy, patient underwent removal of ICD and three leads due to evidence of endovascular lead infection. Despite ICD removal, patient remained bacteremic and after eight days on DAP therapy, gentamicin was added at 1mg/kg every 8 hours for synergy. Subsequent to the persistence of bacteremia and climbing DAP MICs, the patient was switched to CPT 600mg every 8 hours after 10 days of DAP therapy. Blood cultures cleared within 48 hours of CPT initiation and remained negative. The patient was discharged on six weeks of CPT and oral RIF 450mg every 12 hours. Over the course of treatment DAP MICs increased from 0.5 to 1.5mg/L, while VAN MIC remained between 2 and 3mg/L.

Patient 4

- A 45- year- old female with a past medical history of intravenous drug abuse initially presented to an outside institution with complaints of non- productive cough, chest pain, and intermittent fever. The patient's condition quickly deteriorated requiring intubation. Chest x-ray was suspicious for pneumonia, blood and sputum cultures were found to be positive for MRSA, while trans- esophageal echocardiogram was negative for vegetations. LZD was empirically started and continued for three days, after which the patient was transferred to UK HealthCare due to deteriorating condition and persistent MRSA bacteremia. DAP 6mg/kg was added to LZD upon transfer, and after 36 hours additional susceptibility testing via Etest revealed reduced susceptibilities to both DAP and VAN (MIC 3-4 and 2mg/L respectively). LZD was replaced by CPT 600mg every 12 hours. An MRI revealed extensive osteomyelitis and discitis with abscess and phlegmon located within the lower cervical spine 24 hours later. In response, DAP was increased to 9mg/kg. Blood cultures cleared 94 hours after dosage increase. Significant reduction in phlegmon and abscess size was noted on subsequent MRI. After 20 days of DAP and CPT the patient developed a suspected drug- induced rash and was switched to LZD monotherapy. Two weeks later, the patient was discharged home to complete an additional six weeks of oral LZD.

Table 1. Summary of Cases

Patient	1	2	3	4
Diagnosis	C5-C6 discitis, epidural abscess	VP shunt infection/ meningitis	Infected left ventricular assist device, endocarditis (probable)	Epidural abscess, complicated bacteremia, pneumonia
Positive cultures	Blood: days 1-2, 5, 54, 56-57, 59, 61-**62** Tissue: day **63**	CSF: days 1, 20 Shunt: day 21	Blood: days 1, 34, 36-43	Blood: days 1-6, **12**
Antimicrobial MIC (mg/L)	VAN (<1, 4, 3, 6) DAP (6, 16, 12, 6, 8) LZD (<2, 2) CPT (0.5, 1)	VAN (<1, 2, 1.5) DAP (<1, 0.25, 0.75) CPT (0.5, 1)	VAN (<1, 3, 2, 3) DAP (0.5, <1, 1, 1.5) CPT (1)	VAN (<1, 2, <1) DAP (<1, 2, 3, <1) LZD (<2, 2, 2) CPT (1, 0.75)
CPT dose and duration	600mg IV q12 days 62 - 106	400mg IV q8 days 24 - 42	600mg IV q8 days 43 - 87	600mg IV q8 days 8 - 15
Prior and concurrent anti- MRSA agents	VAN days 1 - 9 DAP 7mg/kg days 9 - 56 LZD IV days 57 - 106 TXS 10mg/kg/day PO days 60 - 62	VAN days 1 - 42 RIF 300mg PO q8 days 25 - 28	VAN days 1 - 34 DAP 8mg/kg days 34 - 43 gentamicin days 40 - 43 RIF 450 PO q12 days 49 - 87	DAP 6mg/kg days 7 - 8 DAP 9mg/kg days 10 - 15 LZD IV days 2 - 8
Microbiologic al Cure	Yes (day 64)	Yes (day 28)	Yes (day 45)	Yes (day 14)
Clinical Cure	Yes	Yes	Yes	Yes

Days in bold indicate dates of positive cultures while on CPT
Underlined MIC indicate MIC as determined by Etest

Conclusions

- These cases add to the growing clinical evidence supporting the use of ceftaroline in the treatment of serious MRSA infections including those which have failed previous therapies.
- Further investigation will be required to better elucidate the role of ceftaroline both as monotherapy and as an adjunctive agent in the treatment of serious MRSA infections.

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Disclosure:

The authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities.

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