# *Thermomyces lanuginosus* endocarditis and review of endocarditis due to rare molds

M-1680

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## Abstract

**Background**: Infective endocarditis (IE) due to *Thermomyces lanuginosus* (a thermophilic filamentous fungus) is rare. We report a patient who contracted *T. lanuginosus* IE following valvular surgery for bacterial endocarditis. Despite antifungal therapy, she had multiple relapses, spinal osteomyelitis and aortic bifurcation embolism. Voriconazole and 3 cardiac surgeries have prolonged survival to 8 years despite difficulties with therapeutic drug levels and drug toxicity. Absence of management guidelines prompted a review of the clinical aspects and management of rare mold IE.

**Methods**: MEDLINE search was conducted for rare mold IE in humans from 1902-2012. Additional articles were identified by scanning the references. Pooled cases/reviews without clinical data, *Aspergillus* IE and disseminated mold infections were excluded. Demographics, risk factors, clinical features, diagnostic modalities, treatment, drug side effects and outcomes were reviewed.

**Results:** 78 cases of rare mold IE were reviewed. There were 31 hyalohyphomycosis, 28 phaeohyphomycosis and 19 mucormycosis. Median age was 47-52 years. 68-82% were males. 28-43% were immunocompromised hosts. Native valve was involved in 38-81% of cases. Time from surgery to presentation with endocarditis ranged from 6 days to 14 years. Fever was not a presenting feature in 29-32% of cases. Peripheral embolism occurred in 61-95%. Concurrent bacterial IE was documented in 3%. The mold was isolated in blood cultures in 11-64%. 42-77% had surgical management. 47-77% had antifungal therapy. 17% had side effects to antifungals. Duration of antifungal therapy ranged from a few days to ongoing life-long therapy. The mortality rate was 71-74%.

**Conclusions**: Rare mold IE more often affects younger patients and males. Risk factors (e.g. valvular defects, immunosuppression) may not be present. Major peripheral embolism is common. Mortality and relapse rates are high. Aggressive surgical management and prolonged antifungal therapy are required. Voriconazole prolonged survival in our patient. It was difficult to achieve therapeutic drug levels and there was severe skin toxicity.

## Case report

A 31 yr old lady, 10 weeks post partum, developed fever, chills and lethargy after a caesarean section in July 2003. She was febrile at 39.3ºC, had a vasculitic lesion on her right great toe and new ejection systolic and diastolic murmurs. Blood cultures grew *Enterococcus faecalis* and a transoesophageal echocardiogram (TOE) showed a 12mm mobile aortic valve vegetation with moderate aortic regurgitation. A porcine aortic valve prosthesis was inserted. Microscopy of the native valve showed polymorphs and gram positive cocci; cultures were negative. She received 6 weeks of intravenous (IV) ampicillin and gentamicin with good clinical response.

Twelve months later, she represented with fevers and emboli to her left great toe and sole of the foot. Multiple blood cultures were negative. Her TOE demonstrated a 13 x 5mm vegetation at the left coronary cusp. She underwent radical debridement, bioprosthetic aortic valve replacement and reconstruction of the ascending aorta with autologous pericardium. *Thermomyces lanuginosus*, confirmed morphologically and with ITS sequencing, was isolated from valve culture. E test MICs (mg/L) were : amphotericin 32, voriconazole 0.006 and itraconazole 0.032. She was commenced on IV liposomal amphotericin (6 mg/kg daily) and then, oral voriconazole (400mg daily).

Six weeks later she presented with back pain. An MRI scan of the spine demonstrated multiple lesions within vertebral bodies involving discs at T10-11, L2-3 and L 3-4. Abdominal CT scan showed a left common femoral artery mycotic aneurysm, which was repaired with a venous patch. Blood cultures and a CT guided core biopsy of the spine were unrevealing. Repeat TOE did not demonstrate any vegetations. She had a course of empiric ceftriaxone and vancomycin. Voriconazole was continued for a total of 18 months and was ceased in July 2005.

In December 2007, she again presented with a 6 week history of anorexia and fatigue. Blood cultures grew *Streptococcus acidominimus*. No vegetations were seen on TOE. She was treated with 6 weeks of IV penicillin (and 2 weeks of gentamicin) with clinical improvement.

In June 2009, she presented with vasculitic/ embolic lesions to the foot. Multiple blood cultures were negative. TOE was unremarkable. Serology for causes of culture negative endocarditis including Bartonella, Q fever, Mycoplasma and Legionella were negative. HIV serology was negative. She had another 6 week course of ceftriaxone and vancomycin for presumed culture negative endocarditis.

In October 2010, she presented with acute onset of bilateral pale, cold and pulseless lowerlimbs. There were no systemic symptoms of fever, anorexia or weight loss. An urgent CT angiogram demonstrated bilateral common iliac artery occlusive thrombus (Figure 1).

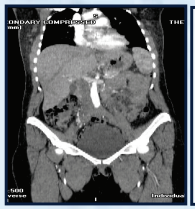

**Figure 1**: CT scan showing bilateral common iliac artery occlusive thrombi, from the aortic bifurcation to the proximal external and internal iliac arteries.

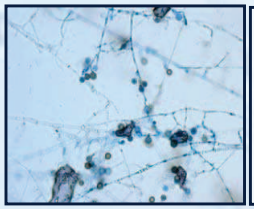

**Figure 2**: *T.lanuginosus* conidiospores are short, straight or flexuose, unbranched or irregularly branched, smooth walled and brownish in colour. The conidia are 7-12µm in diameter and are solitary, dark brown, spherical to subspherical, blackish brown, thick walled and are coarsely verrucose.

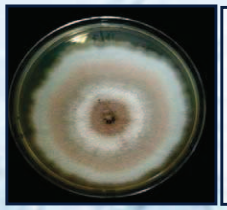

**Figure 3**: *T. lanuginosus* grows best in Potato Dextrose Agar forming green-grey to black colonies with pink to vinaceous pigment diffusing into the agar.

TOE revealed the prosthetic aortic valve to be dehisced from the aortic root, with dilated root adjacent to the dehiscence, and large thrombi. She had an urgent aorto-iliac thromboembolectomy, followed by mechanical aortic valve replacement. She also required a dual chamber permanent pacemaker for complete heart block complicating her cardiac surgery. Histopathology of valvular tissue as well as tissue from embolectomy demonstrated numerous colonies of branching filamentous fungal elements, and the tissue grew *T. lanuginosus* (Figures 2 and 3).

MIC results (mg/L) using E-test and microdilution with Sensititre YeastOne (TREK) performed at 35ºC and 42ºC were: Amphotericin 4, posaconazole 0.25, voriconazole 0.06. She was commenced on voriconazole 200mg twice daily and was discharged with view to lifelong voriconazole therapy. On follow up, she remained well and her voriconazole levels fluctuated between 0.8 to 1.7.

In April 2011, she developed worsening cardiac failure. Her WCC and inflammatory markers were normal. An urgent TOE demonstrated moderate aortic regurgitation and mobile vegetations. She underwent her 4th cardiac surgery which involved replacement of the aortic valve and root with a homograft. Operative tissue again cultured *T. lanuginosus*. The MICs were similar to the results from 2010. Whilst awaiting susceptibility testing, she was commenced on posaconzole given apparent failure of voriconazole. However, once the susceptibilities were available she was changed to voriconazole. In addition, she received oral terbinafine 250mg daily. She had severe photosensitivity rash and hepatitis with voriconazole, particularly with higher doses to maintain adequate drug levels. She is currently on 400mg twice daily with plasma levels at 1.1mg/l. She has no evidence of relapse at 15 months follow up. We plan to continue her on life-long voriconazole therapy.

## Literature review

The clinical aspects and management of opportunistic molds causing valvular endocarditis are not well defined. A MEDLINE search was conducted using the terms "fungi" and "endocarditis", for human studies in English between years 1902 – 2012. References were scanned for additional studies. Pooled cases/reviews without detailed clinical information, *Aspergillus* endocarditis (reviewed in detail elsewhere) and non-valvular cardiac infection as part of disseminated mold infection were excluded. In total, 78 cases were reviewed and the details are summarised in table 1.

**Table 1**: Summary of data

| | Hyalohyphomycosis | Phaeohyphomycosis | Mucormycosis |
|---|---|---|---|
| **No. of reported cases** | 31 | 28 | 19 |
| **Oldest published case report (year)** | 1963 | 1971 | 1962 |
| **Most recent published case report (year)** | 2011 | 2010 | 2010 |
| **Demographics:** | | | |
| **Age (median, range)** | 47 yrs (0-80 yrs) | 52 yrs (0-84 yrs) | 48 yrs (2-76 yrs) |
| **Sex (M (%))** | 68% | 82% | 74% |
| **Risk factors:** | | | |
| **Immunocompromised status:** | 8 (26%)<br>*Corticosteroids (4)*<br>*Diabetes (2)*<br>*Pregnancy (1)*<br>*Lung transplant (1)*<br>*Haematological malignancy (1)* | 12 (43%)<br>*Corticosteroids (4)*<br>*HIV/AIDS (1)*<br>*Liver transplantation (2)*<br>*Bone marrow transplant (1)*<br>*Prematurity (1)*<br>*Diabetes (4)* | 8 (42%)<br>*Haematological disorder (6)*<br>*Renal transplant (1)*<br>*T cell immunodeficiency (1)* |
| **Prior surgery:** | | | |
| Valvular surgery | 21 (68%) | 12 (43%) | 4 (21%) |
| CABG | 4 (13%) | 2 (7%) (+ valvular surgery) | - |
| PPM/AICD | 3 (10%) | 3 (11%) | - |
| Other cardiac/vascular surgery | 2 (6%) | - | 1 (5%) |
| No prior cardiac/vascular surgery | 4 (13%) | 13 (46%) | 14 (74%) |
| **Clinical features:** | | | |
| **Fever** | 22(71%) | 20 (71%) | 13 (68%) |
| **Systemic embolisation** | 19 (61%) | 21 (75%) | 18 (95%) |
| **Time from surgery to presentation** | 10 days – 9 yrs | 2 wks – 14 yrs | 6 days – 2 yrs |
| **Affected valve:** | N=32 | N=32 | N=21 |
| Native | 12 (38%) | 18 (56%) | 17 (81%) |
| Tissue valve | 8 (25%) | 10 (31%) | 0 |
| Mechanical | 9 (28%) | 1 (3%) | 4(19%) |
| Homograft/allograft | 1 (3%) | 2 (6%) | 0 |
| Unclear | 2 (6%) | 1 (3%) | 0 |
| **Anatomical site (valve)** | N=32 | N=32 | N=21 |
| Aortic | 19 (60%) | 15 (47%) | 7 (32%) |
| Mitral | 10 (31%) | 10 (31%) | 10 (48%) |
| Tricuspid | 3 (9%) | 6 (19%) | 2 (10%) |
| Pulmonary | 0 | 1 (3%) | 2 (10%) |
| **Diagnosis** | | | |
| **Positive blood culture** | 7 (23%) | 18 (64%) | 2 (11%) |
| **Positive operative tissue or other fluid histopath/culture/PCR** | 25 (81%) | 22 (79%) | 11 (58%) |
| **Positive post mortem tissue histopath/culture** | 8 (26%)<br>(Diagnosis from post mortem tissue only: 4 (13%)) | 7 (25%)<br>(Diagnosis from post mortem tissue only: 1 (4%)) | 9 (47%)<br>(Diagnosis from post mortem tissue only: 5 (26%)) |
| **Dual infection** | *Engyodontium album + Coagulase negative staphylococci* (1) | *Pseudallescheria boydii +Clostridium limosum* (1) | *Mucor + aspergillus* (2) |
| **Management** | | | |
| **Antifungal therapy** | | | |
| Azole | 15 (48%) | 12 (43%) | 6 (32%) |
| Amphotericin | 20 (65%) | 19 (68%) | 8 (42%) |
| Other or unknown antifungal | 8 (26%) | 4 (14%) | |
| **No antifungal therapy** | 7 (23%) | 8 (29%) | 10 (53%) |
| **Received ≥2 antifungals** | 16 (52%) | 12 (43%) | 6 (32%) |
| **Side effects to antifungals** | 5 (16%)<br>*5-FC: bone marrow suppression (1)*<br>*Ketoconazole: hepatotoxicity (1)*<br>*Amphotericin: renal failure (2)*<br>*Voriconazole: debilitating nausea (1)* | 7 (25%)<br>*Ketoconazole: gynecomastia, impotence (1)*<br>*Amphotericin: renal failure (5)*<br>*Voriconazole: hepatotoxicity (1)* | 1 (5%)<br>*Amphotericin: renal failure (1)*<br>*Voriconazole: "unable to tolerate" (1)* |
| **Duration of antifungal therapy** | Days – ongoing | Days – ongoing | Days – ongoing |
| **Valvular surgery** | 24 (77%) | 19 (68%) | 8 (42%) |
| **Outcome and follow up** | | | |
| **Survived** | 9 (29%)<br>*Surgery + antifungals (8)*<br>*Ongoing antifungals without surgery (1)* | 8 (29%)<br>*Surgery + antifungals (7)*<br>*Antifungals alone (1)* | 5 (26%)<br>*Surgery + antifungals (5)* |
| **Died** | 22 (71%)<br>*Surgery + antifungals (13)*<br>*Surgery alone (3)*<br>*Antifungals alone (2)*<br>*No treatment (4)* | 20 (71%)<br>*Surgery + antifungals (10)*<br>*Surgery alone (2)*<br>*Antifungals alone (3)*<br>*No treatment (5)* | 14 (74%)<br>*Surgery + antifungals (3)*<br>*Surgery alone (0)*<br>*Antifungals alone (1)*<br>*No treatment (10)* |
| **Maximum duration of follow up** | 2.5 years | 5 years | 21 months |

**Table 2:** Rare molds and the number of cases reported in the literature

| Hyalohyphomycete | No. of cases |
|---|---|
| *Acremonium species* | 1 |
| *Acremonium strictum* | 1 |
| *Arthrographis kalrae* | 1 |
| *Chrysosporium species* | 1 |
| *Coprinus species* | 1 |
| *Engyodontium album* | 2 |
| *Fusarium dimerum* | 1 |
| *Fusarium oxysporum* | 1 |
| *Fusarium solani* | 2 |
| *Fusarium species* | 1 |
| *Homographiella aspergillata* | 1 |
| *Microascus cinereus* | 1 |
| *Paecilomyces javanicus* | 2 |
| *Paecilomyces lilacinus* | 1 |
| *Paecilomyces species* | 2 |
| *Paecilomyces variotii* | 3 |
| *Penicillium species* | 3 |
| *Scopulariopsis brevicaulis* | 3 |
| *Scopulariopsis species* | 1 |
| *Thermomyces lanuginosus* | 1 |
| *Trichoderma species* | 1 |
| **TOTAL** | **31** |

| Phaeohyphomycete | No. of cases |
|---|---|
| *Amium leporinum* | 1 |
| *Bipolaris spicifera* | 2 |
| *Curvularia geniculata* | 1 |
| *Curvularia lunata* | 1 |
| *Exophiala castellanii* | 1 |
| *Exophiala dermatitidis* | 1 |
| *Lecythophora mutabilis* | 1 |
| *Petriellidium boydii* | 2 |
| *Phaeacremonium parasiticum* | 1 |
| *Phialemonium curvatum* | 3 |
| *Phialemonium obovatum* | 1 |
| *Phialophora richardsiae* | 1 |
| *Pseudallescheria boydii* | 2 |
| *Scedosporium apiospermum* | 6 |
| *Scedosporium inflatum* | 1 |
| *Scedosporium prolificans* | 2 |
| *Wangiella dermatidis* | 1 |
| **TOTAL** | **28** |

| Mucormycosis | No. of cases |
|---|---|
| *Absidia corymbifera* | *1* |
| *Conidiobolus* | *1* |
| *Cunninghamella bertholletiae* | *3* |
| *Mucor pusillus* | *1* |
| *Mucor spp.* | *10* |
| *Rhizopus mucor* | *1* |
| *Saksenaea vasiformis* | *2* |
| **TOTAL** | **19** |

## Discussion

- Valvular endocarditis due to mold fungi is rare.
- The entity more often affects younger people with a male predominance.
- Risk factors include prior cardiac/vascular surgery (26-87%) and immunodeficiency (26-43%). In prosthetic valve endocarditis, time delay from initial surgery to diagnosis ranges from a few days to 14 years. The valve may be contaminated at the time of surgery, as is likely in our patient, or become infected later.
- Signs and symptoms include : fever (70%), chills, neurological symptoms (weakness, confusion and visual impairment), respiratory symptoms, skin lesions, chest pain, leg pain and constitutional symptoms.
- Systemic embolisation, especially large vessel embolisation, is common.
- Diagnosis may be delayed as blood cultures are insensitive (negative in 36-89% cases) and slow. Histopathological examination of affected tissue is often necessary with 4-26% of cases being diagnosed post-mortem.
- Concurrent bacterial endocarditis can also occur.
- Mortality is high. 23-53% of patients die prior to initiation of antifungal therapy. Overall mortality is 71-74%, despite antifungal therapy.
- Successful treatment requires aggressive medical and surgical management. Relapses occur, and may be late as in our patient. Long term follow up is required (years).
- Lifelong suppressive antifungal therapy may be essential for patients who survive long enough to complete acute treatment. Amphotericin is recommended in mucormycosis, Voriconazole should be considered in the management of hyalohyphomycetes and phaeohyphomycetes. Voriconazole and aggressive surgery prolonged survival in our patient, despite multiple relapses.
- Monitoring of blood voriconazole levels is recommended . Relapses can occur with subtherapeutic voriconazole levels. Persistence/progression of invasive fungal infection has been found to be significantly higher in patients with trough levels <1mg/L. Maintaining appropriate therapeutic levels can be challenging given large inter and intrapersonal variations in levels due to various factors including nonlinear saturable pharmacokinetics and genetic polymorphisms of CYP2C19. Balancing the debilitating side effects such as photosensitivity and hepatic impairment, whilst maintaining therapeutic levels can be problematic when life-long suppressive therapy is required.

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# Early Experience with Ceftaroline Fosamil Therapy at an Academic Hospital System

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## Abstract (updated)

**Background:** The US Food & Drug Administration (FDA) recently approved ceftaroline fosamil (CPT), a cephalosporin, for acute bacterial skin and skin structure infections (ABSSSI) & community-acquired bacterial pneumonia (CABP). CPT is indicated for ABSSSI caused by *S. aureus* (SA) infections including methicillin-susceptible & resistant SA (MSSA & MRSA, respectively). Currently there is limited evidence regarding the use CPT for other infections. The objective of this evaluation is to describe the outcomes of patients (pts) treated with CPT for various infections.
**Methods:** A retrospective cohort review of pts who received > 48 hours of CPT at the Detroit Medical Center from January 2011-July 2012. Clinical & microbiological outcomes were analyzed. Clinical cure (CC) defined as infection resolved at the end of CPT therapy & no additional therapy needed.
**Results:** 72 pts were treated with CPT for various infections: 47% with bacteremia (including 10 endocarditis, 12 pneumonia, 6 ABSSSI, 2 spinal abscesses, & 3 IV catheter-related infections), & 53% without bacteremia (21 pneumonia & 6 ABSSSI). 35% (25/72) patients were treated within its FDA label. Median APACHE II score was 11 (interquartile range [IQR] 6.25-15). 86% (62/72) pts had positive cultures, 81.9% were SA (49 MRSA & 10 MSSA) infections. There were 33 SA bacteremia (SAB): 5 MSSA, 1 hVISA, & 1 VISA. 29% (18/62) were polymicrobial with Gram-negative bacteria. Median total length of stay was 13.5 days (7.25-24.75) & median duration of CPT therapy was 5.5 days (3-12.75). The median CPT MIC for SA was 0.5 mg/L (0.5-1). The most common CPT dosage was 600mg Q12h, and was adjusted for renal function. The median length of time to clearance of SAB was 3 days (1-5.25) from the start of CPT. 93% (63/68) achieved CC or improvement at the end of CPT therapy. 6 pts expired in the hospital where 1 had organism persistence, 3 had microbiologic cure & the remaining 2 had no follow up cultures. 13 pts were re-admitted within 30 days after discharge, 6 had re-admission for the same infection.
**Conclusions**: The majority of pts with SA infections treated with CPT 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.
- There is limited evidence regarding the use of CPT in complicated infections.

References: Product information. Teflaro (ceftaroline fosamil). St. Louis, MO: Forest Laboratories, Inc; April 2011. Steed ME, Vidaillac C, Rybak MJ. Evaluation of ceftaroline activity versus daptomycin (DAP) against DAP-Nonsusceptible methicillin-resistant *Staphylococcus aureus* strains in an in vitro pharmacokinetic/pharmacodyamic model. Antimicrob Agents Chemother. 2011 July;55(7):3522-3526. Vidaillac C, Leonard SN, Rybak MJ. In vitro activity of ceftaroline against methicillin-resistant *Staphylococcus aureus* and heterogeneous vancomycin-intermediate *S. aureus* in a hollow fiber model. Antimicrob Agents Chemother. 2009 Nov;53(11): 4712-4717. Ho TT, Cadena J, Childs LM, et al Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. J Antimicrob Chemother. 2012 May;67(5):1267-70.

## Purpose and Methods

- Our objective was to evaluate the characteristics and outcomes of patients with infections treated with CPT including off-label indications.
- A single-center, retrospective cohort analysis conducted from January 2011 to July 2012 at the Detroit Medical Center (Detroit, MI), an academic hospital system with 8 facilities.
- Consecutive adult patients with an infection treated with CPT for > 48h during hospitalization.

- **Patient Characteristics and Clinical Data:**
  - Clinical data was collected from medical charts of patients
  - Outcome assessments of clinically evaluable included patients with documentation of end of therapy outcome:
    - Clinical cure: resolution of all signs and symptoms of infection with no further need of antibiotic treatment while on CPT.
    - Microbiological cure: eradication of the infecting organism while on CPT.
    - Length of hospital stay (LOS)
  - Patients were also assessed for adverse reactions, readmission, and mortality.
- **Microbiologic Assessments:**
  - Minimum inhibitory concentrations (MIC) were determined by Etest according to Clinical Laboratory Standards Institute guidelines.
- **Statistical Analysis:**
  - SPSS, version 20.0 (IBM SPSS Inc., Chicago, IL) was used to perform descriptive statistics including data frequencies and distributions.

## Results

- 72 patients received CPT and were included for evaluation.

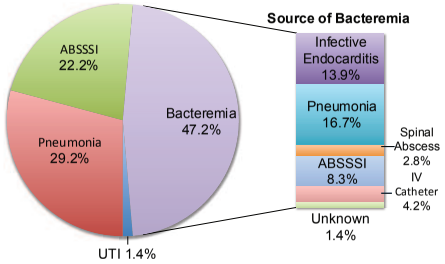
| Baseline Characteristics | Median (IQR) or n (%) (n = 72) |
|---|---|
| Age (years) | 56 (41.3-66) |
| APACHE II Score | 11 (6.3-15) |
| Charlson Comorbidity Score | 3 (1-5) |
| Weight (kg) | 77.9 (66.1-108.9) |
| Creatinine Clearance (mL/min) | 47.4 (20.7-103.5) |
| Prior hospitalization* | 44 (61.1) |
| Male Gender | 43 (59.7) |
| ICU admission | 16 (22.2) |
| Diabetes | 20 (27.8) |
| Heart Disease | 18 (25) |
| Chronic Kidney Disease | 23 (31.9) |
| Hemodialysis | 14 (19.4) |
| COPD | 13 (18.1) |
| Previous antibiotics (3 months) | 16 (22.2) |

*Prior Hospitalization within 1 year for >/= 72 hours, COPD = chronic obstructive pulmonary disease

## Results

### Clinical and Microbiological Characteristics

**Types of Infections n = 72**



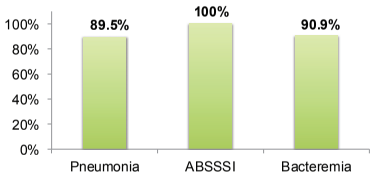

| Pathogens | n |
|---|---|
| *S. aureus* | 59 |
| *K. pneumoniae* | 3 |
| *E. coli* | 2 |
| *M. catarrhalis* | 2 |
| *H. influenzae* | 2 |
| Other Gram negatives | 4 |
| Other Gram positives | 5 |

- 62 patients had positive cultures and 18 patients were treated for polymicrobial infections. Pathogens are listed above.
- The most frequent (69.4%) dose of CPT was 600mg IV Q12h, adjusted for renal function.
  - High dose CPT (600mg IV Q8h) was used in 22 (30.6%) of the infections.
    - 12 bacteremia, 8 pneumonia, & 2 ABSSSI
- 87.5% (63/72) received another antibiotic for the infection prior to CPT administration.
  - Median time to change to CPT was 4 days (IQR 2-7)
- Median duration of CPT was 5.5 days (IQR 3-12.75)

### Clinical and Microbiological Outcomes

- 68 patients were clinically evaluable at end of CPT therapy
  - 92.6% (63/68) had clinical cure.
- Clinical cure by infection is presented to the right.
- 43 patients had follow-up cultures
  - 93% (40/43) had micro cure.
- 61.1% (44/72) received CPT as their definitive therapy for their infection
- Median total length of stay was 13.5 days (IQR 7.25-24.75).

**Clinical Cure by Infection**




- 6 patients died during hospitalization
  - 3 had microbiological cure
  - 1 had organism persistence (MRSA IE)
    - treated on CPT 600mg Q12h + RIF 300mg Q12h
  - 2 had no follow-up cultures (MRSA VAP and MRSA CABP)
    - MRSA VAP treated with CPT 600mg Q12h
    - MRSA CABP with *M. catarrhalis* treated with CPT 600mg Q24h
- 13 patients were re-admitted within 30 days from discharge
  - 6 patients were readmitted for the same infection
    - 2 MRSA pneumonia cases (both cystic fibrosis patients)
    - 1 MRSA BSI with concomitant epidural spinal abscess
    - 2 HCAP (no cultures)
    - 1 necrotizing fasciitis (no cultures)

### Safety

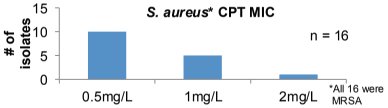
| Patient # | Adverse Outcome | Days of CPT | Outcome |
|---|---|---|---|
| 1 | AIN | 4 | Acute interstitial nephritis improved when changed to linezolid for MRSA BSI |
| 2 | Purpuric rashes | 17 | Rash on bilateral lower extremities was alleviated when changed to DAP for MRSA IE |
| 3 | CDAD | 1 | *Clostridium* difficile-associated diarrhea, continued on CPT for MRSA & *P. stuartii* ABSSSI |
| 4 | Breakthrough bacteremia | 14 | CPT for MRSA and *K. oxytoca* pneumonia. MRSA cleared but had *K. oxytoca* breakthrough bacteremia with elevated MIC (from 0.06 to 1mg/L) |

### *S. aureus* Bacteremia Subset

| Characteristics | Median (IQR) or n (%) (n = 33) |
|---|---|
| MRSA bacteremia | 28 (84.8) |
| Concomitant Infection | |
| Infective Endocarditis | 10 (30.3) |
| Pneumonia | 12 (36.4) |
| ABSSSI | 6 (18.2) |
| Spinal abscess | 2 (6.1) |
| CPT dose and frequency | |
| 600mg* IV Q12h | 22 (66.7) |
| 600mg* IV Q8h | 11 (33.3) |
| Antimicrobial combination with CPT | 13 (39.4) |
| Time to change/add to CPT (days) | 6 (3-10) |
| Duration of CPT (days) | 10 (4-15) |
| Length of stay (days) | 21 (12-29) |
| Duration of SAB^ (days) n = 21 | 3 (1-5) |
| Clinical Outcomes (of evaluable subset) | |
| Clinical cure | 29 (90.6) |
| Microbiological cure | 28 (93.3) |

*dose adjusted for renal insufficiency, ^from the start of CPT therapy

- 16 isolates were tested for CPT MIC. CPT MIC is presented to the right.
  - 2 DNS, 1 hVISA, & 1 VISA
- 4 died during hospitalization
- 1 was re-admitted to hospital




## Conclusions

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

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# Relationships between Gender, Early Valve Surgery (EVS) and Mortality in Patients with Infective Endocarditis (IE) Analyzed in a Multicenter Cohort

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## Abstract

**Background**: A study reported that mortality of IE was higher in women than in men, which was attributed to a lower rate of EVS. Whether gender-related differences in the prognosis of IE are due to a treatment indication bias or to confounding factors is unclear. Our objective was to address this issue using the pooled database of 2 population-based cohorts of IE started in 1999 and 2008.
**Methods**: Demographic and baseline characteristics, complications, and outcome were compared in men and women with Duke-definite, left-sided IE. Information on indications for EVS was available only for the 2008 cohort. Probability of EVS (defined as surgery performed during antibiotic treatment of IE) was analyzed in regression models and results are expressed as OR [95% CI]. Probability of death was analyzed in Cox models and results are expressed as RR [95% CI].
**Results**: The population included 466 (75%) men and 154 (25%) women. As compared to men, women were older (64.3 vs 60.4 y, p=.005), more often on hemodialysis (5.2% vs 1.9%, p=.04), had more often a mitral valve IE (50.0% vs 35.8%, p=.02), less often underwent EVS (37.0% vs 52.4%, p=.002) but had comparable in-hospital mortality rates (20.1% vs. 20.0%, p=.96). 1-year survival probability was not different in men and women (logrank p=.68). In 2008, 181 men (75.7%) and 44 women (59.5%) reportedly had an indication for EVS (p=.007), among whom EVS was performed in 64.1% of the 181 men and 45.5% of the 44 women (p=.02). In multivariable models, EVS was not associated with female gender (OR 0.7 [0.5-1.1]), mortality was not associated with female gender (RR 1.1 [0.8-1.7]), marginally associated with EVS (RR 1.5 [1.0-2.1]) in the whole population, and associated with EVS in women (RR 2.7 [1.3-5.4]) but not in men (RR 1.3 [0.9-2.0]).
**Conclusion**: IE characteristics are different in men and women. Although EVS was performed less often in women, female gender was not an independent predictor of EVS. Overall, in-hospital and 1-year mortality rates were not higher in women. The reasons for a higher risk of mortality in women who underwent EVS must be elucidated.

## Patients and Methods

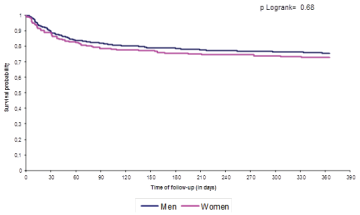
- IE occurs significantly more frequently in men than women.
- Some studies showed that the prognosis of IE was poorer in women than in men. In one study the poorer outcome of IE in women was attributed to a lower rate of early valve surgery in women (Sambola et al., Am J Cardiol 2010;106:92–98).
- Whether gender-related differences in the prognosis of IE results from different comorbid patterns in men and women, a treatment indication bias, gender-related physiological differences, or unidentified confounding factors remains unclear.
- Our objective was to address this issue using the pooled database of 2 population-based cohorts of IE that were started in 1999 and 2008.
- A 5-year patients' follow up was planned for each cohort. Because this time point has not been reached for the second cohort, follow-up was censored at 1 year in the analyses presented hereinafter.
- The study population included 466 (75%) men and 154 (25%) women with Duke-definite, left-sided IE.
- Demographic and baseline characteristics, complications, and outcome were compared in men and women using appropriate tests.
- Early valve surgery (EVS) was defined as surgery performed during antibiotic treatment of IE.
- Probability of EVS was analyzed in logistic regression models and results are expressed as OR [95% CI].
- Probability of death was analyzed in Cox models and results are expressed as HR [95% CI].
  - In all Cox models, EVS was analyzed as a time-dependent variable.
  - In some models, the impact of EVS on outcome was further analyzed after partitioning the follow-up time after valve surgery in 2 periods:
    - from Day 0 to Day 14 after surgery
    - from D15 to Day 365 after surgery.

## Characteristics of patients according to gender

| | Men N=466 (75.2%) | | | Women N=154 (24.8%) | | | |
|---|---|---|---|---|---|---|---|
| | N | %* | SD* | N | %* | SD* | p |
| **Patients' characteristics** | | | | | | | |
| Age, years* | 466 | 60.4 | 14.5 | 154 | 64.3 | 15.9 | 0.0048 |
| Hypertension | 171 | 36.7 | | 70 | 45.5 | | 0.0532 |
| Diabetes | 83 | 17.8 | | 38 | 24.7 | | 0.0624 |
| Cancer | 62 | 13.3 | | 24 | 15.6 | | 0.4780 |
| Dialysis | 9 | 1.9 | | 8 | 5.2 | | 0.0439 |
| Immunosuppression | 29 | 6.2 | | 10 | 6.5 | | 0.9046 |
| Current smoker | 119 | 26.3 | | 21 | 14.0 | | 0.0020 |
| Intravenous drug user | 15 | 3.2 | | 3 | 1.9 | | 0.5826 |
| History of valve disease | | | | | | | 0.9790 |
| No known valve disease | 240 | 51.5 | | 80 | 51.9 | | |
| Native valve disease | 131 | 28.1 | | 42 | 27.3 | | |
| Prosthetic valve | 95 | 20.4 | | 32 | 20.8 | | |
| **Microorganisms** | | | | | | | |
| Streptococcaceae | 280 | 60.1 | | 83 | 53.9 | | 0.1765 |
| Streptococci | 222 | 47.6 | | 67 | 43.5 | | 0.3727 |
| Oral streptococci | 95 | 20.4 | | 31 | 20.1 | | 0.9453 |
| Group D streptococci | 107 | 23.0 | | 20 | 13.0 | | 0.0078 |
| Pyogenic streptococci | 20 | 4.3 | | 16 | 10.4 | | 0.0050 |
| Enterococci | 48 | 10.3 | | 12 | 7.8 | | 0.3614 |
| Other streptococcaceae | 10 | 2.1 | | 4 | 2.6 | | 0.7565 |
| Staphylococcaceae | 121 | 26.0 | | 47 | 30.5 | | 0.2703 |
| Staphylococcus aureus | 95 | 20.4 | | 35 | 22.7 | | 0.5361 |
| Coag-neg staphylococci | 26 | 5.6 | | 12 | 7.8 | | 0.3209 |
| Other microorganism | 34 | 7.3 | | 9 | 5.8 | | 0.5386 |
| **Characteristics of IE** | | | | | | | |
| Location of IE | | | | | | | 0.0202 |
| Aortic | 205 | 44.0 | | 54 | 35.1 | | |
| Mitral | 167 | 35.8 | | 77 | 50.0 | | |
| Aortic and mitral | 79 | 17.0 | | 19 | 12.3 | | |
| Other | 15 | 3.2 | | 4 | 2.6 | | |
| Size of vegetation | | | | | | | 0.5849 |
| No vegetation | 38 | 8.2 | | 15 | 9.7 | | |
| < 10 mm | 108 | 23.2 | | 43 | 27.9 | | |
| 10-15 mm | 123 | 26.4 | | 41 | 26.6 | | |
| >15 mm | 93 | 20.0 | | 24 | 15.6 | | |
| Unknown size | 104 | 22.3 | | 31 | 20.1 | | |
| Perforation | 77 | 16.5 | | 18 | 11.7 | | 0.1487 |
| Intracardiac abscess | 106 | 22.7 | | 23 | 14.9 | | 0.0384 |
| Severe regurgitation | 216 | 48.3 | | 53 | 35.1 | | 0.0047 |
| **Clinical and biological events** | | | | | | | |
| Fever | 409 | 88.3 | | 139 | 90.3 | | 0.5119 |
| Heart failure | 145 | 31.7 | | 40 | 27.2 | | 0.3084 |
| Septick choc | 40 | 8.8 | | 6 | 4.0 | | 0.0563 |
| Vascular event | 134 | 28.8 | | 38 | 24.7 | | 0.3269 |
| Creatinine> 180 µmol/l | 138 | 30.4 | | 40 | 26.5 | | 0.3615 |
| C-RP > 120 mg/l | 188 | 42.9 | | 77 | 53.5 | | 0.0274 |
| **Outcome** | | | | | | | |
| Early valve surgery | 244 | 52.4 | | 57 | 37.0 | | 0.0010 |
| In-hospital death | 93 | 20.0 | | 31 | 20.1 | | 0.9629 |

## One-year survival, by gender

Kaplan-Meir curves and Logrank comparison




## Variables associated with 1-year mortality

Multivariate Cox model, overall population

| | Multivariate Cox model | | |
|---|---|---|---|
| | HR | 95% CI | P |
| Female sex | 1.2 | 0.8 – 1.7 | .40 |
| Age ≥ 65 years | 2.8 | 1.9 – 4.0 | <.0001 |
| Number of comorbidities | 1.3 | 1.1 – 1.4 | .0001 |
| Cardiac failure | 1.4 | 1.0 – 2.0 | .05 |
| Vascular event | 1.8 | 1.3 – 2.5 | .001 |
| Septic shock | 2.1 | 1.3 – 3.3 | .003 |
| Serum creatinine > 180 µmol/L | 2.7 | 1.9 – 3.8 | <.0001 |
| C-RP > 120 mg/L | 2.7 | 1.2 – 4.4 | <.0001 |
| Early valve surgery (time-dependent) | 1.5 | 1.0 – 2.1 | .05 |

## EVS and1-year mortality, by gender

in multivariate Cox models, with EVS as a time-partitioned variable

| | HR | 95% CI | P |
|---|---|---|---|
| Whole population (n = 620) | | | |
| EVS (D0 – D14) | 2.9 | 1.6 – 5.2 | .0003 |
| EVS (D15 – D365) | 0.8 | 0.5 – 1.4 | .44 |
| Men (n = 466) | | | |
| EVS (D0 – D14) | 2.0 | 1.0 – 3.9 | .04 |
| EVS (D15 – D365) | 0.6 | 0.3 – 1.1 | .12 |
| Women (n = 154) | | | |
| EVS (D0 – D14) | 9.1 | 2.6 – 31.6 | .0005 |
| EVS (D15 – D365) | 1.9 | 0.8 – 4.9 | .18 |

## Variables associated with EVS

Univariate and multivariate logistic regression analyses

| | Bivariate regression | | | Mutivariate regression | |
|---|---|---|---|---|---|
| | OR | 95% CI | P | OR | 95% CI |
| Female sex | 0.5 | 0.4 – 0.8 | .0009 | 0.7 | 0.5 – 1.1 |
| Age < 65 years | 2.8 | 2.0 – 3.9 | <.0001 | 2.3 | 1.6 – 3.4 |
| Number of comorbidities | 0.8 | 0.7 – 0.9 | .002 | 0.8 | 0.7 – 1.0 |
| Diabetes | 0.6 | 0.4 – 0.9 | .02 | | |
| Current smoker | 2.0 | 1.4 – 3.0 | .0007 | | |
| Location of IE (vs. mitral° | | | | | |
| Aortic | 1.9 | 1.4 – 2.8 | <.0001 | 1.8 | 1.2 – 2.7 |
| Aortic + mitral | 4.2 | 2.5 – 7.0 | | 3.4 | 1.9 – 6.0 |
| Valve perforation | 3.8 | 2.3 – 6.2 | <.0001 | 3.1 | 1.8 – 5.5 |
| Intracardiac abscess | 3.2 | 2.1 – 4.9 | <.0001 | 2.1 | 1.3 – 3.5 |
| Severe regurgitation | 3.9 | 2.7 – 5.4 | <.0001 | 3.0 | 2.0 – 4.4 |
| Cardiac failure | 2.1 | 1.5 – 3.0 | <.0001 | 2.1 | 1.4 – 3.3 |

## Summary and Discussion

- As compared to men, women
  - were significantly older (64.3 vs 60.4 years, p = .005),
  - were significantly more often on hemodialysis (5.2% vs 1.9%, p = .04),
  - more often had a mitral valve IE (50.0% vs 35.8%, p = .02),
  - less often underwent EVS (37.0% vs 52.4%, p = .002).
- However women had comparable
  - in-hospital mortality rates (20.1% vs. 20.0%, p=.96).
  - 1-year survival probability (logrank p=.68).
- In multivariable adjusted models
  - EVS was not associated with female gender (OR 0.7 [0.5-1.1]),
  - Mortality was not associated with female gender (RR 1.1 [0.8-1.7]),
  - Mortality was marginally associated with EVS (RR 1.5 [1.0-2.1]) in the whole population,
  - The increased risk of mortality observed during the first 14 days after EVS was more pronounced in women than in men. These findings remain to be explained.

**Conclusions**

IE characteristics are different in men and women.

Although EVS was performed less often in women, female gender was not an independent predictor of EVS.

Overall, in-hospital and 1-year mortality rates were not higher in women. The reasons for a higher risk of early mortality in women who underwent EVS is a new finding that remains to be explained.

# Evaluation of Population Analysis Profile (PAP) Susceptibility as a Predictor of Patient Outcomes with Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infective Endocarditis (IE)

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## Abstract

**Background:**
MRSA IE is a serious infection associated with high morbidity & mortality. Vancomycin (VAN) continues to be the treatment of choice for MRSA IE. Emergence of vancomycin heteroresistance (hVISA), defined as modified PAP >/=0.9, may affect outcomes. The objective of this study was to evaluate clinical outcomes of MRSA IE treated with VAN.
**Methods:**
Retrospective cohort review of patients (pts) with MRSA IE from 2004-2012 at Detroit Medical Center. Modified population analysis profile was used to measure VAN susceptibility, such as PAP-MIC and PAP-AUC ratio. Pt characteristics, outcomes and molecular subtyping of isolates were also compared. Composite VAN treatment failure was defined as bacteremia >= 7 days on VAN, new onset of infection on VAN, change of antibiotic therapy or death by MRSA. Classification and regression tree analysis (CART) was used to select VAN failure breakpoint between PAP-AUC ratios.
**Results:**
A total of 102 pts were included for evaluation. Baseline characteristics: Median age 53 (interquartile range [IQR] 45-60), APACHE II 11 (7-14.5), previous hospitalization <= 1yr: 52%, intravenous drug users: 54%, *mec* type 4: 69%, agr type 1: 61%, and hVISA 23%. Overall VAN failure rate was 76%; 49% persistent bacteremia; 49% changed therapy and 17% mortality. On logistic regression analysis, *mec* type 4 (OR, 4.04; 95% CI 1.15-14.13), and PAP-MIC > 2mg/L (OR, 3.18; 95% CI 1.12-9.07) were associated with VAN failure ($P$ = 0.030 and 0.029, respectively). CART breakpoint between VAN failures and success for PAP-AUC ratio was 0.89944.
**Conclusion:**
PAP-MIC greater than 2mg/L and *mec* type 4 were significant for VAN failure for pts with MRSA IE. hVISA with PAP-AUC ratio greater than 0.89944 predict failure. Further research is warranted for PAP, PAP-MIC in pts with MRSA infections.

## Introduction and Purpose

- Vancomycin (VAN) remains the drug of choice for the treatment of MRSA bloodstream infection and infective endocarditis (IE) despite its association with persistent bacteremia and high failure rates.
- Prolonged use of VAN has led to the emergence of MRSA strains with reduced susceptibility, including heteroresistant vancomycin-intermediate *Staphylococcus aureus* (hVISA).
- Characterization of treatment outcomes with respect to patient underlying conditions, organism susceptibility and overall drug exposure is important to understand the reason for poor drug performance and potential for alternative strategies.
- Our objective was to evaluate the clinical outcome of patients with MRSA IE, who were treated with vancomycin on the basis of vancomycin susceptibility.

## 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), persistent or new onset of signs and symptoms while on VAN, change of antibiotic therapy (change VAN to an alternative anti-MRSA agent or addition of another anti-MRSA agent) or death by MRSA
- 30-day mortality
- Length of hospital stay (LOS)
- Days of bacteremia (time from 1st positive blood culture to first day of 48 hours of negative blood culture)

**Microbiological Assessment:**
- VAN minimum inhibitory concentration (MIC) were determined by broth microdilution per Clinical Laboratory Standards Institute guidelines.
- VAN population analysis profiles (PAP) were determined at an inoculum of approximately 1 x $10^9$ CFU/mL, 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.
- Area-under-curve (AUC) for each strain was determined by the trapezoid rule with SigmaPlot 9.0 (Systat Software, Inc., Richmond, CA).
- VAN PAP-MIC were determined from VAN PAP and was defined as the lowest VAN concentration when the inoculum is below the level of detection.

**Statistical Analysis:**
- Continuous variables were assessed by Student's *t*-test or Mann Whitney *U* test for non-parametric variables.
- Categorical variables were analyzed using Chi-squared or Fisher's exact test were appropriate.
- Factors with a $P$ value of </= 0.2 by univariate analysis were included in the logistic regression analysis. $P < 0.05$ was considered significant.
- Classification and regression tree analysis (CART) was used to select the PAP-AUC ratio to Mu3 PAP-AUC to determine the influence of VAN treatment failure.
- SPSS Statistics, version 20.0 (IBM SPSS Inc., Chicago, IL) was used to perform statistical analysis and classification and regression tree analysis (CART).

## Results

### Clinical Characteristics

**Clinical Characteristics of Patients with Vancomycin Treatment Success vs. Failure**

| Characteristics | VAN Success Median (IQR) or n (%) (n = 25) | VAN Failure Median (IQR) or n (%) (n = 77) | *P* value |
|---|---|---|---|
| Age (years) | 49 (37.5-58) | 54 (47.5-60) | 0.061 |
| APACHE II Score | 10 (6-14.5) | 11 (7-14.75) | 0.538 |
| Weight (kg) | 72 (64.9-75) | 71 (59-85) | 0.959 |
| Creatinine Clearance (mL/min) | 50 (28.7-89.9) | 52.3 (16.5-79.1) | 0.407 |
| Prior hospitalization </= 1 year | 15 (60) | 38 (49.4) | 0.354 |
| Previous S. aureus | 4 (16) | 18 (23.4) | 0.436 |
| Intravenous Drug User | 17 (68) | 38 (49.4) | 0.104 |
| Diabetes | 3 (12) | 20 (26) | 0.146 |
| Renal Disease (ARF, CKD, or HD) | 8 (32) | 34 (44) | 0.283 |
| Prior VAN </= 30 days | 7 (28) | 16 (20.8) | 0.453 |
| Left-sided IE* | 5 (20) | 36 (46.8) | 0.018 |

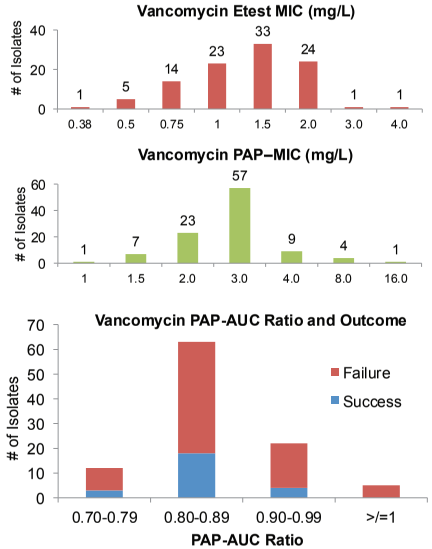
*VAN = vancomycin; ARF = acute renal failure; CKD = chronic kidney disease; HD = hemodialysis; Left-sided IE = included patients with both left and right-sided IE

### Microbiological Characteristics

| Characteristics | n (%) (n = 102) |
|---|---|
| VAN BMD MIC | |
| 0.5mg/L | 12 (11.8) |
| 1.0mg/L | 66 (64.7) |
| 2.0mg/L | 24 (23.5) |
| PAP-AUC median (IQR) | 0.8658 (0.8260-0.8993) |
| hVISA | 23 (22.5) |
| SCC*mec* type | |
| Type II | 32 (31.4) |
| Type IV | 70 (68.4) |
| *agr* genotype | |
| Group I | 62 (60.8) |
| Group II | 37 (36.3) |
| Group IV | 4 (3.9) |
| *agr* function | |
| Preserved | 85 (83.3) |
| Dysfunctional | 17 (16.7) |
| PVL function | |
| Positive | 64 (62.7) |
| Negative | 38 (37.3) |
| USA300 | 55 (53.9) |

BMD = brothmicrodilution, VAN = vancomycin, *agr* = accessory gene regulator, PVL = Panton-Valentine leukocidin, hVISA = heteroresistant vancomycin *S. aureus*

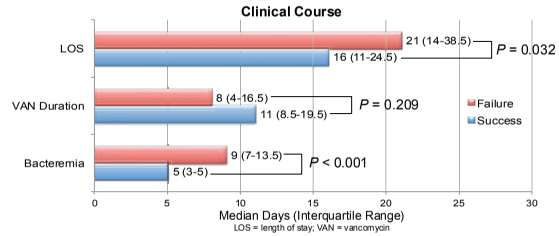
The PAP-AUC ratio breakpoint derived by CART analysis that partitioned VAN failure was 0.89944.




### Microbiological and Clinical Outcomes

**Microbiological Characteristics of Patients with VAN Treatment**

| Characteristics | VAN Success n (%) (n = 25) | VAN Failure n (%) (n = 77) | *P* value |
|---|---|---|---|
| VAN MIC > 1mg/L, Etest method | 13 (52) | 46 (60) | 0.496 |
| SCC*mec* type IV | 21 (88) | 49 (64) | 0.090 |
| *agr* function present | 23 (96) | 57 (78) | 0.959 |
| USA300 | 17 (68) | 38 (49) | 0.104 |
| hVISA | 2 (8) | 21 (27) | 0.045 |
| PAP-MIC > 2mg/L | 14 (56) | 57 (74) | 0.089 |
| Initial VAN trough < 15mg/L | 8 (33) | 39 (55) | 0.067 |




- Overall 17 (16.7%) patients died within 30 days from first positive blood culture
- A logistic regression was used to assess VAN treatment failure. The variables that remained in the model is listed below.

**Logistic Regression Results for Vancomycin Treatment Failure**

| Variable | OR (95% CI) | *P* value |
|---|---|---|
| PAP-MIC > 2 mg/L | 3.18 (1.12-9.07) | 0.029 |
| SCC*mec* type IV | 4.04 (1.15-14.13) | 0.030 |

### Conclusions

- Vancomycin is associated with treatment failure in patients with MRSA IE
- Patients that failed vancomycin therapy are associated with hVISA, longer length of hospitalization and prolonged duration of bacteremia
- PAP-MIC > 2mg/L and *SCCmec* type IV are two independent predictors of vancomycin treatment failure in patients with MRSA IE
- PAP-AUC ratio > 0.89944 predicts VAN treatment failure consistent with the definition of hVISA identification

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