A Retrospective Review of the Pathogenicity of *Corynebacterium jeikeium* at ECU Health Medical Center

Rebecca E. Smidy MD, Shakiba Hassanzadeh,

John E. Markantonis D.O. D(ABMM) FCAP FASCP

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Introduction

Overview of Corynebacterium species and *C. jeikeium*

Corynebacterium species

- Aerobic Gram-positive rods, catalase positive
- Have a characteristic “picket-fence” appearance on Gram-stain due to “snapping” replication method, called coryneform morphology
- When an organism has this characteristic gram-stain morphology and is not considered to clinical represent *C. diphtheriae* the name “dipthroids” is commonly used

Corynebacterium species

- Closely related to aerobic actinomycetes (such as *Nocardia* spp.) and *Mycobacterium* species and related-genera.
- Some species are lipophilic and can be difficult to culture in standard bacterial media, needs blood agar or a media supplemented with lipids (oleic acid) such as Middlebrook agar/broth.
- Most are common flora of the skin and other mucosal surface and were largely considered non-pathogenic historically; however, with the ability to rapidly identify these organisms with MALDI-TOF additional pathogenic species have been identified.

DT-producing *Corynebacterium* species

- *C. diphtheriae*
  - DT producing strains causes diphtheria, respiratory and cutaneous form
    - Toxin produces lethal systemic impairment while organism remains at local site of infection
  - Non-DT producing stains commonly cause of non-healing cutaneous wounds
- *C. ulcerans*
  - Similar pathogenicity to C. *diphtheriae*
- *C. pseudotuberculosis*
  - Necrotizing lymphadenitis, pneumonia, ocular infections

Non-DT-producing *Corynebacterium* species

- Key Examples of Pathogenic *Corynebacterium* species
  - *C. minutissimum*
    - Erythrasma
  - *C. urealyticum*
    - Encrusted cystitis
  - *C. kroppenstedtii*
    - Granulomatous mastitis
  - *C. macginleyi*
    - Ocular infections
  - C. otitidis
    - Inner & outer ear infections
  - *C. pseudodiphteriae*
    - Pneumoniae especially in critically ill patients intubated patients
  - *C. striatum*
    - Wide-range of pathogenicity especially in cases with indwelling medical devices

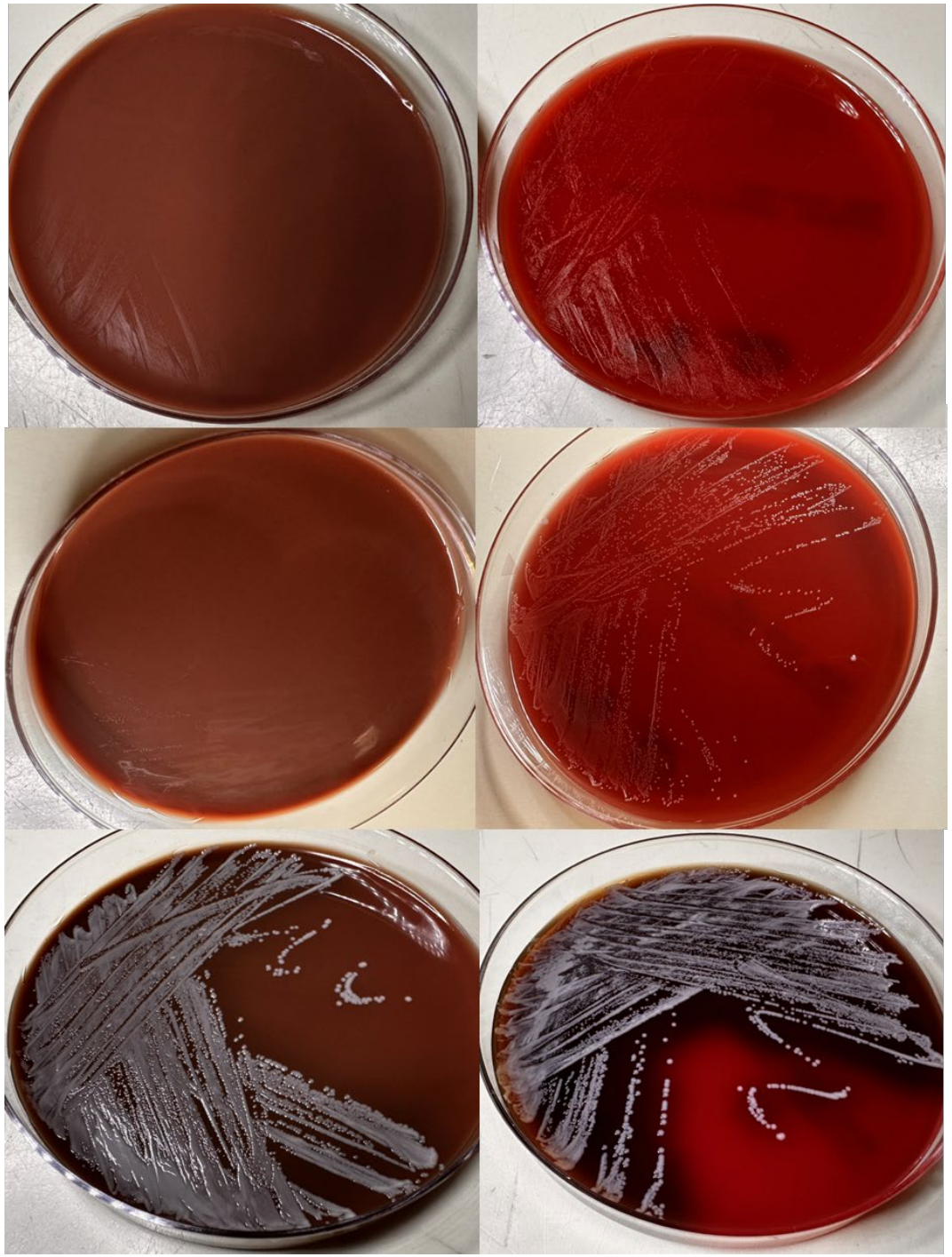
Corynebacterium jeikeium

- Also, a non-DT producing *Corynebacterium* species
- Lipophilic organism, takes at least 48 hours to grow on blood agar
  - Even then it tends to be weakly growing and MALDI-TOF may struggle to ID it
  - Not uncommon for it to not grow on our routine bacterial cultures at ECU Health Medical Center but be picked up in our AFB culture which uses a lipid enriched media
- Often a Multidrug-resistant (MDR) organism

Corynebacterium jeikeium (24 hours)

Corynebacterium jeikeium (48 hours)

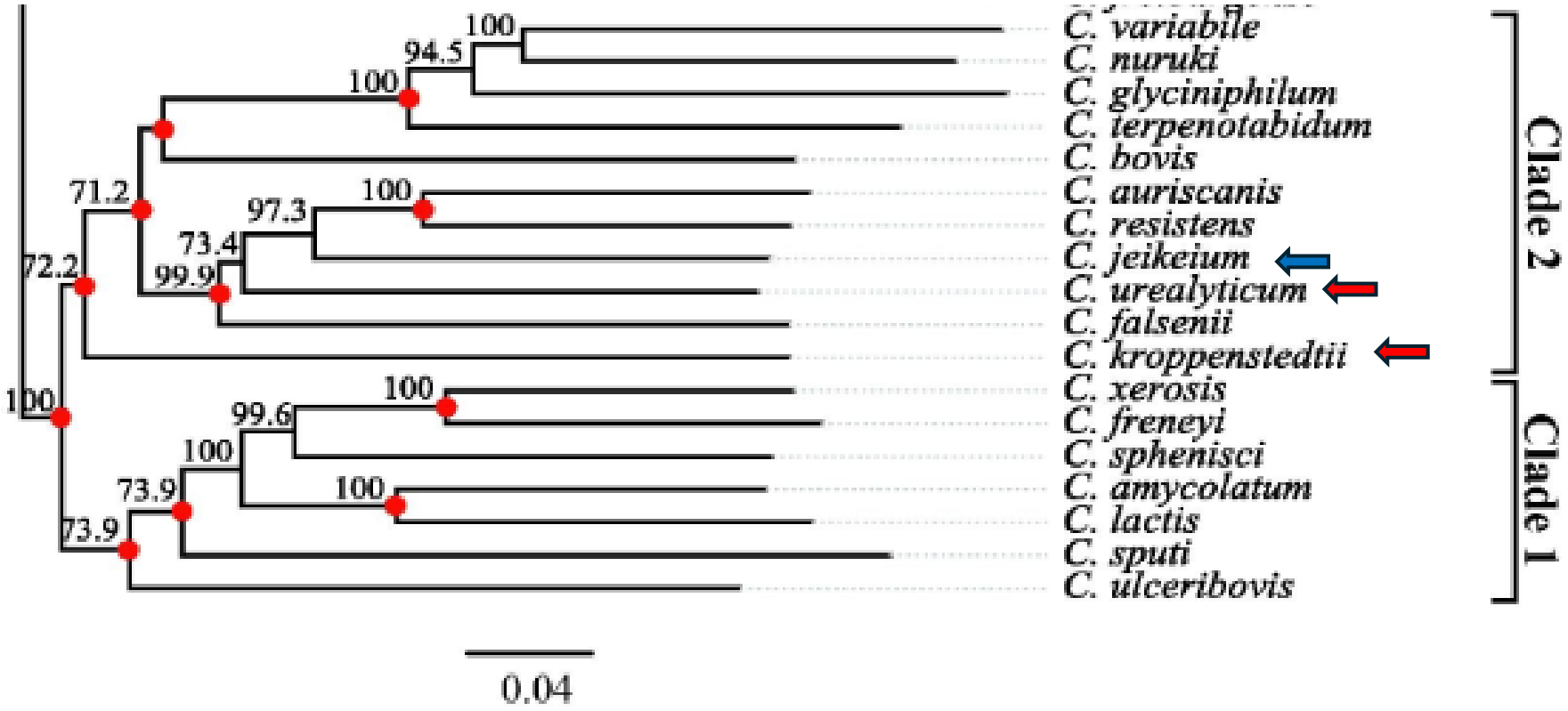
Corynebacterium striatum (24 hours)



Corynebacterium jeikeium

- Commonly colonizers the skin of individuals especially chronically ill hospitalized patients.
- Literature has shown that it can be a virulent organism for certain patient populations, largely immunosuppressed patient especially those with hematolymphoid malignancies or status post–BMT.
  - Has been associated with high mortality in disseminated cases
  - Also shown to cause infective endocarditis and blood stream infections in immunocompetent individuals as well

Corynebacterium jeikeium



Zhi XY, Jiang Z, Yang LL, Huang Y. The underlying mechanisms of genetic innovation and speciation in the family Corynebacteriaceae: A phylogenomics approach. Mol Phylogenet Evol. 2017 Feb;107:246-255. doi: 10.1016/j.ympev.2016.11.009. Epub 2016 Nov 15. PMID: 27864136., Figure 5 altered

C. jeikeium-association with HLM/BMT

- There is a known association between disseminated *C. jeikeium* and patient with hematolymphoid malignancies
- Typically, the source is from either a cutaneous wound source or from endovascular catheter.

Table 1 Demographic and clinical characteristics of 53 patients with positive blood cultures for *Corynebacterium jeikeium*

Characteristic	*Number*	*(%)*[a]
Age, years mean (range)	40	(3–74)
Sex		
Male	41	(77)
Female	12	(23)
Diagnosis		
Acute lymphocytic leukemia	5	(9)
Acute myelocytic leukemia	17	(32)
Chronic myelogenous leukemia	10	(19)
Lymphoma	7	(13)
Myelodysplastic syndrome	8	(15)
Multiple myeloma	3	(6)
Breast cancer	1	(2)
Neuroblastoma	1	(2)
Severe combined immunodeficiency	1	(2)
Type of transplant[b]		
Allogeneic	41	(77)
Autologous	8	(15)
High-dose steroids for GVHD[c]		
Yes	16	(39)
No	25	(61)
Reason for blood draw		
Fever	46	(87)
Surveillance	6	(11)
Unknown	1	(2)
ANC[d] on day of culture		
0	14	(27)
≤500	16	(30)
>500	23	(43)
Days after transplant median (range)[e]	17	(1–375)

[a]Unless otherwise specified.
[b]49 of 53 patients underwent bone marrow transplant.
[c]High-dose steroids defined as methylprednisolone 2 mg/kg/day in 41 patients undergoing allogeneic bone marrow transplant and at risk for graft-versus-host disease.
[d]Absolute neutrophil count.
[e]45 patients with positive blood cultures on or after day of transplant.

C. jeikeium BSI

Table 1. Patients with *Corynebacterium* species detected in blood cultures, Japan, 2014–2020

Corynebacterium species	Total, n = 115	True bacteremia, n = 60	Contamination, n = 55
C. striatum	67	47	20
C. jeikeium	14	10	4
Other, total	34	3	31
C. accolens	1	0	1
C. afermentans	6	0	6
C. amycolatum	4	1	3
C. aurimucosum	4	0	4
C. coyleae	1	0	1
C. glucuronolyticum	1	0	1
C. minutissimum	4	0	4
C. mucifaciens	1	0	1
C. pseudodiphtheriticum	1	0	1
C. resistens	2	0	2
C. riegelii	1	1	0
C. simulans	3	0	3
C. singulare	2	0	2
C. tuberculostearicum	2	0	2
C. urealyticum	1	1	0

Yamamuro R, Hosokawa N, Otsuka Y, Osawa R. Clinical Characteristics of Corynebacterium Bacteremia Caused by Different Species, Japan, 2014-2020. Emerg Infect Dis. 2021 Dec;27(12):2981–7. doi: 10.3201/eid2712.210473. PMID: 34812137; PMCID: PMC8632174.

C. jeikeium IE

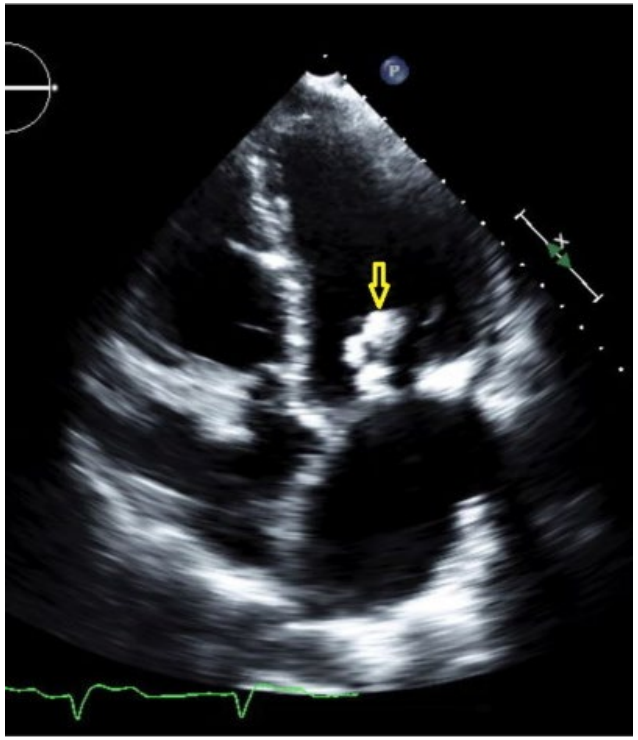


TABLE 2. Cases Associated With Valvular Endocarditis Due to *Corynebacterium Jeikeium*

No.	Author	Year	Age	Sex	Co-morbidities	History of Valve Replacement	Endocarditis Site	Indwelling Line	Antibiotic Therapy	Antibiotic Duration	Surgical Treatment	Outcome
1	Etienne et al[11]	1988	68	Male	AI	AVR (Medtronic)	Aortic valve	No	Vancomycin, Rifampicin	not specified	No	Recovery
2	Vanbosterhaut, et al[12]	1989	77	Female	AS, MR	AVR and MVR	Mitral valve	No	Vancomycin	6 weeks	MVR	Recovery
3	Vanbosterhaut, et al[12]	1989	51	Male	MR, Dental carries	NA	Mitral valve	No	Vancomycin, Gentamicin	6 weeks	MVR	Recovery
4	Vanbosterhaut, et al[12]	1989	54	Male	ESRD, HD, MR	No	Mitral valve	No	Vancomycin	10 weeks	No	Recovery
5	Vanbosterhaut, et al[12]	1989	57	Female	MS, TI, CAD requiring CABG	AVR, MVR, tricuspid annuloplasty	Mitral valve	No	Piperacillin, Netilmicin, Erythromycin	not specified	No	Death
6	Vanbosterhaut, et al[12]	1989	45	Male	Mixed AS/AI, LV dilatation	AVR	Aortic valve	No	Vancomycin	30 days	AVR	Recovery
7	Moffie, et al[13]	1990	32	Female	ESRD on HD	No	Aortic and mitral valves	No	Vancomycin	4 weeks	No	Death
8	David, et al[14]	1992	56	Female	Alcoholic, liver transplant, Immunosuppressed, ESRD on HD	No	Aortic valve	Dialysis catheter, central line	Vancomycin, Amphotericin	2 weeks	AVR	Recovery
9	Martinez-Vea, et al[15]	1993	41	Male	FSGS leading to ESRD on HD, Failed renal transplant, postsplenectomy	No	Aortic valve	No	Vancomycin, Gentamicin	not specified	AVR	Death
10	Ross, et al[16]	2001	63	Female	CAD requiring CABG	No	Aortic valve	Right femoral cannulation	Vancomycin, Gentamicin	4 days	AVR	Death
11	Knox and Holmes[17]	2002	53	Male	Not specified	MVR (Mechanical)	Mitral valve	Dialysis catheter	Vancomycin, Rifampicin	6 weeks	No	Death
12	Mookadam, et al[4]	2006	84	Male	AS	AVR (Porcine bioprosthetic)	Aortic valve	No	Vancomycin, Gentamicin, Rifampicin	6 weeks	AVR	Recovery
13	Marques, et al[18]	2007	66	Male	DM type 2, HTN	No	Aortic valve	No	Vancomycin	7 weeks	No	Recovery
14	Bechara, et al[19]	2011	72	Male	Permanent pacemaker, PR3-ANCA positive	No	Pacemaker	No	Vancomycin, Doxycycline, Rifampicin	Vancomycin 2 weeks followed by Doxycycline + Rifampicin 4 weeks	Pacemaker change	Recovery
15	Lappa, et al[20]	2012	57	Male	AS	AVR (Mechanical)	Aortic valve	No	Daptomycin, Rifampicin, Ceftazidime	6 weeks	AVR	Recovery
16	Syed, et al[21]	2014	49	Male	ESRD on HD	No	Aortic valve	No	Vancomycin	6 weeks	AVR	Recovery
17	Clarke, et al[22]	2019	53	Female	FSGS leading to ESRD on HD	No history before first episode, but AVR, MVR in subsequent episodes	Aortic and mitral valves	No	Vancomycin, Daptomycin	Vancomycin - 8, 6, 12 and 12 weeks; Daptomycin 15 days	AVR and MVR	Recovery
18	Not published	2019	72	Female	Atrial fibrillation, MR	MVR (Bioprosthetic)	Mitral valve	No	Daptomycin	6 weeks	MVR	Recovery
19	Not published	2019	46	Male	Bicuspid aortic valve, AI and MR	AVR and MV Repair	Aortic and mitral valves	No	Vancomycin, Ceftriaxone	6 weeks	Mechanical AVR and MV repaid	Recovery

AI indicates aortic insufficiency; ANCA, anti-neutrophil cytoplasmic antibody; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass graft; DM, diabetes mellitus; CAD, coronary artery disease; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HD, hemodialysis; MR, mitral regurgitation; MS, mitral stenosis; MVR, mitral valve replacement; TI, tricuspid insufficiency.

Rezaei Bookani K, Marcus R, Cheikh E, Parish M, Salahuddin U. Corynebacterium jeikeium endocarditis: A case report and comprehensive review of an underestimated infection. Idcases. 2018 ;11:26-30. DOI: 10.1016/j.idcr.2017.11.004. PMID: 29619320; PMCID: PMC5881414. Figure 1

Gupta R, Popli T, Ranchal P, Khosla J, Aronow WS, Frishman WH, El Khoury MY. Corynebacterium Jeikeium Endocarditis: A Review of the Literature. Cardiol Rev. 2021 Sep-Oct 01;29(5):259-262. doi: 10.1097/CRD.0000000000000355. PMID: 32976125.

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C. jeikeium Blood Isolates

- Due to its known virulence *C. jeikeium* isolated from blood should be reported to species level
  - Ideally Corynebacterium spp. not *jeikeium* should be used to alert the treating team that it is not this known pathogen which is associated with BSI and dissemination.
  - It also important to know, given it is a known skin colonizer, it may be a blood culture contaminant from inoculation of the skin plug into the blood culture bottles after ineffective skin decontamination.
  - Careful clinical determination is needed when this organism is detected in blood cultures.

C. jeikeium Isolates from Other Body Sites

- Its significance in cultures from other body sites has not been well established in the literature and through societal procedural recommendations (example: ASM Procedure Manual).
- *C. jeikeium* is frequently isolated at ECU Health Medical Center. It is likely missed on some cultures due to its fastidious nature and difficulty in obtaining a MALDI-TOF identification. It is commonly reported as “Coryneform GPR” or Dipthroid” as our current standard operating protocol (SOP) for most bacterial cultures call for the medical technologist to largely disregard these organism in many culture situation (mixed cultures)

Evaluating a Change to our SOPs for QI

- Key considerations when evaluating a change to our SOPs for workup and reporting of this organism
  - Overreporting to species level can result in overtreatment if the organism is mostly a colonizer or contaminant
  - Under reporting can lead to untreated infections
    - How often is *C. jeikeium* a primary pathogen when recovered from culture?
    - How often is it a contaminant?
    - What is the clinical impact associated with underreporting & overreporting of this organism
  - Does the organism have a predictable antimicrobial susceptibility profile
    - Is their benefits to performing susceptibility testing on this organism

Methods and Materials

QI project design

Methods and Materials

- Retrospective study ECU Health Medical Center
  - *C. jeikeium* isolates obtained at ECU Health Medical Center
    - Both reported and unreported C. jeikeium isolates
    - 01/01/2020 through 12/31/2023
    - Only 1 isolate per individual per day was counted in this study.
  - Data analysis
    - Direct specimen Gram stain result
    - Culture Interpretation
    - ID consultation obtained prior to or after specimen collection
    - Targeted treatment of *C. jeikeium* by clinical team
      - Treatment regiment
    - Patient demographics
      - Diabetic
      - Immunosuppressed
      - Active hematolymphoid malignancy or under therapy

Data Analysis

- Specimen source
  - Superficial vs deep (sterile) collections
    - Example of superficial collection: diabetic toe ulcer (swab), sacral decubitus ulcer swab
    - Example of a deep (sterile) collection: bone obtained from OR amputation, IR drainage of an abdominal abscess, blood, CSF, other sterile body fluids
- Direct specimen Gram stain result
  - Quantification of in-vivo organism load
    - Aide in culture interpretation
- ID consultation and directed treatment
  - Aides in determining the clinical significance of this pathogen in our patient population and our institutional treatment practice towards this organism
- Patient demographics
  - The workup of a polymicrobial diabetic ulcer toe swab is different then an invasively collected sample from an immunosuppressed patient
  - Is the literature associated with HLM and *C. jeikeium* applicable to our patients

Data Analysis

- Culture Interpretation
  - Predominant organism (1 or 2 organism with heaviest growth in culture)
    - Example: 3+ *C. jeikeium* with 3+ *S. aureus* in an OR bone sample
  - Co-pathogen in mixed culture (3+ pathogens with no predominant organism)
    - Example: 4+ *C. jeikeium*, 4+ *S. epidermidis*, 4+ *P. aeruginosa & 4*+ mixed anaerobes in a surface wound swab
  - Likely contaminant or colonizer
    - Example: 1 colony from a CSF sample obtained for MS diagnosis, or 1+ in a skin biopsy with histopathology consistent with a pyogenic granuloma

Results

Results of retrospective chart review

Results

- 60 isolates from 52 unique individuals were identified in the study
  - Primary Pathogen
    - N=12
  - Copathogen in a mixed infection
    - N=23
  - Likely Contaminant or colonizer
    - N=17

Results

- Probable Infections
  - Prosthetic joint or orthopedic hardware infections
    - N=8
  - Peritoneal dialysis catheter-associated bacterial peritonitis
    - N=2
  - Deep post-surgical space infection
    - N=1
  - Disseminated infection from a cutaneous source
    - N=1, patient with active HLM

Results

- Most blood culture and urine culture isolates were likely contaminants.
  - Blood cultures
    - 7/9 collections are contaminants
      - 2 sets grew C. jeikeium in disseminated case
  - Urine cultures
    - 7/7 cultures considered contaminants

Results

Table 1. Antimicrobial Susceptability Testing

Penicillin	Ceftriaxone	Meropenem	Vancomycin	Ciprofloxacin	Doxycycline	Trimethoprim/Sulfamethoxazole	Clindamycin	Linezolid	Daptomycin*
I	R	I	S	NT	S	R	R	S	NT
R	R	R	S	S	S	R	R	S	1
R	R	R	S	R	S	NT	NT	NT	NT
I	R	I	S	R	S	R	R	S	1
R	R	R	S	R	S	R	R	S	0.5
R	R	R	S	NT	NT	NT	NT	NT	NT
R	R	R	S	NT	NT	R	NT	NT	NT
R	R	R	S	NT	NT	NT	NT	NT	NT
R	R	R	S	NT	NT	NT	NT	NT	NT
R	R	R	S	NT	NT	NT	NT	NT	NT
R	R	R	S	R	S	R	R	S	NT
R	R	I	S	S	S	S	R	S	1

Abbreviations: S, susceptible; I, intermediate; R,; resistant
*no clinical breakpoints are available for interpretation, minimum inhibitory concentration listed

Discussion

Analysis of study findings and impact of Institutional SOP changes

Discussion

- *C. jeikeium* pathogenicity was most often identified in patients with musculoskeletal infections, especially in patients with retained orthopedic hardware and prosthetic joint infections.
- Severe disease in hematolymphoid malignancy was also seen.
- Lipophilic coryneform GPRs should be identified to species level to rule-out *C. jeikeium* when found to be a primary or predominant pathogen in tissue/fluid cultures, especially in prosthetic joint/hardware-associated infections and peritoneal dialysis-catheter infections.
- It is often a contaminant in blood and urine cultures.
  - But disseminated cases can occur in HLM and IS patients.
- Susceptibility testing may be warranted when deemed a pathogen due to the multi-drug resistant nature of this pathogen.

Discussion

- Proposed SOP changes
  - The presence of *C. jeikeium* should be ruled out in cultures obtained from sterile sites (blood, CSF) and invasively collected samples, especially hardware-associated sites.
  - Lipophilic coryneform GPRs (pinpoint colonies on blood agar) require a minimum of 48 hours prior to MALDI-TOF to accomplish this.
  - Corynebacterium species, not *C. jeikeium* should be reported in corynebacterium isolated from clinical samples when this rule out has occurred due to the relatively frequent occurrence of this isolate in our microbial population in eastern NC.
  - Susceptibility testing should be considered due to the variability in drug-resistance profile seen in this organism including MDR strains.
    - Vancomycin, daptomycin, linezolid and doxycycline are likely the best options for empirical therapy.

Discussion

- Study limitations
  - Relatively small sample period (48 months and number of unique organisms (N=52).
  - *C. jeikeium* is likely underreported in the study due to its fastidious nature and difficulty identifying through use of MALDI-TOF without extended incubation (48 hours).
  - Number of organisms submitted antimicrobial susceptibility testing in low, ideally 30 isolates should be tested per drug to generate an antibiogram for an organism.
  - Continued study of the clinical implications and best reporting considerations for this organism is required in our institution.