hVISA and MRSA endocarditis – an 8-year experience in a tertiary care center

Yasmin Maor[1,3], Natasha Belausov,[2] Debby Ben-David[1], Gili Smollan[2], Nathan Keller,[2] Galia Rahav[1,3]

Infectious Disease Unit and microbiology laboratory, Sheba Medical Center, Tel Hashomer, Tel-Aviv University, Israel

Correspondence to:
Yasmin Maor, MD,
Infectious Disease Unit,
Sheba Medical Center,
Tel Hashomer, 52621, Israel
yasmin.maor@sheba.health.gov.il

BACKGROUND

- IE due to *Staphylococcus aureus* with heterogeneous intermediate resistance to vancomycin (hVISA) is an emerging disease
- Patients with hVISA bacteremia have
  - Higher rates of infectious endocarditis (IE) compared to MRSA bacteremic patients
  - Bacteremia in hVISA patients is significantly longer compared to MRSA bacteremic patients
- Infectious attributable mortality is high in both groups of patients (~40%)

Maor. J Infect Dis 2009;199:619-624

- Only one study addressed the clinical course of hVISA IE
  - 19 hVISA IE patients were compared to 46 MRSA IE patients
  - Patients with hVISA IE were older, and more likely to have native valve IE
  - None were injection drug users
  - Patients with hVISA had a higher rate of persistent bacteremia and congestive heart failure
  - Rates of other complications and in-hospital mortality did not differ significantly between groups

Sea. J Infect Dis 2009;200:1355–66

AIM OF STUDY

To assess the prevalence, clinical course and outcomes of hVISA IE and to compare these patients to patients with MRSA IE

METHODS

- All cases of hVISA and MRSA IE diagnosed at the Sheba Medical Center from 2003-2010 were included
- IE was diagnosed according to the modified Duke criteria
- All isolates were screened prospectively for hVISA by Etest macromethod
- The Etest macromethod was validated against the population analysis profile at our laboratory
  - Specificity was 100%, sensitivity was not assessed
- Tolerance was defined as MBC/MIC ≥16
- Medical records were reviewed
- T-test, χ^2 were and Fisher exact tests were used as appropriate

RESULTS

- 14 and 32 cases of hVISA and MRSA IE were identified
- Pacemakers and implantable cardioverter-defibrillators (P/ICDs) were significantly more common in the hVISA group
- P/ICDs IE occurred in 29% of hVISA patients and 6.3% of MRSA patients
- hVISA patients had significantly more positive blood cultures and a trend toward lengthier bacteremia
- CNS involvement (bleeding/new neurological deficits) tended to be more common in MRSA patients

Figure 1. Number of patients with hVISA and MRSA IE

Table 2. Antibiotic susceptibility of *S. aureus* isolates

	hVISA IE N=14	MRSA IE N=32	P value
Vancomycin Etest MIC mi/l (SD)	1.5 (0.59)	1.1 (0.50)	0.11
Vancomycin tolerance (%)	6 (54.5)	2 (15.4)	0.08
Daptomycin Etest MIC mi/l (SD)	0.75 (0.72)	0.32 (0.16)	0.049
Linezolid Etest MIC mi/l (SD)	0.55 (0.27)	0.83 (0.62)	0.4
Tigecycline Etest MIC mi/l (SD)	0.17 (0.07)	0.26 (0.21)	0.5

- Mean vancomycin MIC was >1mg/l in both groups
- Tolerance to vancomycin was more common in hVISA isolates
- MIC to daptomycin was higher in hVISA isolates regardless of past exposure to daptomycin
- All MRSA patients were treated with vancomycin
- hVISA patients were switched to daptomycin, linezolid, or SMX-TMP

Patients' outcomes

- Cardiac surgery and/or P/ICDs extraction was performed more commonly in hVISA patients
- Mortality was high in both groups
- Median time from 1st positive blood culture to death was longer in hVISA patients

Table 1. Patients' characteristics

	hVISA IE N=14	MRSA IE N=32	P value
Sociodemographic details			
Age (years) (SD)	74.2 (12.8)	77.4 (20.1)	0.6
Males (%)	10 (71.4)	20 (62.5)	0.6
General medical history			
Charlson score (SD)	4.4 (3.4)	4.6 (2.7)	0.8
Diabetes (%)	6 (42.9)	11 (34.4)	0.6
Chronic renal failure (%)	5 (35.7)	14 (43.8)	0.6
Cardiac medical history			
Artificial valves (%)	3 (21.4)	8 (25.0)	0.8
Pacemaker/ICD (%)	7 (40.0)	7 (21.9)	0.05
Definition and site of IE			
Definite IE (%)	10 (71.4)	23 (71.9)	0.98
Native valve IE (%)	4 (28.6)	17 (53.1)	0.12
Artificial valve IE (%)	3 (21.4)	8 (25.0)	0.8
Pacemaker/ICD IE (%)	4 (28.6)	2 (6.3)	0.06
IVDU IE	0	0	-
Clinical course and outcome			
Number of blood cultures (SD)	8 (4.7)	5 (2.4)	0.007
Median length of bacteremia (days)	15	7.5	0.08
Embolic phenomena (%)	4 (28.6)	7 (21.9)	0.6
CNS bleeding/new neurological deficits (%)	0	7 (21.9)	0.08
Cardiac surgery and/or P/ICDs extraction (%)	7 (50.0)	5 (15.6)	0.027
Mortality (%)	8 (57.1)	21 (65.6)	0.6
Median time from 1st positive blood culture to death (days)	39	19	0.09

DISCUSSION

- hVISA IE is associated more often with p/ICDs than MRSA IE and less often with native valves, probably reflecting more exposure to vancomycin in this group
- CNS involvement in hVISA patients was rare, perhaps due to more p/ICD IE
- Emerging resistance to daptomycin is of concern in hVISA patients
- Both hVISA and MRSA IE cause devastating disease with high mortality
- Low rates of surgical intervention and P/ICDs extraction reflect the high co-morbidity of these patients
- The results underscore the importance of early diagnosis of hVISA

K-1898

Significant Epidemiological Differences Exist Between Geographical Regions for *Staphylococcus aureus* Infective Endocarditis

S.Y.C. Tong[1,2], P.A. Pappas[1], S. Bukovski[3], M. Rodriguez-Créixems[4], T. Korman[5], J.M. Miro[6], G.R. Corey[1], C.W. Woods[1], V.H. Chu[1], V.G. Fowler Jnr[1], International Collaboration on Endocarditis Investigators

[1]Duke University Medical Center, Durham, NC, United States; [2]Menzies School of Health Research, Darwin, Australia; [3]University Hospital for Infectious Diseases, Zagreb, Croatia; [4]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [5]Southern Health, Melbourne, Australia; [6]Hospital Clinic–Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona

CONTACT INFORMATION:
Steven Tong
Department of Medicine
Duke University Medical Center
Box 3281 Medical Center
Durham, NC 27710
Phone: 919-684-[illegible]
Fax: 919-684-[illegible]
E-mail:
steven.tong@duke.edu

Abstract

Background: The epidemiology of infective endocarditis (IE) may demonstrate geographical regional variation.

Methods: We examined the International Collaboration on Endocarditis database for cases of *Staphylococcus aureus* IE. Cases were stratified by region and differences in demographics, comorbidities and outcomes were determined.

Results: Of definite *S. aureus* IE, 320, 597, 268 and 73 cases were from North America, Europe, Australasia and South America respectively. Cases from North America were significantly more likely to be receiving hemodialysis, have diabetes, have methicillin-resistant *S. aureus* (MRSA) infections and have persistent bacteremia, but less likely to receive surgery. Survival analysis of mortality at one year revealed significant regional differences (P=0.033) with survival greatest in Australasia and lowest in North America. Although there were distinct variables associated with mortality on multivariate analysis for each region, there were also consistent associations across the regions.

Conclusion: Even with a single causative organism, there are significant differences in IE epidemiology when infections are compared across developed regions of the world where standards of healthcare should be similar. Therefore homogeneity across regions cannot be assumed and caution needs to be exercised in extrapolating findings from one region to another.

Background and methods

Infective endocarditis (IE) is now most commonly caused by *Staphylococcus aureus* in the developed world[1]. In this setting, *S. aureus* IE (SAIE) is also associated with an increased mortality risk compared to non *S. aureus* IE[1]. However, heterogeneity exists within SAIE with differences in clinical disease according to host factors such as healthcare versus community acquisition and organism factors such as the presence of methicillin-resistance[2]. A further source of heterogeneity is geography.

The purpose of this study was to investigate the nature of geographical regional differences for cases of SAIE in the International Collaboration on Endocarditis – Prospective Cohort Study (ICE-PCS) using an updated and expanded dataset and with a focus on the outcome of one year survival.

For ICE-PCS, data on patients with IE from 61 centers in 28 countries were collected prospectively between June 2000 and December 2006. Patients with definite IE were determined by Duke criteria[3]. For this study, all patients from sites in North America, Europe, Australasia (Australia and New Zealand) and South America with SAIE were included.

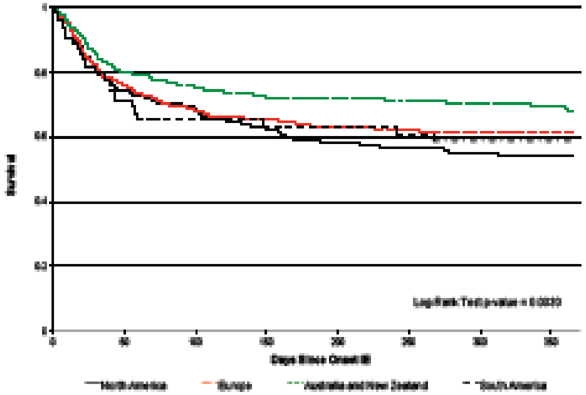
Results

Of 1297 cases of definite IE due to *S. aureus* in the ICE-PCS database, 320, 597, 268 and 73 cases (total of 1258 cases) were from North America, Europe, Australasia and South America respectively. A comparison between the four regions is presented below. Key differences were that cases from North America were significantly more likely to be receiving hemodialysis (30% compared to <10% elsewhere), be healthcare-associated, have diabetes, have MRSA infections, have persistent bacteremia, and have had a previous episode of IE, but less likely to receive surgery.

	All regions (N=1258)	North America (N=320)	Europe (N=597)	Australasia (N=268)	South America (N=73)	P
Age (median, IQR)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Native valve IE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Prosthetic valve IE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Healthcare associated	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
Comorbidities						
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Diabetes mellitus	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
Hemodialysis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
IDU	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
Previous IE episode	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Microbiology						
MSSA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
MRSA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
Echocardiographic findings						
AV vegetation	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
MV vegetation	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Paravalvular complications	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Surgery this episode	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Complications						
Stroke	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Embolization	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Intracardiac abscess	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Congestive heart failure	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Persistent bacteremia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	<0.001
In-hospital death	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Results (cont)

<u>Survival analysis</u> of mortality at 1 year found significant regional differences in survival (P=0.03); survival was greatest in Australasia and lowest in North America.



<u>Multivariate Cox Proportional Hazards models</u> were built separately for North America, Europe and Australasia. There were three shared predictors of mortality between all regions, and three further factors shared by two of three regions.

Variable	North America	Europe	Australasia
	Hazard ratio with 95% CI		
Age in 1 year intervals	1.02 (1.0,1.0)	1.03 (1.0,1.0)	1.05 (1.0,1.1)
Surgery this episode	0.50 (0.3,0.7)	0.68 (0.5,0.9)	0.46 (0.3,0.8)
Stroke	2.07 (1.4,3.1)	1.63 (1.2,2.2)	2.95 (1.8,4.7)
Congestive heart failure	1.82 (1.3,2.6)	1.67 (1.3,2.2)	
Hemodialysis	1.73 (1.2,2.5)	1.73 (1.2,2.5)	
Persistent bacteremia	1.47 (1.0,2.1)		2.68 (1.6,4.4)
Conjunctival hemorrhage		1.96 (1.2,3.3)	
Native valve predisposition		1.63 (1.2,2.2)	
MRSA		1.41 (1.0,1.9)	
Paravalvular complications		1.44 (1.1,2.0)	

Conclusions

- Regional differences do exist for SAIE, even when the analysis was restricted to areas of the developed world with similar access to healthcare resources. Thus, homogeneity cannot be assumed and caution needs to be exercised in extrapolating findings from one region to another.
- The high prevalence of hemodialysis patients in the US cohort may be related to less use of native arteriovenous fistulas in the US compared to Europe[4].
- Although this analysis has uncovered regional differences, important aspects of SAIE are also shared across the regions and provides reassurance that previously published findings from datasets such as ICE-PCS are generalizable.

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DUKE MEDICINE

Dr Tong is supported by an Australian National Health and Medical Research Council Postdoctoral Training Fellowship ([illegible]), an Australian-American Fulbright Scholarship and a Royal Australasian College of Physicians Bayer Australia Medical Research Fellowship. Dr Fowler is supported by [illegible].

Aspirin plus Ticlopidine Prevents Experimental Endocarditis induced by Continuous Low-Grade Bacteremia: a role in Prophylaxis of Endocarditis Due to Spontaneous Bacteremia in Humans?

T.R. Veloso[1], A. Chaouch[2], V. Rousson[2], M. Giddey[1], J. Vouillamoz[1], P. Moreillon[1], J.M. Entenza[1]
[1]DMF and [2]IUMSP, University of Lausanne, Switzerland
contact: Rafael.Veloso@unil.ch

UNIL | Université de Lausanne
Departement de microbiologie fondamentale

Introduction

Platelets (Figure 1) have a strong role in infective endocarditis (IE) as they are key players in vegetations structure (1). Thus, there is a rational for the use of antiplatelet drugs to prevent IE. Combinations of aspirin (ASA) and ticlopidine (TCL) were previously tested to prevent *Staphylococcus aureus* experimental endocarditis (2), but this strategy was unsuccessful. One of the reasons could be that prophylaxis was overwhelmed by the artificial inoculation of large bacterial numbers resulting in high-grade bacteremia. In humans, IE usually follows cumulative low-grade bacteremia, which often results from routine daily activities such as tooth brushing (3, 4).

Aim

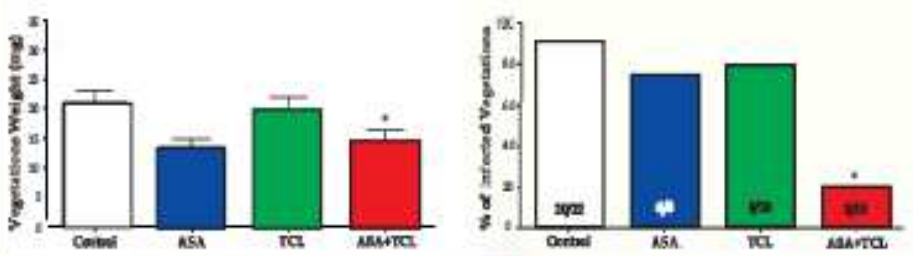
To test the prophylactic effect of ASA+TCL, using a new rat model of experimental endocarditis induced by continuous low-grade bacteremia, mimicking bacteremia following cumulative daily events in humans (6). *Streptococcus gordonii* and *S. aureus* Newman were used as infecting organisms.

Figure 1 - Targets of antiplatelet drugs (adapted from 5).

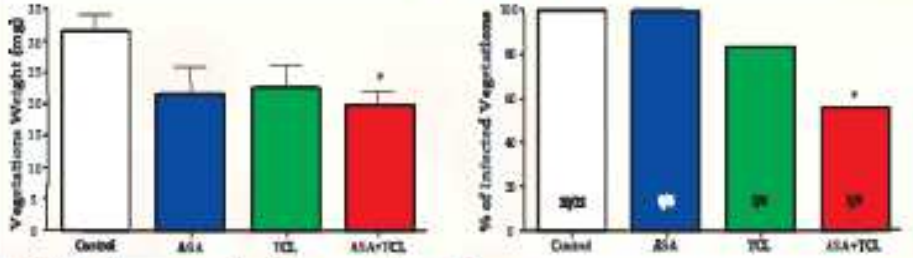
Experimental Design

Results

S. gordonii Challis



S. aureus Newman



* $P < 0.05$ when compared with the respective control.

Conclusions and Perspectives

ASA plus TCL successfully reduced the vegetations weight and infection rate when implemented in a realistic model of low-grade bacteremia experimental endocarditis. These results suggest that ASA plus TCL, which are often used to prevent cardiovascular events, could also be effective in preventing IE that follows spontaneous low-grade bacteremia in humans.

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Sonication of Removed Devices for Microbiological Diagnosis of Cardiac Device Infections

A. OLIVA, B.L. NGUYEN, M.T. MASCELLINO, F. CHIARINI, F. MENGONI, A. CICCAGLIONI, F. FATTORINI, P. PAVONE, V. VULLO, C.M. MASTROIANNI

Sapienza University, Rome, Italy

ABSTRACT

Background: Microbiologic diagnosis is essential for the optimal diagnosis of Cardiac Device Infections (CDIs). We evaluated the role of sonication of explanted devices for the detection of causative organism of CDI. **Methods:** A total of 60 explanted devices (20 generators, 5 grafts and 35 lead tips) were obtained from 20 patients with CDI (pocket infection=18; device related endocarditis=2). As controls, 20 non-infected generators were collected. Devices were inoculated in tryptone soy broth (TSB) for 24 h and cultured with traditional methods. They were also vortexed for 30 sec and sonicated for 5 min at a frequency >20 kHz using the Ultrasonik 300 bath (Ney, BarkMeyer Division, Yucaipa, CA). **Results:** Among the 60 infected devices, 47 (77%) grew bacteria after sonication and 36 (60%) with conventional culture methods (p=0.001). Considering both generator and grafts, 75% yielded bacteria following traditional technique and 100% showed bacterial growth after sonication. The overall bacterial growth of lead tips was 68%. 16/35 (45%) were positive without sonication and 24/35 (68%) after sonication. Bacterial cell count was significantly higher in sonication fluid culture than standard culture (p=0.001), especially when the UFC/ml in TSB was < 10^4 UFC/ml. Pocket swab cultures were positive in 6/18 subjects (33.4%). Blood cultures were negative in all 18 patients with pocket infections and positive in the 2 patients with device-related endocarditis (*S. epidermidis* and *C. albicans*). Among the non-infected generators, 12 (60%) were sterile, 4 (20%) yielded bacteria with and without sonication, 4 (20%) grew only after sonication. **Conclusion:** Sonication of explanted devices may represent a useful tool to improve microbiologic diagnosis of CDI and asymptomatic bacterial colonization.

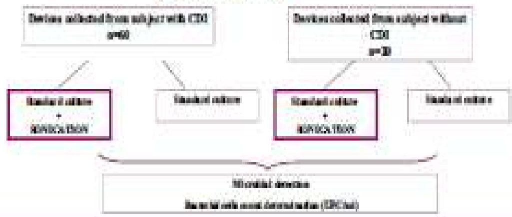
INTRODUCTION

The overall rate of CDI has been increasing over the time, with a global incidence of 1.9/1000 devices-year. Most of CDI involve the subcutaneous pocket; however, a device-related endocarditis represents 10% of CDI. Known risk factors for CDIs are previous pocket revision, renal failure and anticoagulant use. *Staphylococcus spp* causes 60-80% of CDIs whereas 7-21% of CDIs are culture negative. Although intraoperative pocket swabs and pocket tissue cultures are often performed for the microbiological diagnosis of CDIs, they have a poor sensitivity (34% and 69%, respectively). **Thus, there is a lack of a *"gold standard"* for the microbiological diagnosis of CDIs.**

MATERIALS AND METHODS

Over a six months period, a total of 40 subjects who underwent device removal or revision was included in the study: 20 patients with CDI (18 pocket infection, 2 device-related endocarditis) and 20 patients without CDI. In the first group, intraoperative pocket swabs and blood cultures were performed and all cardiac device components (generator, graft and atrial/ventricular lead tips; n=60) were collected; in the non-infected group, only the generators (n=20) were collected. The collected devices (n=80) were submitted both to standard microbiological culture (without sonication) and to culture after sonication. Briefly, the devices were inoculated in TSB for 24 h, then vortexed for 30 s, sonicated for 5 min at a frequency > 20kHz, vortexed again for 30 s and centrifuged at 3200 rpm for 15 min. The resulting sonication fluid was cultured following the traditional methods. Both the sonicated and non-sonicated fluids were cultured for the determination of the bacterial cell count (UFC/ml). Statistical analysis were performed using STATA 9 software (STATA corp. LP, College Station, Texas, USA).

STUDY DESIGN



RESULTS

Table 1: General characteristics of population

[illegible]

Table 2: Characteristics of subjects with CDI

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Fig. 1: Microbiology of CDI

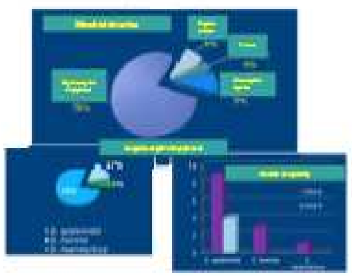

Fig. 2: Comparison of the different diagnostic techniques among subjects with CDI. The sensitivity of sonication is higher than standard culture and pocket swab culture

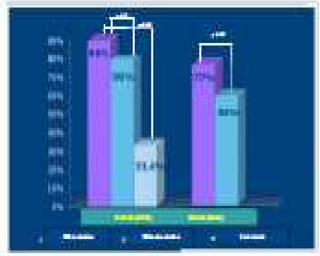

Fig. 3: Difference in bacterial cell count between culture with and without sonication

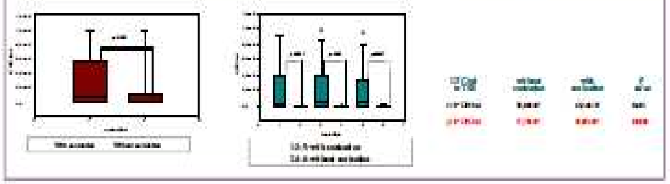

Fig. 4: Antibiotic therapy has no effects on the diagnostic performance of sonication culture

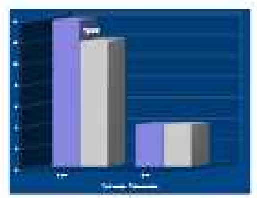

Fig. 5: Asymptomatic bacterial colonization in subjects without CDI

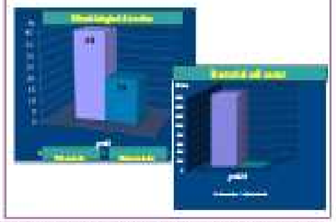

Fig. 6: Bacterial cell count value in order to discriminate infected vs colonized devices in sonication fluid culture. A value < 10^4 UFC/ml is associated with bacterial device colonization.

CONCLUSION

The sensitivity of sonication fluid culture is higher than standard culture, both in infected and non-infected cardiac devices. Bacterial cell count is significantly higher in sonication fluid culture than traditional culture, especially when the amount of bacterial cells is lower than 10^4 UFC/ml. **Sonication of explanted devices may represent a useful tool to improve microbiologic diagnosis of CDI and asymptomatic bacterial colonization.**

REFERENCES

[illegible]