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Role of Sonication in the Microbiological Diagnosis of Implant-Associated Infections: Beyond the Orthopedic Prosthesis

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Abstract

Implant-associated infections are difficult-to-treat conditions associated with high morbidity, mortality and length of hospitalization. They are characterized by biofilm formation on implant surface, which makes the microbiological diagnosis difficult and requires a complete device removal for the correct management. The sonication method, which is based on the application of long-wave ultrasounds radiating in a liquid medium, has been recently validated for the diagnosis of prosthetic joint infections. Additionally, this technique has been considered a potential tool in order to improve the microbiological diagnosis of infections associated with other foreign bodies, such as breast, urinary, endovascular and cerebral implants. In the present study, the application of sonication in the setting of implant-associated infections other than orthopedics will be reviewed.

Keywords

Implant Associated Infections (IAIs) • Sonication • Microbiological diagnosis

1 Introduction

The rate of implant positioning has increased over time, mostly due to the rise of median age and the increased prevalence of cardiovascular, neurological and bone/joint diseases (Zhang et al. 2014; Bradshaw et al. 2014). In addition, the growing incidence of tumors has led to the need of breast reconstruction surgery, long-term central venous and urinary catheters use (Jung et al. 2015).

Although rare, implant-associated infections (IAIs) have been increasing worldwide and are associated with high morbidity and mortality.

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The diagnosis of IAIs may be a real challenge for physicians, due to the wide variety of presenting symptoms and to their chronic and relapsing nature (Trampuz and Zimmerli 2008; Baddour et al. 2010; Hasse et al. 2013). In order to obtain a microbiological diagnosis, the complete device removal is required; however, traditional cultures often give negative results because adherent bacteria that are encased in biofilms on the surface of implanted device can encumber microorganism detection (Stewart and Costerton 2001). In recent years, the development of ultrasounds-based technologies aimed at improving the microbiological diagnosis of IAIs has been investigated.

So far, many studies evaluated the role of sonication method in the setting of prosthetic joint infections (PJIs), leading to its validation in the microbiological diagnosis of these infections (Tunney et al. 1998; Trampuz and Zimmerli 2005; Trampuz et al. 2007). In fact, culture of samples obtained by prostheses sonication has found to be more sensitive than conventional periprosthetic-tissue cultures for the microbiological diagnosis of prosthetic hip and knee infections, especially in patients with previous antimicrobial therapy (Trampuz et al. 2007). In addition, sonicate fluid culture was more sensitive than periprosthetic tissue culture in the setting of prosthetic shoulder infections (Piper et al. 2009) and at least as sensitive as periprosthetic tissue culture to detect prosthetic elbow infections (Vergidis et al. 2011).

Among several advantages including the possibility of performing molecular (Achermann et al. 2010; Portillo et al. 2012) and immunological studies on sonication fluid, the quantification of the number of microorganisms and the detection of polymicrobial growth represent additional important tools whose knowledge might augment and spread the use of this method. In fact, a CFU cut-off in the sonication fluid has been established for distinguishing PJIs from aseptic failures (Trampuz et al. 2007) and for diagnosing Central Venous Catheters (CVC)-related infections (Mermel et al. 2009) whereas only preliminary data are found for external ventricul drains (EVD)/ventriculo-peritoneal shunts infections (VPS) (Jost et al. 2014) or for cardiac device infections (CDIs) (personal data, not shown).

In addition, the sonication method has shown the ability to isolate different bacterial phenotypes such as small colony variant (SCV) and multidrug resistant (MDR) bacteria. SCV, which is a slow-growing phenotype associated with intracellular persistence and fastidious growth requirement, has been recognized as a leading cause of IAIs including CDIs (Tumbarello et al. 2012a) and PJIs (Piffaut et al. 2013).

Furthermore, in an era of MDR bacteria, the microbiological diagnosis of IAIs is crucial for choosing the optimal antimicrobial treatment. In this setting, our group demonstrated that a MDR *Corynebacterium striatum* causing pacemaker lead endocarditis could have been detected only throughout sonication (Oliva et al. 2010).

On the other hand, a disadvantage of sonication is represented by the potential risk of contamination, which might occur during sample processing.

The role of sonication method in the microbiological diagnosis of IAIs other than PJIs is an area of active investigation. This technique has been considered a potential essential tool in order to improve the microbiological diagnosis of infections associated with other foreign bodies such as breast, urinary, endovascular and cerebral implants. In the present study, the application of sonication in the setting of implant-associated infections other than orthopedics will be reviewed.

2 Sonication Technique

Since it has been established in the late 1990s (Tunney et al. 1998), a technique based on the application of long-wave ultrasounds (defined by frequencies above the range of human hearing, 20 kHz) has been used in order to enhance bacterial growth by liberating sessile organisms embedded in biofilm on foreign bodies (Nguyen et al. 2002; Klug et al. 2003; Carmen et al. 2005; Bjerkan et al. 2009; Rieger et al. 2009; Sampedro et al. 2010; Bonkat et al. 2011).

Technically, ultrasound waves radiate through a liquid media and produce high- and

low-pressure areas. During the low-pressure phase, lots of microscopic bubbles form and then collapse during the high-pressure phase by releasing a high amount of energy on the surface of the foreign body. This agitation causes a vacuum-scrubbing action able to dislodge bacteria (Pitt and Ross 2003; Trampuz et al. 2003). The mechanism through which ultrasounds exert their activity on bacteria is the phenomenon of acoustic cavitation (Joyce et al. 2003), which is considered to influence both size and formation of cavitation bubbles.

Another application of this method is the lysis of bacterial cells. Whether bacteria are dislodged from foreign bodies or are lysed depends on several factors such as acoustic frequency, energy, temperature and time of ultrasound exposure. For instance, biofilm removal by sonication strongly depends on the intensity of sonication energy (power density) and, to a lesser extent, on frequency (Pitt 2005).

For low ultrasonic frequencies (20–40 kHz), large cavitation bubbles form and generate high energy when they collapse. However, at higher frequencies (580 kHz), the acoustic cycle is shorter with a minor time for cavitation bubble formation; therefore, the cavitation bubbles are smaller and collapse with low energy (Joyce et al. 2003).

The duration of sonication has been recognized as an important factor influencing the viability of bacteria. In fact, the more is the length of ultrasound exposure, the more is the probability that bacteria are killed. A previous study showed a significant reduction in live/viable bacterial cell numbers after 15 min treatment at low frequencies (Joyce et al. 2003).

Among different sonication protocols (Tande and Patel 2014), the most widely used for dislodging bacteria from foreign bodies are based on 1-min (Trampuz et al. 2007) or 5-min duration of sonication (McDowell and Patrick 2005; Sampedro et al. 2010; Oliva et al. 2013), with or without the centrifugation as a concentration process (Fig. 1). Under these conditions, despite a low amount of bacteria might be killed throughout the mechanical and chemical effects of ultrasounds, the majority of microorganisms remain viable and are able to grow in solid media (Monsen et al. 2009).

In addition, it has been reported that the shape of bacteria might have a significant effect on their sensitivity to ultrasonic treatments. Generally, large bacteria are more sensitive to sonication than small bacteria because of the large surface area exposed to ultrasound. Thus, cocci/spherical bacteria are more resistant to sonication than bacilli/rod shaped bacteria (Joyce 2003). In particular, Gram-negative bacteria seem to be more susceptible to the detrimental effects generated by ultrasounds (cell wall thinning of cell membranes, localised heating and production of free radicals) than Gram-positives due to the lack of a thick and robust cell wall (Piyasena et al. 2003).

3 Breast Implants

Breast implants are increasingly used for aesthetic reasons or in patients after mastectomy (Cook and Perkins 1996; Herdman and Fahey 2001). Although infection occurs in 1.1–2.5 % after aesthetic breast augmentation and up to 35 % after breast implant reconstruction following mastectomy (Washer and Gutowski 2012), common complications after breast surgery with prosthesis implantation are capsular fibrosis and capsular contracture (Spear and Baker 1995).

The aetiology of capsular contracture remains still unclear. Different hypotheses are considered; however, many authors postulated that bacterial colonization and biofilm formation by coagulase-negative Staphylococci (CoNS), *Propionibacterium acnes* and other skin-flora microorganisms might lead to chronic inflammation and subsequent implant fibrosis (Del Pozo et al. 2009; Portillo et al. 2013; Rieger et al. 2014).

Although several authors investigated the role of sonication in determining whether capsular contracture was associated with bacterial colonization, only few studies included subjects with breast implant infection (Table 1).

In 2013, Rieger et al. performed a multicentric study with the aim of investigating the association between the presence of capsular contracture

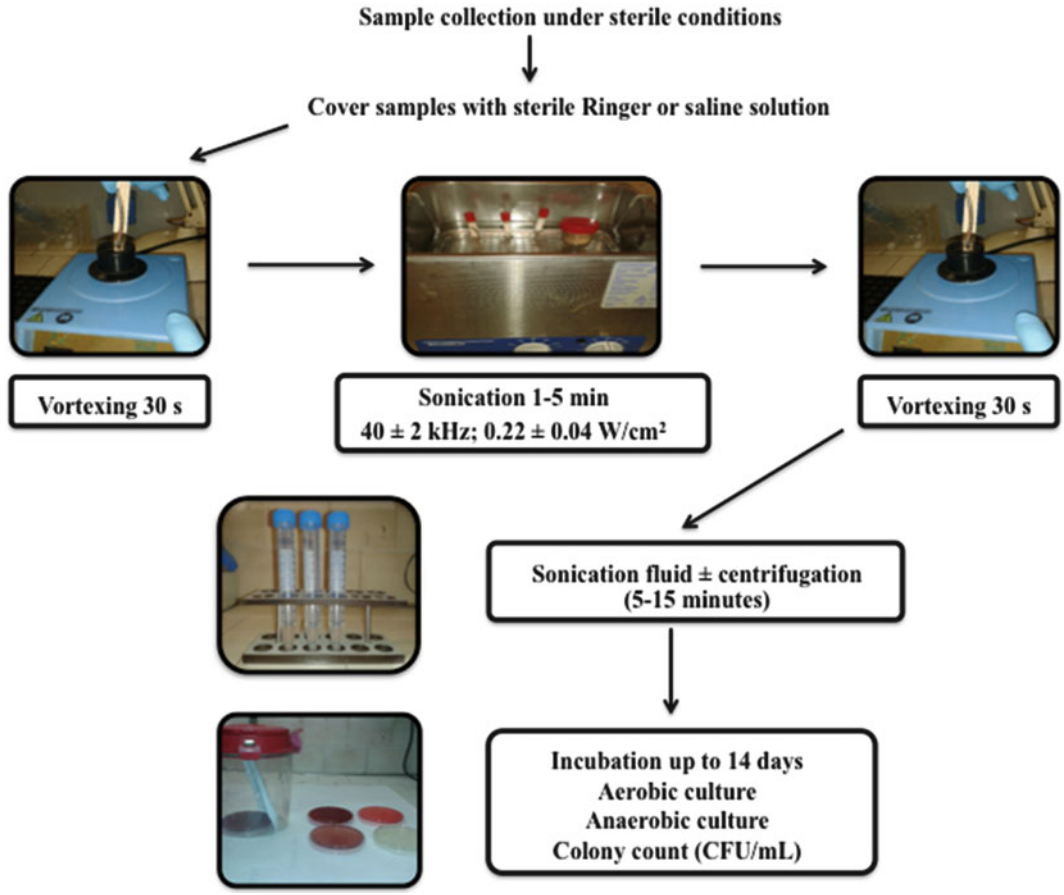

Fig. 1 Sonication protocols for the microbiological diagnosis of Implant-Associated Infections (IAIs), with or without the centrifugation as a concentration process (Tande 2014; Oliva 2013)

and bacterial biofilms on the surface of 121 removed implants. A strong correlation between the degree of capsular contracture and positive sonication culture was shown. Interestingly, all the 9 subjects who had clinical signs of breast infection yielded bacteria with a bacterial amount $>10^3$ CFU/mL, suggesting that a colony count cut-off value might be used to distinguish between colonization and infection in the setting of breast implants (Rieger et al. 2013).

A subsequent study (Karau et al. 2013) prospectively included 328 breast tissue expanders removed for any reason including infection; although the infected subjects were few ($n = 7$), in this subgroup the sonication showed higher sensitivity than tissue cultures.

Therefore, these studies showed that breast prostheses could be asymptomatically colonised by microorganisms producing biofilm, thus leading to chronic inflammation and capsular contracture. In fact, biofilm-embedded microorganisms are able to evade phagocytosis and cause persistent low-grade infection because IgG and complement deposition is diminished on the surface of foreign devices covered by bacteria (Zimmerli and Sendi 2011).

Whether or not the presence of bacteria on breast implant surface of clinically uninfected subjects is a risk factor for future infection or capsular contracture remains unknown. Additional studies investigating the role of bacterial colonization in determining or facilitating

Table 1 Studies investigating the role of sonication of breast implants

Author, year	Type of devices, n	Clinic	Baker class, n (%)	Duration of sonication procedure	Frequency/ power	Vortexing/ shaking	Rate of bacterial detection (SC), n (%)	Comparison with TC	Rate of bacterial detection (TC), n (%)	Microbiology of SC[a]	Quantification of bacteria
Pajkos et al. (2003)	Capsules, 27	No infection	19 (70): III–IV	20 min	42–47 kHz/ not specified	Yes (3 min)	17/19 (89.5): III–IV	Yes[b]	0/27 (0)	CoNS (15)	Yes
			8 (30): I–II				1/8 (12.5): I–II			*Bacillus* spp. (2)	
										P. acnes (2)	
Pajkos et al. (2003)	Implants, 21	No infection	13 (62): III–IV	20 min	42–47 kHz/ not specified	Yes (3 min)	5/13 (38.5): III–IV	Yes[b]	0/21 (0)	CoNS (3),	Yes
			8 (38): I–II				1/8 (12.5): I–II			*Bacillus* spp. (2),	
										P. acnes (1)	
Del Pozo (2009)	Implants, 45	No infection	27 (60): III–IV	5 min	40+/−2 kHz; 0.22+/ −0.04 W/cm^2	Yes (30 s)	9/27 (33): III–IV	Yes	12/27 (44): III–IV	*Propionibacterium* spp. (7),	Yes
			18 (40): I–II							CoNS (5)	
							1/18 (5): I–II		2/18 (11): I–II	*Corynebacterium* spp. (1)	
Rieger (2009)	Implants, 22	No infection	III–IV	5 min	40+/−2 kHz; 0.22+/ −0.04 W/cm^2	Yes (30 s)	9/22 (41)	No	Not applicable	CoNS (7), *Propionibacterium* spp. (6)	Yes
Rieger (2013)	Implants, 89	No infection	21 (23): I–II	1 min	40 kHz/ 0.22 W/cm^2	Yes (30 s)	4/21 (19): I–II	No	Not applicable	*P. acnes* (18), CoNS (16), *Bacillus* spp. (3)	Yes
			68 (76): III–IV				36/68 (53): III–IV			*Candida* spp. (1)	
										Others (2)[c]	
Rieger (2013)	Implants, 9	Infection	Not reported	1 min	40 kHz/ 0.22 W/cm^2	Yes (30 s)	9/9 (100)	No	Not applicable	*S. aureus* (3), CoNS (3), *P. acnes* (2)	Yes
										Citrobacter koseri (1)	
Karau (2013)	Breast tissue expanders, 321	No infection	Not reported	5 min	40+/−2 kHz; 0.22+/ −0.04 W/cm^2	Yes (30 s)	52/321 (16.2)	Yes	37/321 (11)	*Propionibacterium* spp. (45), CoNS (10)	Yes
										Others (5)[d]	
Karau (2013)	Breast tissue expanders, 7	Infection	Not reported	5 min	40+/−2 kHz; 0.22+/ −0.04 W/cm^2	Yes (30 s)	6/7 (85.7)	Yes	4/7 (57)	CoNS (5)	Yes
										P. acnes (1)	
										Serratia marcescens (1)	

SC sonication culture, *TC* traditional culture, *CoNS* coagulase-negative Staphylococci

[a]Polymicrobial growth is included

[b]TC means swab

[c]Others include: *Corynebacterium* spp. (1), *Finegoldia magna* (1)

[d]Others include: *Corynebacterium* spp. (2), *Actinomyces neuii* (1), *Pandoraea* spp. (1), *Ralstonia pickettii* (1)

subsequent capsular contracture are needed. In this setting, the use of sonication method might represent an essential tool.

4 Urinary Tract Implants

During the last decades, the incidence of catheter-associated urinary infections has increased, representing almost 40 % of nosocomial infections in catheterized patients (Holà et al. 2010). The risk of infection has been shown to be dependent on the length of catheterization (Paick et al. 2003; Tenke et al. 2006).

So far, only few authors have investigated the role of sonication method in the detection of microbial growth on the surface of ureteral stents and urinary catheters. Furthermore, most of the studies focused on bacterial colonization rather than infection of devices (Table 2).

Holà et al., who performed a study in order to investigate the biofilm microbial diversity of 535 catheters, was able to isolate a higher number of microorganisms throughout the use of sonication than throughout conventional (urine) culture. Of note, most of the catheters showed polymicrobial growth (Holà et al. 2010).

The results of this study were partially confirmed by Bonkat et al. who investigated the colonization rate of suprapubic catheters (SC). The authors found that sonicate-fluid culture was equally sensitive as urine culture in detecting bacterial colonization, with an increased rate of colonization if the device was *in situ* for more than 14 days. Similarly to other authors, polymicrobial bacterial detection was prevalent and sonication fluid showed the ability to detect more microorganisms than urine culture (Bonkat et al. 2013b). However, whether the presence of microorganisms in suprapubic catheters might represent a predisposing condition for subsequent infections should be further assessed.

In order to evaluate the potential role of sonication in the detection of microbial ureteral stent colonization (MUSC), the same group (Bonkat et al. 2011) made a prospectic study including a total of 408 ureteral stents removed for any reason. Sonication fluid culture showed higher sensitivity in detecting MUSC than traditional culture.

Subsequently, a prospectic randomised study performed in order to compare the roll-plate with the sonication technique in detecting MUSC was conducted by randomly allocating 271 ureteral stents to one of the two aforementioned methods (Bonkat et al. 2013a). In comparison with urine cultures, both roll-plate and sonication resulted in a significantly higher detection rate of colonization. Surprisingly, roll-plate showed a statistical significant higher bacterial detection than sonication whereas sonication was confirmed to be more efficient in identifying mixed biofilms. According to the results of the study, the authors postulated that sonication should not be regarded as the diagnostic procedure of choice for studying MUSC, because it required additional technical equipment, was not cost-effective and not able to identify a greater number of microorganisms than roll-plate method.

Higher sensitivity of sonication in detecting microorganisms from both inner and outer surface of implants has been previously postulated (Cozzaglio et al. 1997), due to the fact that sonication, by radiating in a liquid medium, should uniformly dislodge bacteria from the biofilm whereas roll-plate, by rolling the external surface of the implant on the agar plate, should detect only bacteria present on the external surface. However, this advantage has not been observed in the studies investigating urinary tract catheters and ureteral stents (Barford et al. 2008).

Based on the studies performed so far, sonication did not show any advantage over traditional cultures in detecting bacteria on urinary tract implants.

5 Neurosurgical Devices

EVD and VPS are increasingly used for the treatment of acute and chronic hydrocephalus. Bacterial colonization of these catheters might occur, with subsequent catheter obstruction, infection, or both (Lo et al. 2007; Beer et al. 2008; Hoefnagel et al. 2008).

Table 2 Summary of studies evaluating the role of sonication in the setting of urinary implants (urinary catheters, suprapubic catheters, ureteral stents)

Author, year	Type of devices, n	Clinic	Duration of sonication procedure	Frequency/ power	Vortexing/ shaking	Rate of bacterial detection (SC), n (%)	Comparison with TC	Rate of bacterial detection (TC), n (%)	Microbiology of SC	Quantification of bacteria
Holà (2010)	Urinary catheters, 535	Not reported	10 min	Not specified/ not specified	Yes (2 min)	Not reported[a]	Yes	Not reported[a]	*Enterococcus faecalis* (294), *Escherichia coli* (213), *Pseudomonas aeruginosa* (149), *Candida albicans* (141)	No
									Others (758)	
Bonkat (2013)	Suprapubic catheters, 209	Any reason for removal (n = 209)	1 min	40+/ −2 kHz;	Yes (30 s)	199/209 (95)	Yes	199/209 (95)	*Enterobacteriaceae* (196), *Enterococcus* spp. (110), *Pseudomonas* spp. (44),	Yes
				0.22+/ −0.04 W/ cm^2					Others (78)	
Bonkat (2013)	Suprapubic catheters, 22	Infection	1 min	40+/ −2 kHz;	Yes (30 s)	22/22 (100)	Yes	22/22 (100)	Not specified	Yes
				0.22+/ −0.04 W/ cm^2						
Bonkat (2011)	Ureteral stents, 408	No infection	1 min	40+/ −2 kHz	Yes (30 s)	145/408 (36)	Yes	60/408 (15)	CoNS (41),	Yes
				0.22+/ −0.04 W/ cm^2					*Enterococcus* spp. (40),	
									Enterobacteriaceae (38)	
									Others (105)	
Bonkat (2013)	Ureteral stents, 271	No infection	1 min	40+/ −2 kHz;	Yes (30 s)	77/271 (28)	Yes	96/271 (35)[b]	*Enterococcus* spp. (23), *Candida* spp. (19) *Enterobacteriaceae* (16), CoNS (15)	Yes
				0.22+/ −0.04 W/ cm^2					Others (36)	

SC sonication culture, *TC* traditional culture (urine culture), *CoNS* coagulase-negative Staphylococci
[a]The authors identified a total of 1555 and 727 different strains throughout SC and TC, respectively
[b]TC means roll-plate method

The suspicion of catheter-associated infection is confirmed if ventricular cerebrospinal fluid (CSF) cultures are positive (Horan et al. 2008), irrespective of the presence of bacteria on the explanted ventricular catheter tips or VPS (Mayhall et al. 1984; Lozier et al. 2002).

However, recent data showed that sonication of neurosurgical devices was associated with a significantly higher rate of bacterial growth than CSF cultures (Jost et al. 2014) (Table 3), especially in subjects with EVD and VPS filling the CDC criteria for meningitis. The authors suggested that sonication of neurosurgical devices might represent a potential and useful aid for the diagnosis of meningoventriculitis. Most important, the development of clinical significant meningitis might be anticipated by the positivity of EVD or VPS sonication culture, thus highlighting the potential role of this method in the diagnostic algorithm of infections associated with EVD/VPS.

A previous study investigating the rate of bacterial colonization in cerebral catheters by using roll-out or sonication method found that both antibiotic-impregnated and non-impregnated catheters were colonized whereas CSF cultures were positive only in a minority of patients (Zabramski et al. 2003). However, the authors neither specified the precise protocol used neither the number of catheters tested with roll-plate or sonication.

Other authors investigated the rate of bacterial colonization on catheter tips by adapting for cerebral catheters the sonication technique described for vascular catheter cultures (Sherertz et al. 1990). They found colonization of silver-impregnated catheters whereas all the corresponding CSF cultures were negative (Lackner et al. 2008).

6 Endovascular Implants

6.1 Vascular Grafts

Due to the high occurrence of cardiovascular diseases, there has been a growing use of vascular (peripheral and/or aortic) grafts (Darouiche 2004). Although representing a rare event, vascular graft infections are associated with high morbidity and mortality (Calligaro et al. 2003; Saleem et al. 2010).

Because bacteria isolated from superficial or deep wounds might represent skin flora colonization, obtaining cultures from the explanted graft appears essential. However, broth cultures might be hampered by a previous antimicrobial therapy (FitzGerald et al. 2005; Stone et al. 2008); in this setting, the application of sonication method had been described (Table 4).

In fact, the importance of combining a method able to disrupt biofilm in combination with traditional broth culture in the setting of vascular graft infections has been shown in a canine model of *S. epidermidis* infection since almost 30 years (Bergamini et al. 1989).

Subsequent studies investigating the sonication of vascular graft implants were mainly based on animal models. Only one study dated 1987 evaluated the recovery of bacteria in both a canine model and in 7 graft materials excised from patients undergoing femoral anastomotic pseudoaneurysm repair. The authors found that sonication significantly increased the incidence of positive cultures from excised graft material compared with conventional culture methods (Tollefson et al. 1987).

6.2 Cardiac Devices

The growing use of implantable cardiovascular devices [permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD)] for the treatment of arrhythmias and heart failure has led to a rising incidence of CDIs over the time (Athan 2014), with an estimated rate of infections ranging from 0.13 to 19.9 % (Voigt et al. 2010; Lekkerkerker et al. 2009). Traditional cultures showed low sensitivity and specificity for diagnosing CDIs (Chua et al. 2005), mostly due to biofilm formation on cardiac devices surface (Lekkerkerker et al. 2011). In contrast, the sonication method demonstrated a higher sensitivity than conventional cultures in the microbiological diagnosis of CDIs (Oliva et al. 2010; Rohacek et al. 2010; Oliva et al. 2013) (Table 4).

Table 3 Summary of studies analyzing the sonication of cerebral catheters

Author, year	Type of cerebral devices	Clinic	Duration of sonication procedure	Frequency/ power	Vortexing/ shaking	Bacterial growth (SC) n, (%)	Microbiology of SC	Quantification of bacteria	Bacterial growth (CSF) n, (%)	Microbiology of CSF culture
Jost (2014)	EVD (n = 5)	Meningitis	1 min	40 ± 2 kHz/ 0.22 ± 0.04 W/ cm^2	Yes (30 s)	4 (80)	CoNS (3), CoNS + *Corynebacterium* spp. (1)	Yes	2 (40)	CoNS (2)
Jost (2014)	EVD (n = 9)	No infection	1 min	40 ± 2 kHz/ 0.22 ± 0.04 W/ cm^2	Yes (30 s)	5 (55)[a]	CoNS (5)	Yes	2 (22)[b]	CoNS (1), *P. acnes* (1)
Jost (2014)	VPS (n = 6)	Meningitis	1 min	40 ± 2 kHz/ 0.22 ± 0.04 W/ cm^2	Yes (30 s)	6 (100)	CoNS (3), *E. coli* (1), *Enterobacter cloacae* (1), *Ps. aeruginosa* (1)	Yes	5 (83)	CoNS (2), *E. cloacae* (1), *E. coli* (1), *Ps. aeruginosa* (1)
Jost (2014)	VPS (n = 7)[c]	No infection	1 min	40 ± 2 kHz/ 0.22 ± 0.04 W/ cm^2	Yes (30 s)	5 (83)	CoNS (3), *S. aureus* (1), *P. acnes* (1)	Yes	0 (0)	0
Zabramski (2003)	Antibiotic-impregnated EVD catheters (n = 123)	No infection	Not specified	Not specified	Not specified	22 (17.9)	CoNS (10), uncharacterized Gram positive cocci (3), *Pseudomonas* spp. (3), *Corynebacterium* spp. (2), others (7)[d]	Yes	2/149 (1.3)	*E. faecalis* + *S. aureus* (1), *E. aerogenes* (1)
Zabramski (2003)	Non antibiotic-impregnated EVD catheters (n = 109)	No infection	Not specified	Not specified	Not specified	40 (36.7)	CoNS (33), uncharacterized Gram positive cocci (6), *Corynebacterium* spp. (3), *S. aureus* (2), others (9)[e]	Yes	13/139 (9.4)	CoNS (8), *Acinetobacter calcoaceticus* + *Klebsiella pneumoniae* (1), CoNS+ *Corynebacterium* sp. (1), *Corynebacterium* sp. (1), CoNS+ *E. aerogenes* (1), *S. aureus* (1)
Lackner (2008)	Silver-impregnated EVD catheters (n = 19)	No infection	1 min	55 kHz/125 W	Yes (15 s)	5 (26)	CoNS (5)	No	0 (0)	0

EVD external ventricular drains, *VPS* ventriculo-peritoneal shunts, *CSF* cerebrospinal fluid, *CoNS* coagulase-negative Staphylococci

[a]2 out of 9 patients with EVD without meningitis but with positive sonication fluid culture eventually needed antimicrobial therapy because of a subsequent development of meningitis

[b]Microorganisms in CSF culture were detected only after culture enrichment and considered as contamination

[c]Devices (7) were collected from 6 patients

[d]Others include *E. coli* (1), *E. aerogenes* (1), uncharacterized Gram-positive rods (1), Group D *Enterococcus* spp. (1), *S. capitis* (1), *S. caprae* (1), yeast (1)

[e]Others include *Bacillus* spp. (2), *Pseudomonas* spp. (2), *Acinetobacter calcoaceticus* (1), *A. baumanii* (1), *E. agglomerans* (1), *Micrococcus* spp. (1), uncharacterized Gram-negative rods (1)

Table 4 Studies investigating the role of sonication of endovascular implants (vascular grafts, cardiac devices, CVC)

Author, year	Type of implant	Clinic	Duration of sonication procedure	Frequency/ power	Vortexing/ shaking	Rate of bacterial detection (SC), n (%)	Comparison with standard culture	Rate of bacterial detection (TC)[a], n (%)	Quantification of bacteria
Bergamini (1989)	dacron grafts	Canine model	Not applicable	Not applicable	Not applicable	30/36 (83)	Yes	26/36 (72.2)	No
Tollefson (1987)	Vascular grafts	Canine model + infected humans (n = 7)	Not applicable	Not applicable	Not applicable	7/7 (100)	Yes	Not applicable	No
Wengrovitz et al. (1991)	PTFE + knitted Dacron grafts	*In-vitro* model	Not applicable	Not applicable	No	Not applicable	Yes	Not applicable	Yes
Schmitt et al. (1986)	ePTFE, woven Dacron + velour knitted Dacron	*In-vitro* model	Not applicable	Not applicable	No	Not applicable	No	Not applicable	Yes
Oliva (2010)	Cardiac devices[b]	Infection (n = 1)	5 min	>20 kHz/not specified	Yes (30 s)	1/1 (100)	Yes	0/1 (0)	No
Oliva (2013)	Cardiac devices[b]	Any reason (n = 40); Infection (n = 20)	5 min	>20 kHz/not specified	Yes (30 s)	18/20 (90)	Yes	16/20 (80)	Yes
Rohacek (2010)	Cardiac devices	Any reason (n = 121); Infection (n = 6)	1 min	40 ± 2 kHz/ 0.22 ± 0.04 W/ cm^2	Yes (30 s)	50/121 (41.3)	Yes	34/118 (28.8)	Yes
Mason (2011)	Cardiac devices	Any reason (n = 82); Infection (n = 16)	5 min	42 ± 6 % kHz/ not specified	No	26/82 (31.7)	Yes	21/82 (25.6)	No

Viola et al. (2009)	Cardiac devices[b]	Battery failure (n = 20)	5 min	Not specified/ not specified	Yes (30 s)	Not applicable	Yes	Not applicable	Yes
Sherertz (1990)	CVC	Consecutive removed CVC (n = 1681)	1 min	55 kHz/125 W	Yes (15 s)	774/1681 (46)	No	Not applicable	Yes
Sherertz (1997)	CVC	Consecutive removed CVC (n = 89)	1 min	55 kHz/125 W	Yes (15 s)	26/45 (57.8)[c]	Yes	17/45 (37.8)	Yes
Bouza (2005)	CVC	Consecutive removed CVC (n = 1000); Infection (n = 82)	1 min	55 kHz/125 W	Yes (15 s)	313/1000 (31.3)	Yes	326/1000 (32.6)	Yes
Slobbe (2009)	CVC	Consecutive removed CVC (n = 313); Infection (n = 89)	1 min	23 kHz/Not specified	Yes (15 s)	53/313 (16.9)	Yes	66/313 (21)	Yes
Guembe (2012)	Long-term CVC	Consecutive removed CVC (n = 149); Infection (n = 11)	1 min	55 kHz/125 W	Yes (15 s)	17/149 (11.4)	Yes	37/149 (24)	Yes

SC sonication culture, *TC* traditional culture, *PTFE* polytetrafluoroethylene, *ePTFE* expanded polytetrafluoroethylene, *CVC* central venous catheters

[a]TC means roll-plate method

[b]Cardiac device means both generators and atrial/ventricular leads

[c]The sensitivity of sonication culture was calculated on 45 catheters

A recent study conducted by our group showed that, among 20 subjects with clinically defined infection, sonication culture was positive in 18/20 patients (90 %) whereas traditional culture and intraoperative pocket swab only in 16/20 (80 %) and 6/20 (33 %), respectively. When the components of cardiac devices were analyzed (generators plus electrodes), culture after sonication yielded bacteria in 77 % of the components (46/60) compared with 60 % (36/60) by standard culture. Not surprisingly, the most isolated microorganisms were CoNS and polymicrobial infections were found in 25 % of the subjects. In order to investigate the role of sonication in the setting of asymptomatic bacterial colonization, we included in the study 20 additional subjects without infection: sonication fluid culture was positive in 8 patients (40 %) whereas traditional culture of device was positive in only 4 cases (20 %). We concluded that sonication showed higher sensitivity in pathogen detection compared with traditional culture, both in infected and non-infected cardiac devices (Oliva et al. 2013). In addition, we speculated that the differences in pathogen recovery between generators and electrodes could have been explained by the different characteristics of generators and electrodes in terms of material, surface and position (Merritt et al. 1998; Clauss et al. 2010).

Rohacek et al., who compared traditional swab cultures with sonication in 121 intracardiac devices, found that, among 6 subjects with clinically defined infection, sonication fluid grew bacteria in 6/6 compared to 4/6 in swab cultures; in contrast, among 115 subjects without infections, 44/115 (38 %) sonicate fluids and 30/112 (27 %) swab cultures were positive for bacterial growth.

Mason et al. (2011) demonstrated that ultrasonication of PPM and ICD generators increased the diagnosis of pocket infection over tissue culture and swab culture alone. By using a 5 min sonication-protocol without vortexing, the authors found that, out of 82 patients with PPM or ICD undergoing generator explantation for elective reasons (n = 66) or for pocket infection (n = 16), sonication fluid yielded bacteria in 26/82 (31.7 %) whereas tissue and swab cultures were positive in 21/82 (25.6 %) and 13/82 (15.8 %), respectively.

The latter two studies (Rohacek et al. 2010; Mason et al. 2011) found *P. acnes* as a leading pathogen implicated in asymptomatic bacterial colonization and, to a lesser extent, in infection. *P. acnes*, which is part of the normal human microbiota, has been recognized as a cause of different types of IAIs, including breast prosthesis (Del Pozo et al. 2009; Rieger et al. 2009), neurosurgical shunts (Conen et al. 2008), cardiovascular devices (Delahaye et al. 2005; Lalani et al. 2007), ocular (Deramo and Ting 2001) and orthopedic implants (Piper et al. 2009; Haidar et al. 2010). The discrepancies in the rate of *P. acnes* identification between different studies might rely on the difficulties in culturing this pathogen, which has been shown to require a 14-days aerobic and anaerobic incubation in order to optimize its detection.

On the other hand, Viola et al. reported that culture alone with incubation of cardiac devices for 24 h showed results comparable with those obtained through a combination of different diagnostic methods such as sonication and vortexing (Viola et al. 2008). They performed exclusively an *in-vitro* study with 20 sterilized PPM and leads that had been removed from patients because of battery failure and incubated with a biofilm-producing clinical strain of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Different culturing methods such as incubation alone, vortexing followed by incubation, sonication followed by incubation, vortexing plus sonication followed by incubation were compared. The conclusion of the authors was that incubation alone was more than adequate for culturing cardiac devices; however, the results of this study might have been affected by the fact that it was performed only *in-vitro* whereas the aforementioned experiences proved the efficacy of sonication by applying it in patients with and without infection.

Although in the literature no data could be found regarding the sonication of cardiac devices other than PPM and ICD, it could be supposed that biofilm formation on the surface of heart

valves might interfere with the microbiological diagnosis of prosthetic valve endocarditis, especially in patients receiving antimicrobial therapy. Thus, the potential usefulness of the sonication method in this setting might be considered and deserves further studies.

6.3 Central Venous Catheters

Catheter-related bloodstream infections (C-RBSI) are common nosocomial infections occurring mostly in critically-ill patients, with an incidence of 2.79 per 1.000 catheter-days (Lorente et al. 2005).

Sonication has been widely applied on both long and short-term CVC and is mentioned by Infectious Diseases Society of America (IDSA) current guidelines of Intravascular Catheter-Related Infection as a feasible diagnostic procedure together with the roll-plate technique described by Maki (Mermel et al. 2009). The guidelines recommendation on the use of sonication method in the setting of C-RBSI is mainly based on the results of studies performed in the 90s (Sherertz et al. 1990) (Table 4).

However, there is a clear agreement that roll-plate culture is as accurate as sonication for the diagnosis of catheter-related infections because it is easier, faster and shows a better cost-efficiency profile and less risk of contamination than sonication (Bouza et al. 2005; Slobbe et al. 2009; Erb et al. 2014). Thus, the Maki method is currently used in the routine microbiological diagnosis of C-RBSI.

The rationale of preferring sonication is mainly based on the fact that CVC infections are caused by well-known biofilm producing microorganisms such as CoNS, *S. aureus* (McCarthy et al. 2015) and *Candida* spp. (Tumbarello et al. 2012b). In addition, roll-plate method might occasionally give false-negative results for patients receiving antimicrobials and whose mechanism of colonization is supposed to be endoluminal.

Supporting this concept, in 1997 a clinical trial reported that, compared to roll-plate and flushing methods, sonication of the subcutaneous segment and tip was the most sensitive technique for detecting catheter colonization (Sherertz et al. 1997).

Subsequently, large prospectic and randomized studies have investigated whether sonication was more sensitive than roll-plate in the diagnosis of catheter infection or colonization (Bouza et al. 2005; Slobbe et al. 2009; Guembe et al. 2012; Erb et al. 2014).

Bouza et al. compared vortexing, sonication and roll-plate in 1000 catheter tips. Although the differences were not significant, Maki's technique had higher sensitivity than sonication and vortexing, especially for short-term catheters. Slobbe et al., who randomized 313 catheter tips to be sonicated and cultured with roll-plate technique, found that roll-plate tip culture was positive in 66/313 (21.1 %) whereas only 53/313 (16.9 %) yielded bacteria with sonication. In particular, 89/313 (28.4 %) catheters were removed because of clinical suspicion of C-RBSI and/or exit site infection with concomitant bacteremia; in this subgroup, both methods showed low sensitivity and high specificity.

However, it has to be pointed out that in this study all catheter tips underwent both methods but were randomized to one method first. Some authors postulated that when one method is performed first, the subsequent use of the same sample might affect the sensitivity of the second method (Sherertz et al. 1997; Erb et al. 2014). This assumption was confirmed by this study, where both sonication and roll plate resulted less sensitive when performed in second instance.

In contrast to roll plate method, which is considered able to dislodge bacteria only from the extra-luminal surface, the sonication technique is able to disrupt the whole biofilm on foreign body and detect bacteria from both the endoluminal and exoluminal surfaces. Thus, even if sonication might be considered the best diagnostic method due to the hypothesis that the route of CVC infections is thought to be more often endoluminal, this technique did not show any advantage over roll-plate method. Rather, it appeared to be less cost-effective and more prone to contamination during sample processing than Maki method.

7 Other Implants

Theoretically, each type of implant could lead to biofilm formation. Although some *in-vitro* studies have used the sonication in order to evaluate the bacterial adherence to intraocular lens (Schauersberger et al. 2003), to our knowledge no studies investigating the role of this technique in the diagnosis of colonization or infection of penile, tracheal, intraocular and acoustic prostheses have been performed so far. However, the potential usefulness of the sonication method in these settings might be taken into consideration and deserves further investigations.

8 Clinical Implications of Sonication Method

In the present review, the use of sonication of several implants other than orthopedics has been described. However, an additional value of sonication method could be recognized especially in the diagnosis and pathogenesis of cerebral and cardiac devices infections.

In fact, the study conducted by Jost and colleagues provided information about the usefulness of bacterial quantification in the sonication fluid, suggesting that an EVD/VPS culture with more than 50 CFU might raise the suspicion of meningitis, even if the CSF cultures are negative. Additionally, they speculated that a lower number of bacteria found in the sonication fluid might represent an early condition in the development of infection, thus providing new insights on the pathogenesis of EVD/VPS infections (Jost et al. 2014).

A previous study conducted by our group on subjects with clinically defined CDIs showed that bacterial growth was observed in 65 % of the leads, even in the absence of visible vegetations seen at echocardiography, which is considered to be the most reliable method to identify endocarditis on electrodes, tricuspid valve, or both. These findings, together with the fact that the majority of cultured microorganisms were part of skin flora, were consistent with the pathogenetic hypothesis of wound contamination at the time of implantation or during the device procedure, which might facilitate bacterial colonization of generator pocket and subsequent migration along the intravascular components of the system (Oliva, submitted). Thus, the concept that intracardiac electrodes are colonized by bacteria without visible vegetation might lead to new insights on the early recognition of subjects at major risk of developing endocarditis compared to those who only develop pocket infection.

Furthermore, it has been shown that the sensitivity of sonication fluid is less hampered by antimicrobial therapy than conventional cultures. In contrast to PJIs, where antimicrobial therapy might be stopped at least 2 weeks before prosthesis explanation in order to obtain the highest bacterial yield (Trampuz et al. 2007), subjects with cerebral or cardiac implants are more likely to be on antimicrobial therapy when the device is removed. Thus, the use of a diagnostic method which is minimally affected by antimicrobial therapy appears to be critical.

In fact, the potential effect of antimicrobial therapy on the diagnostic sensitivity of CSF culture might lead to additional difficulties in the interpretation of clinical and laboratory parameters for the diagnosis of meningoventriculitis. Despite the study population was small, the encouraging results of the study conducted by Jost and colleagues might be useful in the early identification of patients with EVD or VPS at high risk of developing meningitis.

In the setting of CDIs, the usefulness of sonication in subjects receiving antimicrobial therapy at the time of device removal has been investigated in a previous study performed by our group. Despite in subjects on therapy >14 days bacterial growth was lower than in subjects who were on therapy <14 days, the difference was not statistically significant, thus highlighting that sonication might retain its diagnostic value in the presence of antimicrobials (Oliva et al. 2013).

9 Conclusions

IAIs are difficult-to-treat infections associated with high morbidity, mortality and length of hospitalization. They are characterized by biofilm

formation on implant surface, which leads to the difficulty in microbiological diagnosis and the need of device removal. The application of sonication method might represent an essential tool in order to improve the microbiological diagnosis in the setting of IAIs other than PJIs whereas the assumption that sonication might have additional diagnostic advantage over traditional culture in urinary tract implants has not been confirmed so far. The potential usefulness of the sonication in the setting of other implants such as heart, penile, tracheal, intraocular and acoustic prostheses might be taken into consideration and deserves further investigations. Moreover, the possibility to perform additional studies including molecular and/or immunological analyses on the sonication fluid might give physicians valuable insights into both IAIs pathogenesis and detection of fastidious microorganisms such as *P. acnes*.

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