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ORIGINAL ARTICLE

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Bacteremia after supragingival scaling and dental extraction: Culture and molecular analyses

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Objective: To study the incidence and magnitude of bacteremia after dental extraction and supragingival scaling.

Subjects and methods: Blood samples were taken before and 5 and 30 min after dental extraction and supragingival scaling from individuals at high (n = 44) or negligible risk (n = 51) for infective endocarditis. The former received prophylactic antibiotic therapy. Samples were subjected to aerobic and anaerobic culture and quantitative real-time polymerase chain reaction to determine the incidence of bacteremia and total bacterial levels.

Results: Patients who did not receive prophylactic antibiotic therapy had a higher incidence of positive blood cultures (30% 5 min after extraction) than patients who received prophylactic antibiotic therapy (0% 5 min after extraction; p < .01). Molecular analysis did not reveal significant differences in the incidence or magnitude of bacteremia between the two patient groups either 5 or 30 min after each of the procedures evaluated. Extraction was associated with higher incidence of bacteremia than supragingival scaling by blood culture (p = .03) and molecular analysis (p = .05).

Conclusions: Molecular methods revealed that dental extraction and supragingival scaling were associated with similar incidence of bacteremia in groups receiving or not prophylactic antibiotic therapy. However, blood culture revealed that antibiotic therapy reduced viable cultivable bacteria in the bloodstream in the extraction group.

KEYWORDS
Bacteremia, dental procedures, infectious endocarditis, Prophylactic antibiotic therapy

1 | INTRODUCTION

Infectious endocarditis (IE) is a relatively uncommon but serious condition, with an estimated incidence of 30–100 cases per 1 million patient-years (Duval et al., 2012; Shih et al., 2014) and a high mortality rate [5-year mortality rate of ≈40% (Bannay et al.,2011)]. Its characteristic lesion (vegetation with bacterial or fungal organisms) affects the endothelial surface of the heart, prosthesis, or implantable cardiac devices (Bascones-Martínez, Muñoz-Corcuera, & Bascones-Ilundain, 2012; Tomás Carmona, Diz Dios, & Scully, 2007). Studies suggest that IE may develop in patients with inadequate oral health or following dental procedures (Lockhart et al., 2009; Nakano et al., 2006). In patients at risk for developing IE whose conditions are associated with the highest risk of adverse outcome from IE, prophylactic antibiotic therapy has been recommended prior to dental interventions that may result in bacteremia (Wilson et al., 2007). The American Heart Association (AHA) recommends prophylaxis for IE in patients with the following conditions (Wilson et al., 2007): prosthetic cardiac valves, previous infective endocarditis, cardiac transplantation recipients who develop cardiac valvulopathy, and congenital heart disease (CHD) including unrepaired cyanotic CHD even with palliative shunts, completely repaired CHD during the first 6 months after procedure, and

repaired CHD with residual defects. The Brazilian Cardiology Society (SBC) recommends that antibiotic prophylaxis should also be provided for patients with rheumatic valvulopathy, mitral valve prolapse with insufficiency, and degenerative or bicuspid aortic valvulopathy (Tarasoutchi et al., 2011).

The frequency of bacteremia after different dental and oral surgical procedures may vary from study to study, and blood culture has traditionally been used to detect bacteria in the blood samples (Bahrani-Mougeot et al., 2008; Ratto-Tespestini et al., 2016; Takai, Kuriyama, Yanagisawa, Nakagawa, & Karasawa, 2005; Tomas et al., 2007). Recently, molecular microbiology methods based on DNA detection have been used for the same purpose (Benítez-Páez et al., 2013; Pérez-Chaparro, Gracieux, Lafaurie, Donnio, & Bonnaure-Mallet, 2008). Molecular methods present advantages such as greater sensitivity and ability to detect difficult-to-grow and as-yet-uncultivated bacteria (Bahrani-Mougeot et al., 2008; Kinane, Riggio, Walker, MacKenzie, & Shearer, 2005; Reis et al., 2016; Takumi, Komatsu, Aoyama, Watanabe, & Takeuchi, 2008). Nonetheless, blood culture is still relevant to infer viability of the bacterial species identified (Bahrani-Mougeot et al., 2008). However, few studies have so far evaluated the incidence of bacteremia after dental procedures by molecular methods in comparison with blood cultures (Benítez-Páez et al., 2013; Castillo et al., 2011; Pérez-Chaparro et al., 2008).

The aim of this study was to evaluate the incidence and magnitude of bacteremia after dental procedures (tooth extraction or supragingival scaling) and the effect of antibiotic prophylaxis by means of blood culture and quantitative real-time polymerase chain reaction (qPCR).

2 | MATERIAL AND METHODS

2.1 | Patients

This cross-sectional study included patients with heart disease from the National Institute of Cardiology (Rio de Janeiro, Brazil) with either a high risk or a negligible risk for IE, according to the Brazilian guidelines for valve disease (Tarasoutchi et al., 2011), who presented teeth with indication for extraction or in need of supragingival dental calculus removal. Patients were recruited among patients followed by the Orovalvar and Coronary Artery Disease departments of the National Institute of Cardiology or during the routine dental evaluation requested by their physician.

2.2 | Ethics

The study protocol was approved by the National Institute of Cardiology Institutional Ethics Committee (#0298/11.11.2010) on December 27, 2010, and was conducted in full accordance with ethical principles including the World Medical Association Declaration of Helsinki (version 2002) and guidelines established by the Brazilian National Commission for Research Ethics (CONEP). All patients included in the study signed informed consent forms after receiving explanations on the risks and benefits of participation.

2.3 | Prophylactic antibiotic therapy

Prophylactic antibiotic therapy consisted of 2 g of oral amoxicillin 1 hour before the procedures (extraction or supragingival scaling), as recommended by the Brazilian Cardiology Society guidelines for patients at risk for IE (Tarasoutchi et al., 2011). These guidelines extend the indication of prophylactic antibiotics to patients presenting with rheumatic heart valve disease, mitral valve prolapse with mitral regurgitation, and bicuspid or degenerative aortic valve disease (Tarasoutchi et al., 2011). In Brazil, rheumatic valve disease is among the most prevalent cardiac risk factors for IE (Casalino et al., 2015; Tarasoutchi et al., 2011). Patients considered as having no risk for IE did not receive prophylactic antibiotics.

2.4 | Dental procedures and sample collection

Before dental treatment (extraction or supragingival scaling), the oral cavity was rinsed with a solution of 0.12% chlorhexidine digluconate for 1 min. All teeth recommended for extraction were unrestorable. The patients who underwent supragingival scaling had teeth with supragingival plaque and calculus on the lingual surfaces of the six mandibular anterior teeth (#33, 32, 31, 41, 42, 43), which were removed using a Cavitron Select Ultrasonic Scaler (Dentsply, Tulsa, OK). Periodontal probing was conducted to evaluate the presence of periodontal pockets. Seventeen (31%) of the patients subjected to supragingival scaling had periodontal pockets.

Before blood sample collection, the skin on the site of the median cubital vein was disinfected with 2% chlorhexidine gluconate, and 20 ml of blood was collected immediately before and 5 and 30 min after the dental procedures. Bacteremia was only considered to be caused by the dental procedures when it was not detected before the procedure or when the load increased as determined by qPCR. The blood samples were immediately processed for aerobic (9 mL) and anaerobic culture (9 mL), and 2 ml blood was stored at −80°C for molecular microbiology analysis.

2.5 | Blood culture analysis

Peripheral blood samples were cultured as previously described (Reis et al., 2016). Briefly, blood was collected in bottles containing aerobic and anaerobic media and was incubated for 5 and 15 days, respectively. Bottles were monitored, and those displaying evident bacterial growth were subcultured onto 5% sheep blood agar plates supplemented with 5 mg/L hemin (Sigma-Aldrich, St Louis, MO) and 1 mg/mL menadione (Sigma-Aldrich). Plates were incubated in aerobic, capnophilic (5% CO_2), and anaerobic (85% N_2, 5% H_2, and 5% CO_2) atmospheres for 48 hr at 37°C. For culture of anaerobic bacteria, samples were handled and incubated inside an anaerobic chamber (Coy Laboratory Products, Grass Lake, MI). Microorganisms were identified with matrix assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF/MS, Bruker Daltonics, Germany). Briefly, a single colony was picked and spotted directly into MALDI sample target plate, overlaid with

formic acid, and left air-dry. After air-dried, spots were covered with matrix solution (CHCA, α-cyano-4-hydroxycinnamic acid; Bruker Daltonics). Measurements were performed with Microflex LT MS (Bruker Daltonics) and Biotyper software using the default parameters.

2.6 | qPCR analysis

DNA from blood samples was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA), according to the manufacturer's recommendations. In order to quantify the total bacterial load, qPCR was carried out using a universal primer pair to the 16S ribosomal RNA gene. Analysis was performed in a total volume of 20 μl containing 2 μl DNA extracted from each clinical sample, primer (0.5 μM), and Power SYBR® Green PCR Master Mix (Applied Biosystems, Foster City, CA) in an ABI 7500 thermocycler (Applied Biosystems). The universal primers used were 5′-GATTAGATACCCTGGTAGTCCAC-3′ and 5′-TACCTTGTTACGACTT-3′ (Asai et al., 2002). Samples were dispensed into 96-well plates (MicroAmp Optical, Applied Biosystems), sealed, and centrifuged. Settings for qPCR were as follows: 95°C for 10 min followed by 40 amplification cycles at 95°C for 1 min, 52°C for 1 min, and 72°C for 1 min. After each cycle, PCR products were monitored for the increase in fluorescence of SYBR® Green. All measurements were performed in triplicate for both samples and controls. For the negative control, ultrapure water was used replacing the clinical sample. To determine the specificity of the amplified products, a melting curve was obtained from 60°C to 95°C, with continuous fluorescence measurements at each 1% increase in temperature. Data acquisition and analyses were performed using the ABI 7500 software, version 2.0.6 (Applied Biosystems).

Bacterial counts were determined for each sample based on standard curves, which were prepared using DNA extracted from known concentrations of *Streptococcus mutans* ATCC 25175 grown in pure culture. Knowing the size of the *S. mutans* genome (2 Mb) and the average molecular weight of one base pair (660 Da), the measured DNA value could be converted into target genomic copy levels per microliter, using the formula $m = [1\ \text{mol}/6 \times 10^{23}\ (\text{bp})]\ [660\ (\text{g})/\text{mole}] = n\ [1.096 \times 10^{-21}\ (\text{g/bp})]$, where m is the genomic mass of a single cell and n is the size of the genome. The genomic copy levels were considered numerically equivalent to the bacterial cell levels. The DNA standards were subsequently diluted 10-fold from 10^7 to 10^2 cells in Tris-EDTA buffer, and used to generate the standard curve. Because distinct oral bacterial species differ in numbers of *rrn* operons, total bacterial levels cannot be precisely calculated. Therefore, DNA from *S. mutans* was used for standard curve construction because it contains five copies of the 16S rRNA gene and five can be regarded as the approximate average copy number in the range of most known oral bacteria (http://www.cbs.dtu.dk/services/GenomeAtlas-3.0).

2.7 | Statistical analysis

All calculations were performed using commercially available statistical software (GraphPad Prism 3.02, GraphPad Software Inc., San Diego, CA) and MedCalc 9.2.0.2 (MedCalc Software, Mariakerke, Belgium).

The sample size to test whether prophylactic antibiotic therapy decreases bacteremia was calculated using the known 80% incidence of bacteremia after extraction (Lockhart et al., 2008) and 54.8% incidence of bacteremia after supragingival scaling (Castillo et al., 2011). Considering that effective antibiotic prophylaxis is expected to decrease incidence of bacteremia by at least 70% (Maharaj, Coovadia, & Vayej, 2012), with 5% significance and 80% power, and a 1:1 ratio, we would need at least 30 patients with extraction and 58 patients with supragingival scaling to be divided into equal proportions in the groups undergoing prophylaxis and in the group not submitted to antibiotic prophylaxis.

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and presented as the mean ± standard deviation or median and interquartile range, as appropriate. Discrete variables were presented as percentages. Comparisons between groups were performed using unpaired Student's t test, Mann–Whitney, or Fisher's exact test, as appropriate with the level of significance set at $p < .05$.

3 | RESULTS

3.1 | Patients

One hundred and five samples were collected from 95 patients from August 2011 to February 2014.

A total of fifty dental extractions were performed in 40 patients (25 men and 15 women) with a mean age of 57 years (ranging from 18 to 77 years). Among these patients, 20 were at high risk for IE and required prophylactic antibiotic therapy. The indications for prophylactic antibiotic therapy were presence of prosthetic cardiac valves (mechanical aortic prosthesis $n = 2$, mechanical mitral prosthesis $n = 4$, biological mitral prosthesis $n = 2$, aortic and mitral mechanical prosthesis $n = 2$), previous infective endocarditis ($n = 2$), rheumatic valvulopathy ($n = 7$), and degenerative aortic valvulopathy ($n = 1$). Twenty patients had negligible risk for IE and no indication for prophylactic antibiotic therapy. Seven patients participated in the study twice, and one patient participated four times. The minimum interval between visits was 8 months. In these cases, single-tooth extraction was performed at a time. The types of extracted teeth were two maxillary incisors (4%), four maxillary canine (8%), six maxillary premolars (12%), 13 maxillary molars (26%), four mandibular incisors (8%), one mandibular canine (2%), nine mandibular premolars (18%), and 11 mandibular molars (22%). No third maxillary or mandibular molars were included.

Among patients who underwent supragingival scaling, 55 interventions were evaluated in 55 patients (36 men and 19 women) with a mean age of 56 years (ranging from 25 to 77 years). Among these patients, 24 were at high risk for IE and required prophylactic antibiotic therapy, and 31 patients had negligible risk for IE, and no indication for prophylactic antibiotics. The indications for prophylactic antibiotic therapy in this group of patients were presence of prosthetic cardiac valves (mechanical aortic prosthesis $n = 4$, mechanical mitral

prosthesis *n* = 3, biological mitral prosthesis and mechanical aortic prosthesis *n* = 1), rheumatic valvulopathy (*n* = 12), bicuspid (*n* = 2), and degenerative aortic valvulopathy (*n* = 2).

3.2 | Blood culture analysis

Patients who did not receive prophylactic antibiotic therapy had a higher incidence of positive blood cultures 5 min after extraction than patients who received antibiotics (30% in the former and 0% in the latter) ($p < .01$). Regarding supragingival scaling, the reported difference between studied patients groups did not achieve statistical significance (Table 1). After 30 min, two patients who underwent extraction and did not receive antibiotics still showed bacteremia. The other groups had no positive blood cultures 30 min after the dental procedures (Table 1).

Bacterial isolates were identified in nine positive blood samples (seven after extraction and two after supragingival scaling): eight after 5 min, and one after 30 min. In only one blood sample two different bacterial species were isolated. The bacterial species identified were *Streptococcus oralis* (two patients), *Parvimonas micra* (one patient, two samples), *Porphyromonas gingivalis* (one patient), *Prevotella disiens* (one patient), *Fusobacterium nucleatum* (one patient), anaerobe Gram-positive bacilli (one patient), *Streptococcus mitis* (one patient), and *Haemophilus haemolyticus* (one patient). In our study, the types of the extracted teeth associated with positive blood culture were one maxillary incisor, one maxillary canine, one maxillary premolar, three maxillary molars, one mandibular incisor, and one mandibular premolar.

3.3 | qPCR analysis

Bacteremia incidence was twice as high in patients who underwent extraction when compared to patients who underwent supragingival scaling among those who did not receive prophylactic antibiotic therapy, as detected by qPCR analysis performed on samples collected 5 min after the procedures ($p = .05$; Table 2). Among patients who received prophylactic antibiotics, bacteremia was also twice as high in patients who underwent extraction when compared to patients who underwent supragingival scaling, but this difference did not reach statistical significance (Table 2). In samples collected 30 min after the procedures, the incidence of bacteremia decreased in both patients groups for both studied procedures but without reaching statistical significance (Table 2). In general, there was no significant difference in the molecular data for incidence of bacteremia between patients who received and not received prophylactic antibiotic therapy.

Table 3 depicts the quantitative data obtained by qPCR analysis. In patients who received prophylactic antibiotics, the bacterial counts

TABLE 1 Bacteremia identified by blood culture analysis after dental procedures

Patient Groups	At Risk for IE (prophylactic antibiotics)		No Risk for IE (no prophylactic antibiotics)	
Procedures	Extraction N=23	Scaling N=24	Extraction N=27	Scaling N=31
Blood culture after 5 min	0	1 (4%)	8* (30%)	2 (6%)†
Blood culture after 30 min	0	0	2 (7%)	0

*P<.01 vs. Patients at risk for infectious endocarditis (IE) after 5 min.
†P=.03 vs. extraction. Fisher's exact test.

TABLE 2 Bacteremia identified by quantitative polymerase chain reaction after dental procedures

Patient Groups	At Risk for IE (prophylactic antibiotics)		No Risk for IE (no prophylactic antibiotics)	
Procedures	Extraction N=23	Scaling N=24	Extraction N=27	Scaling N=31
Baseline	1 (4%)	0 (0%)	1 (4%)	1 (3%)
PCR after 5 min	8 (35%)	4 (17%)	13* (48%)	7 (23%)
PCR after 30 min	5 (22%)	2 (8%)	8 (30%)	5 (16%)

IE, infectious endocarditis.
*P=.05 vs. scaling; Fisher's exact test.

TABLE 3 Bacterial load (counts/mL) in the peripheral blood of the two groups studied as determined by quantitative polymerase chain reaction

Time	At risk for IE (prophylactic antibiotics) (n=23)	No risk for IE (no prophylactic antibiotics) (n=27)
Blood: total bacteria- dental extraction		
After 5 min		
Median	0	9.68×10^1
Interquartile range	3.74×10^2	5.83×10^2
Range	$0 - 2.81 \times 10^3$	$0 - 6.96 \times 10^3$
After 30 min		
Median	0	0
Interquartile range	0	2.35×10^2
Range	$0 - 1.93 \times 10^3$	$0 - 1.38 \times 10^3$
Time	**At risk for IE (prophylactic antibiotics)(n=24)**	**No risk for IE(no prophylactic antibiotics)(n=31)**
Blood: total bacteria – supragingival scaling		
After 5 min		
Median	0	0
Interquartile range	0	4.33×10^2
Range	$0 - 4.36 \times 10^3$	$0 - 8.32 \times 10^3$
After 30 min		
Median	0	0
Interquartile range	0	0
Range	$0 - 2.58 \times 10^2$	$0 - 6.45 \times 10^3$

IE, infectious endocarditis.

5 and 30 min after extraction or scaling were generally lower than in patients who did not receive antibiotics. However, these differences were not statistically significant either. There were no significant differences in the bacterial load 5 and 30 min after gingival scaling or extraction in both groups of patients.

4 | DISCUSSION

The reported bacteremia incidence after dental procedures varies widely depending on the dental procedure and the studied population (Kinane et al., 2005; Lockhart et al., 2008). However, most of the previous studies used blood cultures. Quantitative molecular methods represent another approach to evaluate this issue and may help experts to develop guidelines with indications for prophylactic antibiotic therapy for patients undergoing medical and dental procedures. In the present study, the bacteremia incidence was analyzed by means of both blood culture and qPCR in patients who underwent dental extraction or supragingival scaling with or without antibiotic prophylaxis. It was observed that antibiotic prophylaxis decreased the incidence of viable bacteria in the bloodstream after dental extraction. Bacteremia was more frequent after dental extraction compared to gingival scaling. However, this difference was detected only in samples taken 5 min after the procedures.

Our results on positive blood cultures analysis showed values which are within those reported in the literature. We reported a 30% frequency of bacteremia 5 min after extraction in patients who did not receive antibiotics, as similar to another study (Maharaj et al., 2012), and 7% 30 min after extraction, as also in agreement with others (Rajasuo, Perkki, Nyfors, Jousimies-Somer, & Meurman, 2004). In the group of patients who received prophylactic antibiotic therapy, blood culture did not reveal bacteremia 5 min after dental extraction; this disagrees with Lockhart et al. (2008), who reported bacteremia in 33% of the cases in similar conditions. We also reported incidence of bacteremia 5 min after supragingival scaling similar to others (Kinane et al., 2005), but lower than the 33% incidence reported by Zhang, Daly, Mitchell, and Curtis (2013). As for blood samples collected 30 min after scaling, bacteremia was not detected by culture in either group of patients; this observation differs from the findings from Forner, Larsen, Kilian, and Holmstrup (2006) and Waghmare, Vhanmane, Savitha, Chawla, and Bagde (2013), who observed frequencies of 10% and 25%, respectively. The frequency of bacteremia detected by qPCR in patients with no risk for IE 5 min after scaling was 23%, which is consonance with the reports by Kinane et al. (2005) (23%) and Castillo et al. (2011) (19%). One aspect that may contribute to differences in bacteremia between studies is the use of an oral rinse with chlorhexidine digluconate before procedures, as performed in the present study. Chlorhexidine mouthwashes have been shown to have a significant impact in the reduction in bacteremia following dental procedures (Barbosa et al., 2015; Ugwumba, Adeyemo, Odeniyi, Arotiba, & Ogunsola, 2014).

The bacterial species identified by blood culture after dental procedures in the present study include some that have been associated with IE (Bahrani-Mougeot et al., 2008; Horliana et al., 2014; Lockhart et al., 2008). All positive blood samples in this study, except for one, came from patients who did not receive prophylactic antibiotics. In our study, the identification of a single bacterial species per positive blood culture in most blood samples is probably due to the cultivation method that allows for the growth of the cultivable species that is in greater quantity in a certain sample. Specifically for anaerobes, even though the culture medium used was enriched, the nutritional requirement is usually greater and only the species that are in greater numbers may grow and be identified. Identification of single-species cultures has also been reported previously (Benítez-Páez et al., 2013).

Bacteremia was significantly more prevalent among patients who underwent extraction without prophylactic antibiotic therapy. On the other hand, data from qPCR analysis showed no significant differences between the two groups of patients in terms of incidence and magnitude of bacteremia. Lack of difference may be related to some aspects of the molecular methods discussed below, or the sample size.

In our study, virtually all patients who had positive blood cultures also had positive qPCR results. However, molecular analysis allowed the identification of a higher incidence of bacteremia after dental procedures. This may be related to the fact that these methods possess much higher sensitivity than culture, are capable of detecting difficult-to-culture and as-yet-uncultivated bacteria, and are not significantly affected by concomitant antibiotic therapy (Bahrani-Mougeot et al., 2008; Kinane et al., 2005; Takumi et al., 2008). On the other hand, qPCR analysis may have detected bacteria that had been recently killed by the immune system response or by the use of antibiotics. In addition, molecular detection methods detect DNA and not cells and therefore provide an indirect measure of bacteremia. The use of culture, as done in this study, is also of great important to ensure bacterial viability.

The advantage of quantifying the bacterial load is the capability of determining the magnitude of bacteremia after dental procedures. In spite of the higher incidence of bacteremia after extraction in comparison with after scaling, the bacterial counts evaluated by qPCR in the positive cases did not significantly differ between the two procedures. The bacterial loads were generally below the range of 10^3 to 10^9 bacterial cells per ml of blood, which is the load required to induce experimental IE in animals (Wright & Wilson, 1982). The systemic effects of these bacterial levels are unknown, but they are dependent upon the types of bacteria involved, their virulence, and host predisposition.

In conclusion, this study showed that prophylactic antibiotics decreased the incidence of bacteremia detected by culture methods after extraction. However, molecular methods detected bacteremia in a higher proportion of patients undergoing both dental extraction and supragingival scaling than blood culture. The magnitude of bacteremia after scaling or extraction was relatively low. Dental extraction was associated with higher incidence of bacteremia than supragingival scaling. Our findings may be important for future updates of guidelines on antibiotic prophylaxis for infective endocarditis.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

LCR, INR, JFSJ, MU, RMS: Conceived and designed the experiments; LCR, INR, RMCPD, KRM: Performed the experiments; INR, JFSJ, MU, VSL, RMS: Analyzed the data; LCR, JFSJ, RMS: Wrote the paper. All authors: Critical review of the manuscript.

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