Parvimonas micra bacteremia following endoscopic retrograde cholangiopancreatography: A new route of infection

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Abstract: Parvimonas micra is an anaerobic, Gram-positive coccus belonging to oral, gastrointestinal and genital flora, rarely causing infections in humans. It was mainly deemed to cause bacteremia, septic bone and cerebral infections in patients which have undergone dental procedures or with suboptimal dental hygiene. We report the first case of Parvimonas micra bacteremia following endoscopic retrograde colangiopancreatography performed due to choledocholithiasis in a patient with good oral health. Identification of P. micra was finally performed by Matrix-assisted laser desorption ionization-time of flight mass spectrometry (VITEK MS system, bioMérieux, Marcy l'Étoile, France). All cases reported in english language of Parvimonas micra infections after medical procedure are reviewed in order to alert clinicians about new possible routes of infection of this emerging pathogen.

***Covering Letter**

Anaerobe

To the Editor

14th May, 2018

Dear Sir,

We submit our manuscript "*Parvimonas micra* bacteremia following endoscopic retrograde cholangiopancreatography: a new route of infection" for publication as case report in Anaerobe.

We report the first case of *Parvimonas micra* bacteraemia following endoscopic retrograd colangiopancreatography together with a comprehensive review of *Parvimonas micra* infections after medical procedure in order to alert clinicians about new possible routes of infection of this emerging pathogen.

We think that this kind of paper could contribute to the Anaerobe mission.

All the authors have seen and agree with the contents of the manuscript.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

We also certify that this submission is not currently under review at any other publication and there is no ghost writing by anyone not named on the author list.

Waiting to hear from you at your earliest convenience,

Sincerely,

Matteo Boattini, Gabriele Bianco, Rossana Cavallo, Cristina Costa

***Revision Notes**

Anaerobe

To the Editor

3rd September, 2018

Dear Sir,

We hereby resubmit our manuscript "*Parvimonas micra* bacteremia following endoscopic retrograde cholangiopancreatography: a new route of infection" for peer review to consider eventual publication as case report in Anaerobe.

We thank the Reviewers for their accurate appraisals. We are sure the paper has now been improved after the Reviewers' suggestions. We have revised the manuscript in accordance with the comments and suggestions raised. We enclose below a point-by-point response to the issues raised by the Reviewers specifying the changes made to the revised version of the manuscript.

We hope the revised version will now be suitable for publication in Anaerobe.

Waiting to hear from you at your earliest convenience,

Sincerely,

Matteo Boattini, Gabriele Bianco, Rossana Cavallo, Cristina Costa

Reviewer #2:

Dear Editor

Thank you to give me the opportunity for reviewing this interesting case report.

This case report is interesting, well-written adding a comprehensive review of the literature.

As I think very important to publish new clinical conditions in great journals, I consider that this case report could be accepted for a publication in Anaerobe.

We thank the Reviewer for his/her comment.

Reviewer #3:

Boattini et al. presented case regarding Parvimonas micra bacteriemia following ERCP procedure as a new route of infection. The case is interesting but the abstract and introduction do not achieve enough quality for Anaerobe. Nevertheless the discussion and conclusion are quite good and case seems to be important to present it to the readers. Hence I propose to improve abstract, introduction and also add important information in case description.

Moreover I need some more information about this patient. After these improvement another assessment must be done.

Examples:

1).

Abstract: Parvimonas micra is an anaerobic, Gram-positive coccus
belonging to oral, gastrointestinal and genital flora, mainly causing
bacteremia, septic bone and cerebral infections in patients which have
undergone dental procedures or with suboptimal dental hygiene.

I do not agree that this pathogen mainly is a cause of bacteriemia etc.

Mainly - is isolated form dental plaque, rarely is cause of infection

We thank the Reviewer for these relevant comments.

In agreement with his/her comment we changed the text (lines 30-33) as "Parvimonas micra is an anaerobic, Gram-positive coccus belonging to oral, gastrointestinal and genital flora, rarely causing infections in humans. It was mainly deemed to cause bacteremia, septic bone and cerebral infections in patients which have undergone dental procedures or with suboptimal dental hygiene".

2).

INTRODUCTION:

46 Endogenous microbiota translocation into the bloodstream is deemed to contribute to
47 high morbidity, disability and mortality rates, mainly causing endocarditis,
48 spondylodiscitis and central nervous system infections. It is considered to be result of
49 several mechanisms entailing mucosal or deeper injury. Subotpimal dental hygiene,
50 dental treatment but also routine daily activities as brushing and flossing teeth, using
51 toothpicks have been described to be associated to important endogenous microbiota
52 bacteremia rates [1].

This statement is too general. Pathogenesis of neuroinfections, endocarditis is very complex. the reference number 1 it is a endocarditis guidelines from 2007. It would be better to cite newer guidelines and I doubt that this guidelines are describing problem of nervous system epidemiology/microbiology.

We thank the Reviewer for highlighting this point.

Endogenous microbiota bacteremia can be associated with endocarditis, spondylodiscitis and central nervous system infections. We cited the endocarditis guidelines in order to highlight

pathogenic mechanisms of endogenous microbiota translocation into the bloodstream in developing primarily heart valve infection and, eventually, bone and CNS infections.

In agreement with the Reviewer's suggestion, we have now cited the newer guidelines (lines 173-178): "Suboptimal dental hygiene, dental treatment but also routine daily activities as brushing and flossing teeth, using toothpicks have been described to be associated to important endogenous microbiota bacteremia rates [Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al, 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128. doi: 10.1093/eurheartj/ehv319]."

3) case report

-what was the WBC count, neutrophil percentage, value of CRP, value of procalcitonin

-Did you perform USG of abdomen ?

We thank the Reviewer for highlighting this point. Accordingly, we changed the text (lines 85-88) as: "Biochemistry showed white blood cell count 15,500 [4,500-11,000 per mm^3], neutrophilia of 90%, C-reactive protein 160 mg/L [<5.0] and procalcitonin 2 ng/mL. Chest-X ray showed no lung infiltration. Abdominal ultrasound revealed no significative alterations."

-You mentioned that "two pairs of aerobic and anaerobic blood culture were drawn". Did both pairs were taken before antibiotic?

We thank the Reviewer for these remarks.

Both pairs of blood culture were drawn before antibiotic. We changed the text accordingly (line 90): "Two pairs of aerobic and anaerobic blood cultures were drawn peripherally and Ciprofloxacin (500 mg every 12h) was subsequently started".

- Did pathogen was confirmed in one or both blood cultures?

- Did you perform blood culturing which was negative after or even in the middle of antibiotictherapy

We thank the Reviewer for these remarks.

P. micra was isolated in both blood cultures. No more blood cultures were performed.

The text was changed as (Line 91): "After 30 hours, Gram staining showed gram positive cocci in both anaerobic blood cultures".

- How long patient had fever.

- When (in which day) you switched ciprofloxacin to penicilin.

- have you observed improvement after ciprofloxacin?

- Have you checked WBC, CRP, procalcitonin at the end of treatment

We thank the Reviewer for these relevant comments.

Patient had fever during 4 days, once a day, late in the afternoon. Penicilin was started on hospital day 5 (4^{th} day of fever). No improvement was observed on Ciprofloxacin. WBC, CRP, procalcitonin were checked at the end of treatment reaching normal range.

In agreement with Reviewer's suggestions we changed the text (line 100-103) as "On hospital day 5, patient still had fever. In agreement with the results of susceptibility testing, antimicrobial therapy was switched to intravenous Penicillin G (2 millions units every 4 hours) and it was continued for 14 days obtaining clinical and laboratorial improvement".

Highlights

- A case report on bacteremia following endoscopic retrograd cholangiopancreatography caused by rare anaerobic gram-positive coccus, *Parvimonas micra*
- A new route of *Parvimonas micra* infection is highlighted through this case
- *Parvimonas micra* translocation mechanism into the bloodstream highlighted in this case is imperceptible mucosal injury during endoscopy
- Review of previous cases of *Parvimonas micra* infections after medical procedure are also discussed in order to alert clinicians about new possible routes of infection of this emerging pathogen

PARVIMONAS MICRA BACTEREMIA FOLLOWING ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY: A NEW ROUTE OF INFECTION

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ABSTRACT:

Parvimonas micra is an anaerobic, Gram-positive coccus belonging to oral, gastrointestinal and genital flora, rarely causing infections in humans. It was mainly deemed to cause bacteremia, septic bone and cerebral infections in patients which have undergone dental procedures or with suboptimal dental hygiene. We report the first case of *Parvimonas micra* bacteremia following endoscopic retrograde colangiopancreatography performed due to choledocholithiasis in a patient with good oral health. Identification of *P. micra* was finally performed by Matrix-assisted laser desorption ionization–time of flight mass spectrometry (VITEK MS system, bioMérieux, Marcy l'Étoile, France). All cases reported in english language of *Parvimonas micra* infections after medical procedure are reviewed in order to alert clinicians about new possible routes of infection of this emerging pathogen.

KEYWORDS: Parvimonas micra; bacteraemia; anaerobe; gram-positive coccus; endoscopic retrograd colangiopancreatography; peptostreptococcus micros.

INTRODUCTION:

Endogenous microbiota translocation into the bloodstream is deemed to contribute to high morbidity, disability and mortality rates, mainly causing endocarditis, spondylodiscitis and central nervous system infections. It is considered to be result of several mechanisms entailing mucosal or deeper injury. Subotpimal dental hygiene, dental treatment but also routine daily activities as brushing and flossing teeth, using toothpicks have been described to be associated to important endogenous microbiota bacteremia rates [1]. Medical procedures such as gastrointestinal endoscopy (GIE) can also implicate technique-related mucosal trauma, sterile space or tissue local infections and endogenous microbiota traslocation [2]. However, oral and gastrointestinal commensal flora bacteremia rates following GIE are reported to be lower than in routine daily activities [2] and antibiotic prophilaxis recommendations before endoscopic procedures have been widely debated. When recommended, prior GIE antimicrobial prophilaxis should be provided to aim *Enterobacteriaceae*, enterococci, alpha-hemolytic streptococci, *Bacteroides fragilis* and *Clostridium spp* [3] in order to prevent infectious consequences [3]. Anaerobic commensal flora is an important part of oral and gastrointestinal microbiota and anaerobes other than Gram-negative bacilli can be involved in endogenous translocation. *Parvimonas micra*, previously known as *Peptostreptococcus micros* or *Micromonas micros* [4], is a non-spore forming, strictly anaerobic, slow-growing, occurring in pairs and short chains, Gram-positive coccus, belonging to commensal flora of oral cavity, gastrointestinal and genital tracts. It was deemed to cause bacteremia [5,6], endocarditis [7], pleural effusion [8], septic pulmonary embolism [9], bone [10-13] and cerebral infections, mainly in patients which have undergone dental medical procedures (DMP) [11,12-19] or with suboptimal oral hygiene [20-23]. Few data about clinical features and management of *P. micra* infections after medical procedures, above all in cases of infections after non-dental

medical procedures (NDMP), are reported in literature [8,19,22,24-28]. A case of a patient with *P. micra* bacteremia following endoscopic retrograd colangiopancreatography (ERCP) for choledocholithiasis together with a comprehensive review of *P. micra* infections after NDMP in patients with good oral health and after DMP is presented in order to compare epidemiological and clinical features and to alert clinicians about new possible routes of infection of this emerging pathogen.

CASE REPORT:

In January 2018, a 85-year-old man underwent ERCP due to choledocholithiasis with mild obstructive jaundice. Patient had a medical history of hypertension. ERCP achieved complete biliar drainage with no complications and patient was transferred to the medical ward. On hospital day 2 patient presented with fever (Temperature 39.4ºC) and shivering. The physical examination was unremarkable. Biochemistry showed white blood cell count 15,500 [4,500-11,000 per mm^3], neutrophilia of 90%, C-reactive protein 160 mg/L [<5.0] and procalcitonin 2,1 ng/mL. Chest-X ray showed no lung infiltration. Abdominal ultrasound revealed no significative alterations. Two pairs of aerobic and anaerobic blood cultures were drawn peripherally and Ciprofloxacin (500 mg every 12h) was subsequently started. After 30 hours, Gram staining showed gram positive cocci in both anaerobic blood cultures. After 48 hours incubation, 1 mm diameter, white, glistening and domed colonies grew on anerobic blood agar plates. Matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (VITEK MS system, bioMérieux, Marcy l'Étoile, France) provided identification of *P. micra* (confidence values of 99.9%). The *in vitro* susceptibility of the isolate was assessed with E-test. According to 2018 EUCAST, *P. micra* showed suceptibility for

Penicillin G (MIC: 0.002 µg/mL), Amoxicillin/Clavulanic Acid (MIC: 0.016 µg/mL), Imipenem (MIC: 0.002 µg/mL), Meropenem (MIC: 0.002 µg/mL), Ertapenem (MIC: 0.002 µg/mL), Clindamycin (MIC: 0.19 µg/mL), Vancomycin (MIC: 0.175 µg/mL) and Metronidazole (MIC: 0.032 µg/mL). On hospital day 5, patient still had fever. In agreement with the results of susceptibility testing, antimicrobial therapy was switched to intravenous Penicillin G (2 millions units every 4 hours) and it was continued for 14 days obtaining clinical and laboratorial improvement. Patient was discharged in good clinical condition and he remains under follow-up at the Gastroenterology out-patient clinic.

DISCUSSION:

Anaerobic microbiota translocation predisposing factors are described to include suboptimal dental hygiene, dental treatment, undrained abscesses, surgery such as oral, gastrointestinal, gynecologic or transplantation, cancer, hematologic malignant disease, immunodeficiency, chemotherapy and steroid treatment [29]. This case shows as NDMP such as ERCP should be considered a new possible route of *P. micra* infection. In our case, patient showed no dental alterations nor periodontal disease and *P. micra* probably translocated into the bloodstream due to an imperceptible mucosal injury during endoscopy. Equally, medical procedures other than dental treatment should be also contemplated as possible risk factors for anaerobic infections. For this reason, *P. micra* infections after NDMP in patients with good oral health and *P. micra* infections after DMP have been compared and results are reported in the Table. *P. micra* has been mainly identified in males, middle-aged people or older (45-81 years) and with co-morbidities such as diabetes mellitus, brain tumor, chronic B hepatitis and others widespread non-communicable diseases. *P. micra* infection seems to be also associated

with common conditions such as joint osteoarthritis, spondylolisthesis, hip and heart valve prosthesis and recurrent pneumothorax. These conditions may probably represent a *locus minoris resistentiae* which predispose to *P. micra* mechanism of translocation into the bloodstream or where *P. micra* is able to settle, irrespective of medical procedure is dental or non-dental related. Tooth extraction has been described to be main DMP. NDMP have included neuro, spinal, retropharingeal and heart valve surgery, pleurectomy, transurethral resection of the prostate, spinal instrumentation and joint corticosteroid injection. *P. micra* infections diagnosis after NDMP and DMP have not been reported to be so different, and consist mainly of central nervous system, bone, hip and heart valve prosthesis infections.

Variable time between medical procedure and *P. micra* infection diagnosis has been observed. However, if not considering shorter and longer time values, *P. micra* infections after DMP have been reported to be diagnosed in a shorter time lapse than in NDMP (2-6 months *vs* 2 days-many years).

P. micra translocation mechanism, spread and infection site in NDMP have been supposed to include retropharingeal surgery/contiguous spread/meningoencephalitis, transurethral procedure-related genital mucosa injury/hematogenous spread/spondylodiscitis, endotracheal intubation/aspiration/pleural effusion and pleurectomy causing esophageal pleural fistula/hematogenous spread/central nervous system abscesses.

Nevertheless, the incidence of *P. micra* infections may be underreported due to difficulty in culturing and identifying anaerobic bacteria. Recent introduction of MALDI-TOF mass spectrometry helped to improve the possibilities to phenotypically identify this unusual pathogen, also reducing time of identification. Moreover, 16S

rRNA gene sequencing continues to be a reliable identification systhem but it is rarely performed in clinical practice due to time and cost reasons.

Despite of causing severe infections, *P. micra* has shown wide antimicrobial susceptibility with only few cases of Metronidazole [30], Penicillin and Clindamycin resistance [31].

We highlight the considerable need to report *P. micra* infections above all after NDMP in order to follow new possible routes of anaerobic infections. Equally, we believe that suboptimal dental hygiene as well as report of medical procedure are probably underestimated and it is not always possible to completely understand cause and effect relationship between NDMP and *P. micra* translocation mechanism, above all in bone infections.

Checking oral cavity before medical procedures, considering medical procedure-related trauma in patients with fragile oral, gastrointestinal and genital mucosa, prescribing antibiotic prophilaxis covering anaerobes and monitoring rigorously fever after medical procedure should be suitable measures in order to avoid anaerobic infections, above all in the elderly.

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Table

1 Table. Literature review of *Parvimonas micra* infections after medical procedures

2

Reference	Age/ Gender	Co-morbidity	Medical procedure	Diagnosis	Culture sample	Time lapse between medical procedure and diagnosis	Supposed translocation mechanism and route of infection
Parvimonas micra infections after non-dental medical procedures in patients with good oral health							
Brook *et al.* 1999	N/R (6 cases)	N/R	Spinal surgery	Spinal fusion surgery infection	Vertebral biopsy and pus specimens	4-25 days	N/R
Frat *et al.* 2004	61/M	Diabetes mellitus	Retropharingeal surgery	Meningoencephalitis, epidural abscess	Cerebrospinal fluid	1 month	Surgery, contiguous spread
Uemura *et al.* 2014	70/M	N/R	Transurethral resection of the prostate	Spondylodiscitis	Paravertebral mass biopsy specimen	N/R	Procedure-related genital mucosa injury, hematogenous spread
Jones *et al.* 2015	72/F	Hip and cervical spine osteoarthritis	Spinal corticosteroid injections	Paravertebral abscess, spondylodiscitis	Paravertebral abscess pus	Many years	N/R
Cobo *et al.* 2017	75/F	Diabetes mellitus, hypercholesterolemia	Heart valves replacement, mechanical ventilation	Pleural effusion	Pleural fluid	1-8 days	Endotracheal intubation, aspiration
Shtaya *et al.* 2017	65/M	Asthma, recurrent pnemothorax	Pleurectomy	Brain and cervical epidural abscesses	Epidural abscesses pus	48 years	Esophageal pleural fistula, hematogenous spread
Sultan *et al.* 2018	73/M	Diabetes mellitus, obesity, hypertension, knee osteoarthritis	Intra-articular corticosteroid injection	Septic knee arthritis	Knee joint surgical irrigation fluid	2 days	N/R
Lee *et al.* 2018	49/F	Brain tumor,with hydrocephalus	Neurosurgery	Brain abscess, bacteremia	Blood	N/R	N/R
Boattini *et al.* 2018	81/M	Hypertension	ERCP	Bacteremia	Blood	1 day	Endoscopy-related oral/gastrointestinal mucosa injury, hematogenous spread
Parvimonas micra infections after dental procedures							
Bartz *et al.* 2005	63/F	Hip prosthesis	Tooth extraction	Hip artroplasty infection	Prosthetic joint surgical infected tissue and swab	6 months	
Bassa Malondra *et al.* 2008	74/M	Prosthetic mitral valve	Tooth extraction	Prosthetic Endocarditis	Blood	6 months	

Ko *et al.* 2015	61/M	Chronic hepatitis B, dyslipidemia, peridontal disease	Tooth extraction	Meningitis, bacteremia	Blood	14 days	Dental procedure, hematogenous spread
Jones *et al.* 2015	72/M	N/R	Tooth extraction	Spondylodiscitis	Vertebral biopsy specimens	2 months	
George *et al.* 2015*	45/M	Spondylolisthesis	Tooth extraction	Osteomyelitis, epidural abscess	Spinal surgical tissue and bone specimens	2 months	
Endo *et al.* 2015	55/F	N/R	Dental treatment	Epidural abscess, spondylodiscitis	Vertebral and abscess surgical tissue specimens	> 2 months	
Baghban *et al.* 2016	65/M	Diabetes mellitus, knee osteoarthritis, peridontal disease	Dental treatment	Knee artrhritis	Knee joint synovial fluid	2 months	
Dietvorst *et al.* 2016	68/F	None	Dental treatment	Knee arthritis	Knee joint synovial fluid	2 months	
Cleaver *et al.* 2017**	45/F	Smoker	Dental treatment	Spondylodiscitis	Vertebral surgical tissue and pus specimens	Some years	

* Doubtful case, also with medical history of spinal instrumentation 6 months before;
** Doubtful case, also with medical history of intra-uterine device insertion 2 months before;
N/R: Not reported;

***Conflict of Interest**

CONFLICT OF INTEREST:

All authors report no conflicts of interest.