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Published in:
Anaerobe

DOI (link to publication from Publisher):
10.1016/j.anaerobe.2021.102460

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Kirk, K. F., Andersen, K. L., Tarpgaard, I. H., & Nielsen, H. L. (2021). Three cases of *Sutterella wadsworthensis* bacteremia secondary to abdominal infections. *Anaerobe*, *72*, Article 102460. https://doi.org/10.1016/j.anaerobe.2021.102460

Anaerobe 72 (2021) 102460

Contents lists available at ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe

Three cases of *Sutterella wadsworthensis* bacteremia secondary to abdominal infections

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ARTICLE INFO

Article history:
Received 15 February 2021
Received in revised form
20 September 2021
Accepted 23 September 2021
Available online 24 September 2021

Keywords:
Sutterella wadsworthensis
Bacteremia
Abdominal infections
Diverticulitis
Appendicitis

ABSTRACT

The anaerobic bacterium *Sutterella wadsworthensis* has previously been isolated from the human intestine, both in healthy individuals and patients with gastrointestinal disorders, and the clinical significance of this bacterium is unknown. In this case report, we describe three cases of bacteremia with *Sutterella wadsworthensis,* from patients with recent intraabdominal surgery.

1. Introduction

Sutterella wadsworthensis was originally described by Wexler and colleagues in 1996 [1]. They are Gram-negative, bile-resistant rods, able to grow under anaerobic conditions and in the presence of 6% oxygen. Originally, the bacterium differentiates from the microaerophilic *Campylobacter gracilis*, and was named in memory of Vera Sutter, a respected colleague and former director of the Wadsworth Anaerobe Laboratory [1]. Originally, Wexler et al. included only one type species in the genus *Sutterella*, but since then *Sutterella stercoricanis*, *Sutterella parvirubra* and *Sutterella megalosphaeroides* have been included, all of which have been isolated from human feces [2–4].

Sutterella wadsworthensis has been isolated from a variety of clinical specimens throughout the human gastrointestinal tract, in both healthy individuals and patients with gastrointestinal disease [5–8], but to our current knowledge only one isolate derived from blood has previously been reported [9]. Here, we describe three cases of bacteremia with *Sutterella wadsworthensis,* from patients with recent intraabdominal surgery.

2. Description of the cases

2.1. Case 1

A 59-year-old woman presented to the emergency department (ED) with nausea, diarrhea and diffuse abdominal tenderness. She had a history of diabetes mellitus, chronic pulmonary obstructive disease and pulmonary hypertension.

Laboratory investigations revealed elevated white blood cell count (WBC) of 30.4 $\times$ 10^9/L, and C-reactive protein (CRP) of 323mg/L. Blood, urine and feces was sent to the department of Clinical Microbiology (DCM) and treatment with intravenous piperacillin–tazobactam 4.5g q8h, was initiated. Two days later she was afebrile and recovering, therefore discharged with oral pivmecillinam on suspicion of a urinary tract infection. However, the patient was re-hospitalized three days later, with increasing abdominal pain, therefore piperacillin–tazobactam 4.5g q6h was re-initiated. On admission, the DCM reported a positive blood culture with Gram-negative rods in the anaerobic bottle from the

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https://doi.org/10.1016/j.anaerobe.2021.102460

initial admittance, finally identified as *S. wadsworthensis.* An abdominal CT-scan revealed perforated diverticulitis, complicated by pneumoperitoneum and abscess formation. An open left hemicolectomy (Hartmann's procedure) was performed. Piperacillin−tazobactam was continued for another seven days in combination with fluconazole, and the patient fully recovered.

2.2. Case 2

A 13-year-old boy was admitted to the ED with classic presentation of appendicitis, being acute onset of abdominal pain and tenderness in the right lower quadrant, chills and vomiting. Laboratory investigation revealed elevated WBC of 25.7 x109/L and CRP of 14mg/L. Blood and urine cultures were performed and antibiotic treatment was initiated with intravenous ampicillin 2g q6h, gentamicin 240mg q24h and metronidazole 500mg q12h. An abdominal CT-scan revealed phlegmonous retrocecal appendicitis, resulting in laparoscopic appendectomy, and the patient was discharged the next day without concurrent antibiotic treatment. The following day the anaerobic blood culture bottle was positive for *S. wadsworthensis,* and the patient was called in for reassessment. He was afebrile and clinically recovering, with a CRP of only 23mg/L, and was therefore discharged without further treatment.

2.3. Case 3

A 56-year-old healthy woman was admitted to the ED with symptoms of diarrhea and intermittent fever for seven days. On physical examination she was afebrile and without abdominal tenderness but was severely hypotensive. She was transferred to the ICU for intravenous fluids, and on the suspicion of sepsis, antimicrobial therapy with piperacillin−tazobactam 4.5g q8h was initiated. Laboratory investigations revealed elevated WBC of 35×10^9/L and CRP of 312mg/L. Blood cultures prior to, and following piperacillin-tazobactam-treatment, were sent to the laboratory. An abdominopelvic CT-scan revealed uncomplicated diverticulitis, and the first blood culture set was positive for *Escherichia coli*, *Enterococcus avium*, *Clostridium ramosum* and *Bacteroides fragilis*. The patient was treated nonoperatively with intravenous piperacillin−tazobactam, metronidazole and fluconazole for five days. However, the anaerobic blood culture bottle, from the second blood culture set obtained on piperacillin−tazobactam treatment, showed growth of *S. wadsworthensis*, resistant to piperacillin−tazobactam. Therefore, treatment was changed to ampicillin, ciprofloxacin and metronidazole. Four days later, the patient developed severe abdominal pain and a CT-scan now revealed perforated diverticulitis with pneumoperitoneum therefore an open left colectomy was performed. Antibiotics were switched back to intravenous piperacillin−tazobactam, metronidazole and fluconazole for another six days, and the patient fully recovered.

3. Discussion

This is the first Case series of bacteremia with *S. wadsworthensis.* All blood culture isolates revealed growth in the BD BACTEC™ Lytic anaerobic medium in the BD BACTEC™ FX instrument (Becton, Dickinson and Company, Franklin Lakes, US) with a time-to-detection of 30.3, 30.6 and 24.1 hours, respectively. Microscopy showed Gram-negative straight rods, and all isolates grew after 48−72 hours on the standard anaerobic plate (chocolate agar with added vitamin K and cysteine (SSI Diagnostica, Hillerød, Denmark)) at 35 °C in an atmosphere of 10% CO2, 10% H2, and 80% N2 in an anaerobic chamber. For comparison, all isolates grew in a microaerobic chamber on 5% horse blood agar, but anaerobic conditions yielded a better growth. By use of the MALDI Biotyper (Bruker Daltonics, Bremen, Germany), the three blood isolates (AAUH 34176 (Case 1), AAUH 40984 (Case 2), and AAUH 74476 (Case 3)) were identified as *S. wadsworthensis* with primary log-scores of, 2.380, 2.360, 2.030, respectively. To confirm isolates to species level, we sequenced the isolates with the Illumina MiSeq instrument producing 2 x 300-bp paired-end reads by using Nextera XT library preparation kit (Illumina Denmark ApS, Copenhagen, Denmark). Reads were assembled using CLC Genomics Workbench (version 11) (QIAGEN Bioinformatics, Aarhus, Denmark) to a total sequence length 2,880,938bp, 2,853,154bp, and 2,858,537bp, respectively, with a median GC-content of 55.1%. Next, we uploaded the genome sequences to the Type (Strain) Genome Server (TYGS) [10], that incorporates a Genome-to-Genome Distance Calculator against its database of type (strains) genomes, to confirm the identification of *S. wadsworthensis*, see Fig. 1.

Antimicrobial susceptibility testing (AST) was performed anaerobically, se Table 1. All isolates were interpreted sensitive to meropenem using EUCAST breakpoint tables for Gram-negative anaerobes, version 9.0, whereas one isolate only (AAUH 40984) was sensitive to clindamycin and metronidazole. For piperacillin-tazobactam (no etest available) we included disc diffusion (disc content, 30+6μg), showing no inhibition zones for all isolates. For ciprofloxacin and clarithromycin, we performed AST by use of a microaerobic environment using BD Mueller Hinton Fastidious agar (MF-F) revealing MICs of 0.25 mg/L and 2 mg/L for all isolates, respectively, which could indicate sensitivity to these agents. Finally, we uploaded sequences to the WGS-based AST ResFinder (https://cge.cbs.dtu.dk/services/), but no acquired antimicrobial resistance genes were identified in the database.

Sutterella wadsworthensis was differentiated from *Campylobacter gracilis* in 1996 [1], and our findings confirm the close resemblance to this species. Antibiotic susceptibility profiles with findings of sensitivity to ciprofloxacin and erythromycin combined with metronidazole resistance, could indicate that *S. wadsworthensis* resembles profiles of *Campylobacter*, rather than those of obligate anaerobes. Following taxonomic classification, Molitoris et al. reported data from isolation of 45 *S. wadsworthensis* strains and 16 *C. gracilis* strains, and found that *S. wadsworthensis* was commonly found in samples from appendicitis and peritonitis, and that antimicrobial resistance was more common, than for *C. gracilis,* [9] much in accordance with our findings. Previous studies describing *S. wadsworthensis* in human clinical samples are inconclusive, regarding the role of *S. wadsworthensis* as a possible pathogen.

In 2000, Engberg et al. recovered *S. wadsworthensis* in stool samples from patients with diarrhea and healthy controls [7], and later, researchers from Aberdeen, UK, found *S. wadsworthensis* equally identified by PCR methods in both adult and pediatric populations with IBD and healthy controls [6,8]. Hiippala et al. investigated *S. wadsworthensis* in intestinal biopsies and found the species abundant in the duodenum. By in-vitro analysis, they described mild pro-inflammatory activity when comparing to a non-pathogenic *E. coli* strain [5]. In 2019, Paramsothy et al. analyzed fecal samples from patients undergoing fecal microbiota transplantation for the treatment of ulcerative colitis, and found that an increase in *S. wadsworthensis* was associated with lack of clinical and endoscopic remission [11].

All the cases reported were immunocompetent. Two patients had severe diverticulitis with perforation, a relatively uncommon complication to this disease, and one had bacteremia secondary to appendicitis. In all cases, blood cultures were attained prior to gastrointestinal surgery and the cultivation of *S. wadsworthensis* from blood may have been an indication of the severity of disease. In the third case the first blood culture set was positive for

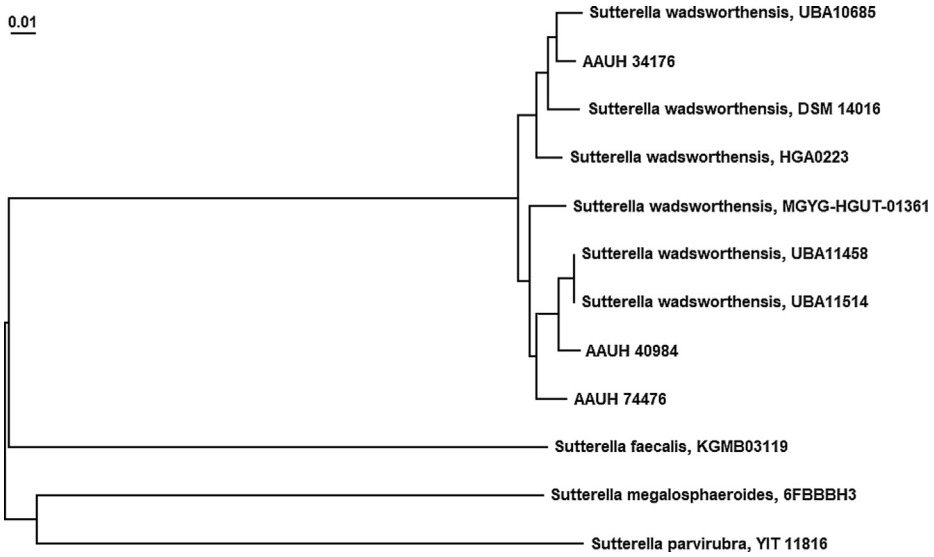

Fig. 1. A phylogenetic tree, including local isolates (AAUH 34176, AAUH 40984 & AAUH 74476) and NCBI-derived reference strains of *Sutterella wadsworthensis*, *S. faecalis*, *S. megalosphaeroides* and *S. parvirubra*, was constructed by use of the online TYGS webtool [6]. The algorithm is based on Genome BLAST Distance Phylogeny (GBDP) distances calculated from genome sequences. The following GenBank (GCA) genome assemblies were included, GCA_000411515.1, GCA_003315195.1, GCA_902374255.1, GCA_003522065.1, GCA_003534655.1, GCA_003448235.1, GCA_003609995.1, GCA_006337085.1, GCA_000250875.1.

Table 1
Antimicrobial susceptibility of the *Sutterella wadsworthensis* blood culture isolates.

	MIC[a] (mg/L) for *S. wadsworthensis* isolates:		
	AAUH 34176	AAUH 40984	AAUH 74476
Antimicrobial agents			
Penicillin	>32	>32	>32
Ampicillin	4	8	8
Amoxicillin-clavulanic acid	2	4	2
Cefotaxim	>32	>32	>32
Meropenem	0,06	0,06	0,06
Clindamycin	8	4	8
Metronidazole	32	1	32

[a] By use of Etest (BioMérieux, Marcy l'Etoile, France) on Brucella agar (5% blood + vitamin K + hemin) with a McFarland equivalent of 1, incubated for 48 hours in an anaerobic chamber.

Escherichia coli, *Enterococcus avium*, *Clostridium ramosum* and *Bacteroides fragilis*, all representatives of the human intestinal microbiota, whereas in the second blood culture set obtained on piperacillin–tazobactam treatment *S. wadsworthensis* was diagnosed from the anaerobic blood culture bottle. In all cases, abdominal surgery and debridement of infected tissue was the curative treatment, and secondary to acute surgical intervention, broad-spectrum antibiotics are indicated for treatment of possible subsidiary infections. While the clinical importance of *S. wadsworthensis* certainly remains uncertain, growth of any microbial organism in a blood culture, should always be evaluated for clinical relevance, and viewed in consideration of the patients' condition. As such, even the presence of gut commensals in blood cultures, should be interpreted carefully, and considerations of possible severe infections and dysfunctional gut epithelial barriers must be considered, even though the microorganism solely may not be considered a pathogen.

In conclusion, this case series describes the identification of *S. wadsworthensis* in blood stream infections in patients undergoing abdominal surgery. Although the clinical relevance of this finding is uncertain, it may warrant closer investigations into the pathogenic potential of this enigmatic organism.

Source of funding

None.

4. Contribution of authors

HLN made the first design of the manuscript. IHT made identification, and WGS-analysis. KFK drafted the manuscript, and KLA treated all patients and obtained informed consent from the patients. All Authors revised the manuscript critically and approved the final version.

Declaration of Competing Interest

None.

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