**Brevundimonas spp: Emerging global opportunistic pathogens**

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**ABSTRACT**
Non-fermenting Gram-negative bacteria are problematic in clinical locations, being one of the most prevalent causes of nosocomial infections. Many of these non-fermenting Gram-negative bacteria are opportunistic pathogens that affect patients that are suffering with underlying medical conditions and diseases. *Brevundimonas* spp., in particular *Brevundimonas diminuta* and *Brevundimonas vesicularis*, are a genus of non-fermenting Gram-negative bacteria considered of minor clinical importance. Forty-nine separate instances of infection relating to *Brevundimonas* spp. were found in the scientific literature along with two pseudo-infections. The majority of these instances were infection with *Brevundimonas vesicularis* (thirty-five cases – 71%). The major condition associated with *Brevundimonas* spp. infection was bacteraemia with seventeen individual cases/outbreaks (35%). This review identified forty-nine examples of *Brevundimonas* spp. infections have been discussed in the literature. These findings indicate that infection review programs should consider investigation of possible *Brevundimonas* spp. outbreaks if these bacteria are clinically isolated in more than one patient.

**Introduction**
Gram-negative, non-fermenting bacteria are an emerging concern in clinical locations, being a common cause of nosocomial infections. Opportunistic pathogens from this group include many different bacterial species, including: *Acinetobacter baumannii*, *Burkholderia cepacia*, *Ralstonia pickettii*, *Pseudomonas aeruginosa*, *Sphingomonas paucimobilis*, and *Stenotrophomonas maltophilia* [1–8]. The group can survive in a wide variety of environments including different water sources (aircraft water, bottled water, hospital water, purified water) [9–12], and are usually resistant to a wide array of antimicrobials [13,14]. Examples include resistance to penicillins, aminoglycosides and monobactams in *R. pickettii* [13] and penicillins, aminoglycosides, carbapenems and monobactams in *S. maltophilia* [14]. Bacteria such as these have the ability to infect patients/individuals with underlying medical conditions and diseases. Examination of the scientific literature showed multiple types of infections resulting from *Brevundimonas* spp. This indicates that the genus may be a more widespread pathogen than was hitherto thought, with infections caused by *Brevundimonas* spp. being invasive and severe. The goal of this study was to give an overview of the range of *Brevundimonas* spp. infections, any underlying conditions associated with *Brevundimonas* spp. infections and the treatment options used in the treatment of any *Brevundimonas* spp. infections in order to assist medical practitioners.

**Genus Brevundimonas**
The genus *Brevundimonas* was first proposed by Segers et al [15]; incorporating *Pseudomonas diminuta* and *Pseudomonas vesicularis* [16,17]. Several species of the genus *Caulobacter* were later transferred to *Brevundimonas* significantly emending the description of the genus [18]. Currently, there are 25 species with valid published names within the *Brevundimonas* genus (http://www.bacterio.net/brevundimonas.html). The type species is *Brevundimonas diminuta*; with the type strain being LMG 2089.

*Brevundimonas* species are aerobic Gram-negative, oxidase and catalase positive, non-fermenting rods 1 to 4 μm in length and 0.5 μm in width, belonging to the Alphaproteobacteria class and Caulobacteraceae.
family with a DNA G + C content of 65% to 68% [15]. Motility is provided by one short polar flagellum. *Brevundimonas* spp. have been isolated from multiple environments, including soils [9–21], deep subsea floor sediment [22] activated sludge,[23] black sand, [24], deep subsea floor sediment [25] numerous aquatic habitats [26], purified water [27] and also from the condensation water of a Russian space laboratory [28].

**Brevundimonas spp.**

**Brevundimonas diminuta**

*Brevundimonas diminuta* is the type species of the *Brevundimonas* genus. It has been isolated from clinical specimens, including blood and urine [15] as well as from the lung sputum of cystic fibrosis patients [29]. *B. diminuta* is not believed to be a significant pathogen and its virulence is generally low. *B. diminuta* is used as a test organism to validate reverse-osmosis (RO) filtration devices for drinking water purification and is also used to test the porosity of pharmaceutical-grade filters (0.2 μm) due to the small size of the bacterium when grown in minimal media [30,31]. The bacterium has however been shown to be capable of penetrating these filters [32]. The bacterium has been used as a potential bioremediator of marine oil pollution including diesels, n-alkanes and polycyclic aromatic hydrocarbons [33,34] and insecticides [35]. *B. diminuta* has also been used to mitigate the toxic effects of heavy metals on plant growth (rice) in contaminated soils [36]. *B. diminuta* also possesses the ability to survive sanitizers such as Hydrogen Peroxide + Peracetic Acid [37]. All available reported incidences of infection credited to *B. diminuta* are listed in Table 1–3.

**Brevundimonas vesicularis**

*Brevundimonas vesicularis* has been isolated from eye, urine, wound cultures, the central nervous system, cervical specimens [38], and also been found in the lung sputum of cystic fibrosis patients [39]. The organism has been shown to support the growth of *Legionella* in nutrient limited water conditions [40]. The mechanism behind this phenomenon has not been elucidated but it is hypothesised to be due to cryptic growth, with *B. vesicularis* having the ability to grow in nutrient limited conditions and *Legionella* growing on this [40]. Further research is required to gain a fuller understanding of this phenomenon. *B. vesicularis* has been used as a potential bioremediator of polyaromatic hydrocarbons [41]. All reported incidences of infection credited to *B. vesicularis* are listed in Table 1–3.

**Identification of Brevundimonas spp**

Members of the *Brevundimonas* spp. are Gram negative with cells appearing as straight slim rods upon Gram staining. They are non-spore forming. They are aerobic with optimal growth temperatures of between 30–37°C. They are oxidase positive and give variable results for catalase (usually positive). *B. diminuta* colonies have a chalk white appearance on MacConkey agar, whereas *B. vesicularis* colonies have an orange colour given by an intracellular pigment. Both grow slowly on ordinary nutrient media [42]. Both *B. vesicularis* and *B. diminuta* can be identified via commercial biochemical identification kits or systems such as the API 20 NE system, the VITEK 2 system (bioMerieux) or the Phoenix-100 automated system (Becton Dickinson). MALDI-TOF identification is also being used for identification of *Brevundimonas* spp. in clinical situations [43,44]. Species specific Real Time PCR primers and Fluorescence in situ hybridization (FISH) probes have been designed for *B. diminuta* [45]. These can be seen in Table 4.

**Factors associated with Infection**

**Underlying causes**

The majority of infections with *Brevundimonas* (Table 1–3) were found to have an underlying condition or disease that allowed patients to succumb to *Brevundimonas* infection. Seven patients, who were suffering with various types of cancer, contracted *Brevundimonas* -related bacteraemia, Urinary Tract Infection (UTI) and Empyema [46]; a 56-year-old female with *Lupus glomerulonephritis* acquired a *Brevundimonas* -related leg ulcer [47] and an infant suffering from Pompe disease was diagnosed with *Brevundimonas* -related bacteraemia [48]. Other examples of patients infected with *Brevundimonas* having underlying conditions are shown in Table 1–3. Such examples demonstrate the role of *Brevundimonas* as an opportunistic pathogen in immunocompromised individuals. Many of these instances of infection were hospital acquired although a large number were community acquired, which is interesting as opportunistic pathogens such as *Brevundimonas* spp or *R. pickettii* are usually contracted in hospital settings [7].

**Co-Infection**

Reports of cases of co-infection with *Brevundimonas* spp and other bacteria were rare with only two instances
### Table 1. Incidences of *Brevundimonas* spp. infection from 1978–2000 — Main characteristics of the case reports.

| Author (Ref)/Species | Year | Sex/Age | Country | Co-morbidity | Type of infection | Susceptible to | Resistance to | Antibiotic treatment | Outcome |
|----------------------|------|---------|---------|--------------|------------------|----------------|---------------|---------------------|---------|
| Otto et al. [53], *B. vesicularis* | 1978 | Multiple cases (5 cases) | USA | N/A | Cervicitis | Ampicillin, Carbenicillin, Gentamicin, Kanamycin, Nitrofurantoin, Streptomycin, Tetracycline | Colistin, Nalidixic acid, Sulfisoxazole | N/A | N/A |
| Vanholder et al. [54], *B. vesicularis* | 1990 | M/62 | Belgium | Hemodialysis | Bacteraemia/HA | N/A | N/A | Cefotaxime, Tobramycin | Complete recovery |
| Vanholder et al. [55], *B. vesicularis* | 1992 | F/62 | Belgium | Hemodialysis | Bacteraemia/HA | N/A | N/A | Cefotaxime, Tobramycin | Complete recovery |
| Planes et al. [56], *B. vesicularis* | 1992 | W/54 | USA | Systemic lupus erythematosus and chronic active autoimmune hepatitis | Bacteraemia/HA | N/A | N/A | Ceftazidime, Tobramycin | Surgical resection of the infected tissue |
| Pasadakis et al. [57], *B. diminuta* | 1993 | N/A | Greece | End-stage renal failure | Peritonitis | N/A | N/A | Initial 500 mg/L ceftazidime in a 1-L + 1.7 mg/kg of tobramycin. Maintenance doses 250 mg/2 L of ceftazidime + 16 mg/2 L of tobramycin | Complete recovery |
| Oberhelman et al. [58], *B. vesicularis* | 1994 | M/5 | USA | Sickle cell anaemia | Pneumonia/CA | N/A | N/A | Ceftriaxone, Gentamicin | Complete recovery |
| Calegari et al. [59], *B. vesicularis* | 1996 | M/60 | Uruguay | Trauma | Botryomycosis/CA | N/A | N/A | Cefuroxime | Complete recovery |
| Gilad et al. [60], *B. vesicularis* | 2000 | F/42 | Israel | Mitrval valve replacement | Bacteraemia/HA | Amoxicillin-Clavulanate, Aminoglycosides, Co-trimoxazole, Impenem, Mezlocillin, Piperacillin, Piperacillin-Tazobactam | Ampicillin, Aztreonam, Cefuroxime, Ceftriaxone, Ceftazidime, Ciprofloxacin | Piperacillin- Tazobactam | Complete recovery |

M- Male, F- Female, N/A – Not Available, CA – Community Acquired, HA- Hospital Acquired.
| Author (Ref) | Year | Sex/Age | Country | Co-morbidity | Type of infection | Susceptible to | Resistance to | Antibiotic treatment | Outcome |
|-------------|------|---------|---------|--------------|------------------|---------------|--------------|----------------------|---------|
| Lee et al. [61], Various | 2000–2010 | Multiple (30 cases) | Taiwan | Cancer patients | Bacteraemia | Ciprofloxacin, Colistin, Doripenem, Tigecycline | Amikacin, Piperacillin/tazobactam | Cefotaxime, Ceftadidine, Cefmetazole, Cefazolin, Cefuroxime, Ceftriaxone, Imipenem, Piperacillin/tazobactam | Complete recovery |
| Seve et al. [62], B. diminuta | 2004 | F/35 | France | Leukaemia | Bacteraemia/HA | Ciprofloxacin, Imipenem | Amikacin, Ceftazidime, Piperacillin | Initially Ceftazidime, Amikacin | Complete recovery |
| Chi et al. [63], B. vesicularis | 2004 | M/38 | Taiwan | None | Tonsillitis/CA | Cefoperazone | Amoxicillin, Aztreonam, Ceftazidime, Ciprofloxacin, Flomoxef, Gentamicin, Tobramycin, Ceftriaxone | Amoxicillin/Clavulanic acid | Complete recovery |
| Chi et al. [63], B. diminuta | 2004 | M/62 | Taiwan | Liver cirrhosis, Encephalopathy, Spontaneous bacterial peritonitis | Bloodstream infection/CA | Amikacin, Aztreonam, Ceftoxime, Cefepime, Chloramphenicol, Ciprofloxacin Flomoxef, Gentamicin, Imipenem, Piperacillin-Tazobactam, Tetracycline, Tobramycin, Cotrimoxazole | Cefotaxime | Complete recovery |
| Han et al. [46], B. diminuta | 2005 | Multiple (7 Cases) | USA | Cancer | Bacteraemia, Urinary Tract Infection, Empyema/HA | Amikacin, Imipenem and Ticarcillin/clavulanate | Amoxicillin, Cefepime, Ciprofloxacin | Cefepime, Imipenem, Levofloxacin, Meropenem, Nafcillin, Tobramycin, Ticarcillin/clavulanate, Vancomycin | Complete recovery |
| Karadag et al. [38], B. vesicularis | 2005–2011 | Multiple (8 cases) | Turkey | Neonates | Septicaemia/HA | Amikacin, Imipenem, Aztreonam, Ceftazidime, Piperacillin/tazobactam | Amoxicillin, Cefepime, Ciprofloxacin, Flomoxef, Meropenem | Ampicillin, Ceftazidime, Ciprofloxacin, Flomoxef, Meropenem | 7 Complete recovery, 1 Died |
| Vahid [64] B. vesicularis | 2005 | W/36 | USA | Acute myelogenous leukaemia | Bacteraemia | Ciprofloxacin, Ticaracillin-Clavulanate | Amikacin, Aztreonam, Ceftazidime, Ceftriaxone, Meropenem, Piperacillin/tazobactam | Ampicillin, Cephalothin, Ciprofloxacin | Complete recovery |
| Papaefstathiou et al., [85], B. vesicularis | 2005 | F/92 | Greece | Cardiac failure | Bacteraemia/CA | Amoxicillin-clavulanate, Aminoglycosides, Azlocillin, Aztreonam Second and Third-generation Cephalosporins, Imipenem, Piperacillin, Tetracycline, Trimethoprim-Sulfamethoxazole | Cefuroxime, Netilmicin | N/A | Died |
| Niedermeier et al. [66], B. vesicularis | 2005 | F/37 | USA | Acute myeloid leukemia, Pregnancy, Pancytopenia | Sepsis/HA | N/A | Clindamycin, Piperaclilin-tazobactam | N/A | Complete recovery from sepsis |
| Mondello et al. [67], B. vesicularis | 2006 | M/24 | Italy | Pilocytic astrocytoma | Meningitis/HA | Ciprofloxacin, Co-trimoxazole, Tetracycline | N/A | Initially: Ceftriaxone, Ciprofloxacin, Co-trimoxazole After Treatment failure: Amikacin | Complete recovery |

(Continued on next page)
| Author (Ref) | Year | Sex/Age | Country | Co-morbidity | Type of infection | Susceptible to | Resistance to | Antibiotic treatment | Outcome |
|------------|------|---------|---------|--------------|------------------|----------------|---------------|----------------------|---------|
| Choi et al. [68], B. *vesicularis* | 2006 | M/55 | South Korea | Diabetes, Continuous ambulatory peritoneal dialysis | Peritonitis/CA | N/A | N/A | Aztreonam, Cefazolin, Ceftazidime, Ciprofloxacin, Vancomycin Cefazolin, Gentamicin | Complete recovery |
| Yang et al. [69], B. *vesicularis* | 2006 | M/40 | Taiwan | None | Endocarditis/CA | Amikacin, Amoxicillin, Gentamicin, Piperacillin, Aztreonam, Cefepime, Meropenem, Netilmicin, Ampicillin, Ciprofloxacin, Cefazolin, Cefmetazole, Cefadroxime, Ceftriaxime, Ceftriaxone, Ticarcillin | N/A | | | |
| Zhang et al. [70], B. *vesicularis* | 2006–2009 | Multiple Cases (22 patients) | Taiwan | Various (Cancer, heart failure, COPD, Kidney disease) | Bacteraemia/CA/HA | N/A | | Various (Penicillin’s, Cephalosporins) | Complete recovery in 21 cases. 1 case of death |
| Pelletier et al. [71], B. *vesicularis* | 2007 | F/45 | USA | None | Keratitis | Ceftazidime, Ciprofloxacin, Gentamicin, Levofloxacin | N/A | Ceftazidime | Complete recovery |
| Sofer et al. [72], B. *vesicularis* | 2007 | F/15 Month old | Israel | None | Septic Arthritis/CA | Aminoglycosides, Aminopenicillins, Cephalosporins, Piperacillin, Quinolones, Trimethoprimsulfamethoxazole | N/A | Cefuroxime | Complete recovery |
| Menuet et al. [29], B. *vesicularis* | 2008 | F/17 | France | Cystic Fibrosis | Pneumonia | Amikacin, Ceftriaxone, Gentamicin, Imipenem, Isopenicillin, Rifampicin, Piperacillin/tazobactam, Ticarcillin, Ticarcillin-Clavulanate, Tobramycin | N/A | Imipenem, Tobramycin | Complete recovery |
| Panasiti et al. [73], B. *vesicularis* | 2008 | M/71 | Italy | None | Cutaneous Infection/CA | Amikacin, Cefoxitin, Ceftazidime, Cefuroxime, Cefalotin, Cepodoxime, Gentamycin, Tobramycin | N/A | Amoxicillin-Clavulanate | Complete recovery |
| Viswanathan et al. [74], B. *vesicularis* | 2009 | M/Infant | India | Newborn | Sepsis/HA | Amikacin, Cefotaxime, Ciprofloxacin, Gentamicin, Meropenem, Ofloxacin, Piperacillin/tazobactam | N/A | Amikacin, Cefotaxime | Complete recovery |
| Chandra et al. [75], B. *vesicularis* | 2010 | M/31 | USA | Biliary Pancreatitis | Bacteraemia | Amikacin, Cefuroxime, Cefepime, Ciprofloxacin, Gentamicin, Piperacillin/tazobactam, Polymyxin B | Aztreonam. Cefuroxime | | Complete recovery |
| Restrepo et al. [76], B. *vesicularis* | 2010 | F/44 | Columbia | None known | Reactive Arthritis + Bacteraemia | Amikacin, Imipenem, Meropenem, Piperacillin/tazobactam | Aztreonam, Ciprofloxacin | Initially: Amikacin, Ciprofloxacin Following Sensitivity testing: Piperacillin/tazobactam | Complete recovery |
| Estrela and Abraham [77], B. *vancomycit* | 2010 | N/A | Germany | N/A | Endocarditis | N/A | N/A | Piperacillin/tazobactam | N/A |

M- Male, F- Female, N/A – Not Available, CA – Community Acquired, HA- Hospital Acquired.
| Author (Ref) | Year | Sex/Age | Country | Co-morbidity | Type of infection | Susceptible to | TResistance to | Antibiotic treatment | Outcome |
|-------------|------|---------|---------|--------------|------------------|----------------|----------------|---------------------|---------|
| Shang et al. [78], B. vesicularis | 2011 | M/83 | Taiwan | Type 2 diabetes, Hypertension | Progressive leucocytosis/HA | Amikacin, Ampicillin/ Sulbactam, Cefazolin, Ceftriaxone, Ceftazidime, Gentamicin, Imipenem, Piperaclidin/Tazobactam | Ampicillin, Ciprofloxacin | N/A | Complete recovery |
| Shang et al. [78], B. vesicularis | 2011 | M/25 | Taiwan | Lymphoma | Febrile neutropenia/HA | Amikacin, Ampicillin/ Sulbactam, Cefazolin, Ceftriaxone, Ceftazidime, Gentamicin, Imipenem, Piperaclidin/Tazobactam | Ceftriaxone, Ceftazidime, Cefepime, Ciprofloxacin | Ceftriaxone | Complete recovery |
| Bhatawadekar & Sharma [79] B. vesicularis | 2011 | F/Infant | India | Infant | Bacteraemia/CA | Amikacin, Amoxicillin, Cefotaxime, Ciprofloxacin, Gentamicin, First Generation Cephalosporins, Imipenem, Meropenem, Piperaclidin, Ticarcillin | Ceftriaxone, Cefoxitin, Co-trimazaxole, Netilmicin | Cefotaxime | Complete recovery |
| Yoo et al. [80], B. vesicularis | 2012 | M/30 | South Korea | N/A | Liver Abscess | Amikacin, Ampicillin/ Sulbactam, Imipenem | Minocycline, Tigecycline | Ceftriaxone, Ampicillin- Sulbactam | Complete recovery |
| Almuzara et al. [47], B. diminuta | 2012 | F/56 | Argentina | Lupus glomerulonephritis | Leg ulcer | Aztreonam, Ceftriaxone, Cefepime, Ciprofloxacin | Ampicillin, Ampicillin/ Sulbactam, Aztreonam, Cefotaxime, Cefoxitin, Cefotaxime, Ceftazidime, Cefepime, Ciprofloxacin, Colistin, Gentamicin, Imipenem, Meropenem, Piperaclidin/ Tazobactam, Trimethoprim-sulfamethoxazo | Ceftriaxone, Ampicillin- Sulbactam, Tigecycline plus imipenem | Complete recovery |
| Karadag et al. [81], B. vesicularis | 2012 | M/Infant | Turkey | Neonate | Neonatal sepsis | Amikacin, Ceftriaxone, Gentamicin, Imipenem | Ampicillin, third- generation Cephalosporins, Piperaclidin-tazobactam | Empirical Ampicillin, Gentamicin. After susceptibility testing Meropenem followed by ciprofloxacin | Complete recovery |
| Khalifa et al. [48], B. vesicularis | 2012 | F/Infant | Tunisia | Pompe disease | Bacteraemia | Amikacin, Aztreonam Cefotaxime, Ceftazidime, Ciprofloxacin, Gentamicin, Imipenem, Ofloxacin, Piperaclidin/ tazobactam | Piperaclidin, Ticarcllin | Ceftazidime 100 mg / kg daily for 10 days and Amikacin 15 mg / kg daily | Complete recovery |
| Pandit et al. [82], B. diminuta | 2012 | F/66 | USA | N/A | Keratitis/CA | Amikacin, Gentamicin, Tobramycin | Ceftriaxone, Ofloxacin, Ciprofloxacin, Moxifloxacin | Besifloxacin and Tobramycin, Following identification Tobramycin was changed to Gentamicin Initially; Ciprofloxacin | Complete recovery |
| Lu et al. [45], B. diminuta | 2013 | M/38 | China | None | Pleuritis | Amikacin, Chloramphenicol, Gentamicin, Cefoperazone-Sulbactam, Meropenem, Piperaclidin/tazobactam, Tetracycline | Aztreonam, Ceftazidime, Cefepime, Ciprofloxacin, Levofloxacin, Trimethoprim-sulfamethoxazole | Ppiperacillin, Ticarcillin | Complete recovery |

(Continued on next page)
| Author (Ref) | Year | Sex/Age | Country | Co-morbidity | Type of infection | Susceptible to | Resistance to | Antibiotic treatment | Outcome |
|-------------|------|---------|---------|--------------|------------------|----------------|---------------|---------------------|---------|
| Nandy et al. [83], *B. vesicularis* | 2013 | F/Infant | India | Infant | Bacteraemia | Meropenem, Cefazidime/Clavulanic acid, Netilmicyn, Cefepime, Ampicillin/Sulbactam, Piperacillin/Tazobactam, Levofloxacin, Ciprofloxacin, Cefazidime, Tobramycin, Gentamicin | Cotrimaxazole, Nalidixic acid | Piperacillin/ Tazobactam, Amikacin, Gentamycin, Fluconazole, Ciprofloxacin, Meropenem | Complete recovery |
| Shobha et al. [84], *B. diminuta* | 2013 | Infant | India | None | Urinary Tract Infection | Amikacin, Amoxicillin-Clavulanate, Cefotaxime, Cefepime, Imipenem, Ticarcillin/clavulanic acid, Trimethoprim-sulfamethoxazole | | Ampicillin, Ciprofloxacin | Ticarcillin/clavulanic acid | Complete recovery |
| Gupta et al. [49], *B. vesicularis* | 2014 | M/24 | India | None | Urinary Tract Infection | Minocycline, Piperacillin/tazobactam Trimethoprim-sulfamethoxazole | | Amikacin, Amoxicillin, Amoxicillin-Clavulanate, Aztreonam Cefazidime, Cefoperazone, Cefoperazone-Sulbactam, Cefoxitin, Cefotaxime, Colistin, Ertapenem, Gentamicin, Imipenem, Levofloxacin, Meropenem, Netilmicin, Norfloxacin, Tobramycin | Complete recovery |
| Shujat et al. [85], *B. vesicularis* | 2014 | F | Pakistan | Gall Bladder issues | Bacteraemia | N/A | N/A | Meropenem | Complete recovery |
| Kishore [86] *B. vesicularis* | 2014 | M/51 | India | Diabetes Mellitus (Type 2), Coronary Artery Disease | Bacteraemia | N/A | Ampicillin-Sulbactam | Amikacin, Amoxyclav | Complete recovery |
| Mahapatra et al. [87], *B. diminuta* | 2014 | M/35 | India | N/A | Post-traumatic abscess peritoneal dialysis-associated peritonitis | Cefepime, Cefotaxime, Gentamicin, Imipenem, Piperacillin | N/A | N/A | Complete recovery following catheter removal |
| Ra et al. [88], *B. vesicularis* | 2015 | F/71 | South Korea | End stage renal disease, Hypertension and diabetes mellitus | Bacteraemia | Ampicillin, Amikacin, Ceftriaxone, Cefepime, Cefazolin, Cefazidime, Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, Piperacillin/tazobactam Trimethoprim-sulfamethoxazole | Aztreonam, Tobramycin | N/A | Complete recovery |
| Cao et al. [89], *B. diminuta* | 2015 | M/62 | China | Myelodysplastic syndrome, Diabetes Mellitus (Type 2) | Bacteraemia | Amikacin, Cefoperazone, Levofloxacin, Piperacillin/tazobactam | | Aztreonam, Tobramycin | N/A | Complete recovery |
| Singh and Bhatia [90], *B. vesicularis* | 2015 | 8 month old | India | Infant | Septicaemia/ CA | Amoxicillin-Clavulanate, Cefazidime | Initially: Amikacin, Ceftriaxone, Vancomycin Following Sensitivity testing: Cefoperazone, Levofloxacin, Piperacillin/tazobactam | | Complete recovery |
| Authors               | Year | Age | Gender | Country | Disease Description                | Pathogen Characteristics | Treatment | Outcome               |
|-----------------------|------|-----|--------|---------|-------------------------------------|--------------------------|-----------|----------------------|
| Chandra et al. [91],  | 2017 | M/18|        | India   | Nephrotic syndrome                | Imipenem, meropenem, amikacin, gentamicin, fluoroquinolones, minocycline, tigecycline, cefoperazone-sulbactam, ceftazidime, cefepime, and cotrimoxazole | Colistin | Complete recovery |
| B. vesicularis        |      |     |        |         |                                     |                          |           |                      |

| Swain and Rout [92]   | 2017 | M/56|        | India   | Type-2 diabetes mellitus, hypertension with epileptic disorder | Amikacin, Ceftazidime, Ceftazidime/clavulanic acid, Cefuroxime, Ceftriaxone, Ciprofloxacin, Levofloxacin, Netilmicin | Amoxicillin/clavulanic acid | Complete recovery |
| B. diminuta           |      |     |        |         |                                     |                          |           |                      |

M- Male, F- Female, N/A – Not Available, CA – Community Acquired, HA- Hospital Acquired.
Acinetobacter and (in a UTI) of was not discovered. Lee subsequently differentiated Brevundimonas as the cause of pseudo-outbreak in a tertiary care centre. The treatment of bacterial infection, even though the organism was detected. The source of the contamination was traced to pre-prepared inoculant media (used in the testing procedures in the USA. The contamination was traced to pre-prepared inoculant media (used in the testing procedures). Pseudo-outbreaks can be problematic as they can result in superfluous treatments given to patients (e.g. unnecessary antibiotics or the removal of indwelling devices such as catheters) and can waste valuable time and resources in the clinical setting. The causes of pseudo-outbreaks may be due to a number of different factors such as contaminated water used in the bacterial testing procedures or contamination of materials used in laboratory testing. However, it should be noted that the majority of cases listed in Table 1–3 cephalosporins, penicillins or aminoglycoside antibiotics were given to treat patients and these were mostly successful.

Little is known about resistance mechanisms in Brevundimonas spp. Resistance to the fluoroquinolone family of antibiotics has been detected in outbreaks due to mutations in the quinolone resistance-determining region (QRDR) of the host gyrA, gyrB and parC genes [46]. Gupta et al. found co-infection (in a UTI) of B. vesicularis along with Candida tropicis and Acinetobacter spp. [49].

Pseudo-outbreaks

As can be seen in Table 5 to date only two pseudo-outbreaks have been reported with Brevundimonas spp. Pseudo-outbreaks can be problematic as they can result in superfluous treatments given to patients (e.g. unnecessary antibiotics or the removal of indwelling devices such as catheters) and can waste valuable time and resources in the clinical setting. The causes of pseudo-outbreaks may be due to a number of different factors such as contaminated water used in the bacterial testing procedures or contamination of materials used in laboratory testing. However, it should be noted that the majority of cases listed in Table 1–3 cephalosporins, penicillins or aminoglycoside antibiotics were given to treat patients and these were mostly successful.

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Breakdown of cases of infection with Brevundimonas spp.

Literature searches presented in Table 1–3 illustrate 49 separate instances of infection relating to Brevundimonas spp. The majority of these instances were infection with B. vesicularis (thirty-five cases – 71%). One outbreak had both B. vesicularis and B. diminuta and one case of infection with B. vancanneytii was reported. The rest of the cases were made up B. diminuta infections (twelve cases -24%). The major breakdown of condition were as follows: seventeen instances of bacteraemia (34%), five instances of septicaemia/sepsis (10%), three instances of pneumonia/pleuritis (6%), two instances each of endocarditis (4%), keratitis (4%), and urinary tract infection (4%). Serious infections with Brevundimonas spp include four instances of septicaemia (8%), two of endocarditis (4%), one of septic arthritis (2%) and one of meningitis (2%). Other conditions include instances of two cases of

Table 4. Molecular methods applied to identify Brevundimonas spp. [45].

| Method                  | Target | Sequence                          | Species                      |
|-------------------------|--------|-----------------------------------|------------------------------|
| Real Time PCR           | gyrB   | Forward Primer: ATCGAGACATCTGCTGCTATGAGGG  |
|                         |        | Reverse Primer: TGTTTGTTGGAGCGACAGCATGG  |
|                         |        | Real-Time Probe: AGCTCATGCAATCCGCCGCCGAGAAA  |
| Real Time PCR           | rpoD   | Forward Primer: AGTCCCTCAAGGCTATTTCGGCT  |
|                         |        | Reverse Primer: GGCCTCATTGCTGGAACTTGGT  |
|                         |        | Real-Time Probe: AGGCACATCAAGGGAATGGCCGT  |
| FISH                    | gyrB   | AAGAACGACAGGTCGCTCCGAGC          |
| FISH                    | rpoD   | TCAAGGCTATTTCGGCTCGGAGAT         |

| (one individual case and four cases as part of an outbreak) of co-infection being described in the literature. Han et al described seven cases of infection with B. diminuta within the same outbreak, four of these cases had other microorganism’s co-isolated (coagulase-negative Staphylococcus – bacteraemia, Moraxella osloensis – catheter, Enterococcus sp. – UTI and Staphylococcus aureus – empyema) [46]. Gupta et al. found co-infection (in a UTI) of B. vesicularis along with Candida tropicis and Acinetobacter spp. [49].

Pseudo-outbreaks

As can be seen in Table 5 to date only two pseudo-outbreaks have been reported with Brevundimonas spp. Pseudo-outbreaks can be problematic as they can result in superfluous treatments given to patients (e.g. unnecessary antibiotics or the removal of indwelling devices such as catheters) and can waste valuable time and resources in the clinical setting. The causes of pseudo-outbreaks may be due to a number of different factors such as contaminated water used in the bacterial testing procedures or contamination of materials used in laboratory testing. However, it should be noted that the majority of cases listed in Table 1–3 cephalosporins, penicillins or aminoglycoside antibiotics were given to treat patients and these were mostly successful.

Little is known about resistance mechanisms in Brevundimonas spp. Resistance to the fluoroquinolone family of antibiotics has been detected in outbreaks due to mutations in the quinolone resistance-determining region (QRDR) of the host gyrA, gyrB and parC genes [46]. Gupta et al. found co-infection (in a UTI) of B. vesicularis along with Candida tropicis and Acinetobacter spp. [49].

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Table 5. Incidences of *Brevundimonas* spp. Pseudo-infection from 1978 – 2017. Main characteristics of the case reports.

| Author (Ref)      | Year | Sex/Age  | Country   | Co-morbidity | Type of infection | Susceptible to                                                                 | Resistance to                                                                 | Antibiotic treatment                                      | Outcome |
|-------------------|------|----------|-----------|--------------|-------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------|---------|
| Kim et al. [50],  | 2011 | Multiple | South     | Multiple     | Pseudobacteraemia  | N/A                                                                         | Amikacin, Ciprofloxacin, Colistin, Ceftazidime, Cefepime, Cefotaxime Imipenem, | Ampicillin / sulbactam, Cefpiran, Metronidazole, Netilmicin | N/A     |
| *B. diminuta*     |      | (3 cases)| Korea     |              |                   |                                                                             | Ceftazidime, Piperacillin / Tazobactam, Tobramycin                          |                                                           |         |
| Lee et al. [51],  | 2017 | Multiple | USA       | Multiple      | Pseudo-infection  | Levofoxin, Meropenem, Piperacillin / tazobactam, Trimethoprim – sulfamethoxazole |                                                                             |                                                           |         |
| *B. diminuta*     |      | (12 cases)|           |              |                   |                                                                             | Ceftazidime                                                                   |                                                           |         |

M- Male, F- Female, N/A – Not Available
tonsillitis (2%), two of liver abscess (2%) and two of botryomycosis (2%). There have also been two reported instances (4%) of *Brevundimonas* spp infection that have caused two or more conditions: bacteraemia and reactive arthritis, bacteraemia, urinary tract infection and empyema. Four instances of death have been related to *Brevundimonas* spp infection, three of bacteraemia and one of septicaemia.

**Conclusions**

*Brevundimonas* spp. are not currently considered as major pathogens. However, this should be re-evaluated in light of our investigations where forty-nine examples of *Brevundimonas* spp. infections have been found in the literature. These species have characteristics, such as ability to pass through sterilising filters, which may allow them to cause potentially harmful infections and even death on occasion. Although it is of low virulence and not as big a risk as other non-fermenting Gram-negative bacteria such as *Burkholderia* etc., it should not be overlooked as a possible cause of nosocomial infections and should be considered for inclusion in hospital screening and prevention programs. These programs should consider investigation of possible *Brevundimonas* spp outbreaks if these bacteria are clinically isolated in more than one patient.

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