Review

The Genus Ochrobactrum as Major Opportunistic Pathogens

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Abstract: Ochrobactrum species are non-enteric, Gram-negative organisms that are closely related to the genus Brucella. Since the designation of the genus in 1988, several distinct species have now been characterised and implicated as opportunistic pathogens in multiple outbreaks. Here, we examine the genus, its members, diagnostic tools used for identification, data from recent Ochrobactrum whole genome sequencing and the pathogenicity associated with reported Ochrobactrum infections. This review identified 128 instances of Ochrobactrum spp. infections that have been discussed in the literature. These findings indicate that infection review programs should consider investigation of possible Ochrobactrum spp. outbreaks if these bacteria are clinically isolated in more than one patient and that Ochrobactrum spp. are more important pathogens than previously thought.

Keywords: Ochrobactrum; nosocomial infection; environmental bacteria

1. Introduction

Gram-negative, non-fermenting bacteria are an emergent worry in medical situations and are becoming a growing cause of severe infections. Pathogens of this type are opportunistic and include many different bacterial species, such as Ralstonia spp., Pseudomonas aeruginosa, Sphingomonas paucimobilis and Brevundimonas spp. [1–5]. Gram-negative, non-fermenting bacteria can infect both patients undergoing treatments and individuals outside of a clinical setting with various underlying conditions or diseases. Another type of these bacteria are the members of the α-proteobacterial genus Ochrobactrum [6].

Ochrobactrum spp. are found in a wide variety of environments including water, aircraft water, soil, plants and animals [6–12]. Several Ochrobactrum spp. have been investigated for their potential to degrade xenobiotic pollutants and for heavy metal detoxification under a variety of environmental conditions [13–16]. Ochrobactrum spp. are very closely related to brucellae, and even though they are considered to be of low virulence, they have increasingly been found to cause infections (some serious including endocarditis and septicaemia) in immunocompetent hosts [17,18].

Investigation of the scientific/medical literature presented a wide variety of infections resultant from Ochrobactrum spp. and these were resistant to wide variety of antibiotics. Our data point to the genus being a more common pathogen than previously supposed, with many of the infections/conditions caused by Ochrobactrum spp. being aggressive and debilitating. The overall aim of this work is to present a summary of the types of Ochrobactrum spp. infections, any underlying disorders/illnesses in patients that accompany these infections and the potential treatments that can be used in the management of infections to support medical specialists.
2. Genus Ochrobactrum

The genus Ochrobactrum emerged from what was previously categorised as the CDC group VD1-2. The type species Ochrobactrum anthropi had previously been called Achromobacter VD based on the Special Bacteriology Section of the US Center for Disease Control [19]. Initial results indicate members of the group grew on MacConkey agar producing catalase, oxidase and urease; strains could be Gram-negative to variable [20]. However, the taxonomic position of Achromobacter became complicated and the name Achromobacter and related CDC group VD were no longer accepted by Bergeys Manual [19] leading to a new classification and the emergence of the genus Ochrobactrum [21]. Ochrobactrum spp. are phylogenetically related to members of the alpha-2 subdivision of Proteobacteria. They are catalogued on the Brucella rRNA branch of rRNA superfamily IV. Thus, from the previous CDC group Vd, a novel genus and a new species, Ochrobactrum anthropi, was proposed [21,22]. The type strain was Gram-negative, aerobic, rod shaped, non-pigmented and motile. It produced acid from a selection of carbohydrates and reduced both nitrate and nitrite and possessed a GC ratio between 56 to 59% [21]. Almost all 56 strains categorised as CDC Group Vd that were used to support the new genus Ochrobactrum came from various human clinical specimens. Since the initial description of O. anthropi, several other species have since been described (Table 1 and Figure 1). Certain Ochrobactrum spp. can be opportunistic pathogens especially in a hospital environment with the majority of reported cases due to hospital-acquired infections in patients with indwelling and invasive medical devices, including central venous catheters and drainage tubes [23]. In addition, the organism shows widespread resistance to penicillins and other antibiotics that cause clinical management issues with immunocompromised hosts [24,25]. The phylogenetic relationship between all described Ochrobactrum spp can be seen in Figure 1.

Table 1. List of current accepted Ochrobactrum species.

| Species                  | Isolation          | Genome Sequences                        | Reference |
|--------------------------|--------------------|------------------------------------------|-----------|
| Ochrobactrum anthropi    | Clinical isolate   | Strain: OAB; Size: 4.9 Mbp; Ref Genome:  |
|                          |                    | GCA_000742955.1 (41 genomes)            | [22]      |
| Ochrobactrum ciceri      | Nodules of Cicer   | No Genome                                | [26]      |
| Ochrobactrum cytisi      | Cystisus nodules   | Strain: IPA7.2; Size: 5.96 Mbp; Ref Genome: |
|                          |                    | GCA_001876955.1 (1 genome)              | [27]      |
| Ochrobactrum daejeonense| Sludge             | Strain: JCM 16234; Size: 4.8 Mbp; Ref Genome: |
|                          |                    | GCA_012103095.1 (1 genome)              | [28]      |
| Ochrobactrum endophyticum| Roots of Glycyrrhiza| No Genome                                | [29]      |
| Ochrobactrum gallinaeacis| Chicken faeces     | Strain: ISO196; Ref Genome: GCF_006476605.1; Size: 3.74 Mbp (1 genome) | [11]      |
| Ochrobactrum grignonense | Wheat Roots        | Strain: OgA9a; Size: 4.84 Mbp; Ref Genome: NZ_NNRL00000000.1 (1 genome) | [9]       |
| Ochrobactrum haemophilum | Clinical Isolate   | Strain: LIIsuc1; Size: 4.91 Mbp; Ref Genome: GCA_003550135.1 (3 genomes) | [30]      |
| Ochrobactrum intermedium | Human blood        | Strain: NCTC12171; Size: 4.73 Mbp; Ref Genome: GCA_900454225.1 (18 genomes) | [22]      |
| Ochrobactrum lupini      | Lupinus albus      | Strain: LUP21; Size: 5.5 Mbp; Ref Genome: GCA_002252535.1 (2 genomes) | [31,32] *|
| Ochrobactrum orgae       | Rice rhizosphere   | Strain: OA447; Size: 4.47 Mbp; Ref Genome: NZ_PTRC00000000.1 (1 genome) | [33]      |
| Ochrobactrum pecoris     | Farm Animals       | Strain: 08RR263; Size: 5.06 Mbp; Ref Genome: GCA_006376675.1 (1 genome) | [34]      |
| Ochrobactrum pitutosum   | Industrial Environment | Strain: AA2 Size: 5.47 Mbp; Ref Genome: GCA_002025625.1 (4 genomes) | [35]      |
| Ochrobactrum pseudintermedium | Clinical isolate | Strain: CCUG34735; Size: 4.39 Mbp; Ref Genome: GCA_008932435.1 (1 genome) | [36]      |
| Ochrobactrum pseudogrignonense | Clinical isolate | Strain: K8; Size: 4.99 Mbp; Ref Genome: GCA_001652485.1 (6 genomes) | [30]      |
| Ochrobactrum quorumnocens | Potato rhizosphere | Strain: A44; Size: 5.5 Mbp; Ref Genome: GCA_002278035.1 (2 genomes) | [37]      |
| Ochrobactrum rhizosphaerae | Potato rhizosphere | Strain: PR17; Size: 4.9 Mbp; Ref Genome: GCF_002252475.1 (2 genomes) | [38]      |
Ochrobactrum soli  Cattle farm soil  Strain: BO-7; Size: 45 Mbp; Ref Genome: GCA_003664555.1 (3 genomes)  
Ochrobactrum thiophenivorans  Industrial Environment  Strain: DSM 7216; Size: 4.4 Mbp; Ref Genome: GCA_002252445.1 (2 genomes)  
Ochrobactrum teleogrylli  insect Telogryllus occipitalis root soil  No Genome  
Ochrobactrum tritici  wheat rhizosphere root soil  Strain: DSM 13340; Size: 5.5 Mbp; Ref Genome: GCA_012395245.1 (6 genomes)  

* First described as Ochrobactrum lupini by Trujillo et al. [31] and later reclassified as Ochrobactrum anthropi by Volpiano et al. [32] following whole-genome sequence analysis.

**Figure 1.** Phylogenetic structure of the genus Ochrobactrum along with the genus Brucella. (a) The tree based on partial 16S rRNA gene sequences obtained using neighbour joining with Maximum Composite Likelihood method (MEGA package). GenBank accession numbers are given with the species name. Numbers at nodes are bootstrap values based on 1000 resamplings. Bar, 0.0050 substitutions per site [41,42].

3. Identification of Ochrobactrum spp.

Ochrobactrum species are Gram-negative and composed of short rods that are straight or slightly curved with one end flame shaped. They are generally motile and do not produce haemolysis on blood agar [43].
3.1. Biochemical Identification

Biochemical identification can be carried out using biochemical-testing kits such as the API 20NE or Vitek-2 (BioMérieux, France). When biochemical testing is carried out, it is normal to test isolates against Brucella agglutinating sera to prevent misdiagnosis with Brucella its close neighbour [44]. It has been shown that commercial kits are generally unsuitable for identification or differentiation amongst Ochrobactrum [45]. Analysis of 103 clinically relevant Ochrobactrum strains indicated that biochemical reaction profiles of the API and BD Phoenix™ 100 systems for identifying Ochrobactrum isolates can only be used at the genus level [46]. Care is required when identifying Ochrobactrum in clinical situations as misidentification has occurred with Brucella melitensis [47].

For identification of Ochrobactrum spp., it was proposed that the isolation of non-fastidious, non-fermenting, oxidase-positive, Gram-negative rods that are resistant to Beta-lactams (except imipenem) indicates the isolate is from the genus Ochrobactrum [43]. The API 20NE will confirm the identification to genus level for the majority of strains (Table 2). In addition, it has been proposed that urease activity, the mucoidy of the colonies and growth at 45 °C on tryptic soy agar coupled to susceptibility to colistin, tobramycin and netilmicin should be used as differentiating characteristics in the determination of O. anthropi and O. intermedium to the species level [43].

In many clinical situations, the Microscan Walkaway system is used for primary identification and any unusual non-fermentative bacteria are analysed via biochemical analysis methods such as the RapID NF Plus system. This strategy has been shown to generally perform very well [48]. There have been cases of misdiagnosis of Ochrobactrum anthropi (subsequently confirmed by VITEK) as Shewanella putrefaciens [48]. Of course, the opposite has also been reported where a Brucella suis bacteraemia was mistakenly identified as Ochrobactrum anthropi by the VITEK 2 system [49,50]. These studies underscore the difficulty encountered in identifying unusual Gram-negative, non-fermentative bacteria such as Ochrobactrum.

| Using the API 20E, API 20NE, Biolog GN 1 | Reaction |
|----------------------------------------|----------|
| Indole                                 | -ve      |
| Catalase                               | +ve      |
| Cytochrome oxidase                     | +ve      |
| H₂S                                   | -        |
| Acetoin                                | -ve      |
| Citrate utilisation                    | -ve      |
| Carbohydrate fermentation              | -ve      |
| Adipate assimilation                   | -ve      |
| Detection Arginine dihydrolase         | -ve      |
| Detection Lysine decarboxylase         | -ve      |
| Detection Ornithine decarboxylase      | -ve      |
| Detection Beta galactosidase           | -ve      |
| Detection Gelatinase                   | -ve      |
| Urease O. anthropi                     | +ve      |
| O. intermedium                         | variable |
| O. grignonense                         | -ve      |
| O. tritici                             | -ve      |
| O. gallinafacis                        | -ve      |
| Assimilation glucose, arabinose, mannose, N-acetylglucosamine, maltose and malate | +ve      |

3.2. Fatty Acid Analysis

Use of fatty acid analysis as a differentiation marker using the Sherlock System and comparison with the Sherlock database provided the identification result for O. anthropi with an ID score of 0.556, indicating its poor utility for differentiation at the species level [45].
3.3. Molecular Identification

Molecular tools have long been applied to the typing of Ochrobactrum species. Early studies utilised pulsed-field gel electrophoresis and rep-PCR for the epidemiological analysis [52] followed by AFLP (Amplified Restriction Fragment Length Polymorphism) to confirm the relatedness of O. anthropi and O. intermedium with its Brucella relatives [53] using a limited number of isolates. The molecular diversity of a larger number of Ochrobactrum strains were investigated by comparing environmental isolates from soil and the rhizosphere and comparing these to a number of clinical isolates [12]. Rep-PCR using a combination of BOX and REP primers were used to profile the isolates. The isolates used in this study clustered according to their species designation [12] indicating that rep-PCR profiling offered a good tool for species delineation.

However, the differentiation of species is somewhat difficult because of their phenotypic similarity and indeed confusion amongst 16s rDNA sequences [45]. Errors still occur such as in the case of bacteraemia where the causative agent was recognised as Ralstonia paucula by the Microscan Walkaway system but later following DNA sequencing was identified as O. anthropi [54].

16s rDNA sequence similarity between O. anthropi and O. intermedium ranged from 97.9% to 98.7% depending on the strains compared [43] suggesting a higher genetic deviation in O. intermedium than is found in O. anthropi. The genetic structure of a collection of 65 isolates (37 clinical, 11 environmental and 17 from culture collections) illustrative of the known natural distribution of O. intermedium was analysed by MLSA (Multi-Locus Sequence Analysis) [53].

A recA-PCR RFLP (Restriction Fragment Length Polymorphism) assay was also developed to study interspecies variability within Ochrobactrum using recA sequences from known isolates including 38 O. anthropi strains and type strains of O. intermedium, O. tritici and O. lupini and comparing these with closely related Brucella strains [54]. It was concluded that recA-sequence analysis provided a reliable molecular subtyping tool for Ochrobactrum at both the inter- and intraspecies level. Subsequently, a sensitive recA gene-based multi-primer single-target PCR assay has been created to differentiate O. anthropi, O. intermedium and Brucella that had been reported to cause diagnostic difficulty (Table 3) [55–57]. Teyssier et al. used 35 clinical isolates and the type strains of all known Ochrobactrum species (all confirmed as Ochrobactrum species by 16s rDNA sequencing) to examine comparative identification techniques ranging from commercial kits to biochemical and ribotyping [43].

Table 3. Molecular methods applied to identify Ochrobactrum spp. [57].

| Method | Target | Sequence | Amplicon (bp) | Species               |
|--------|--------|----------|---------------|-----------------------|
| PCR    | recA   | Anth-f GCAAGCTGGTGCTCGATCTGG | 544 | Ochrobactrum anthropi |
|        |        | Anth-r TTTCGACGCCACCGCCTTTTA |
|        |        | Inter-f CGCGTTGGTGCTGCTTCAA   | 402 | Ochrobactrum intermedium |
|        |        | Inter-r GGAACGAGAGATAGACGGGTAT |

3.4. MALDI-TOF MS

MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionisation–Time-of-Flight) was initially used to identify Ochrobactrum intermedium from a range of difficult to identify strains as an alternative to Vittek, API or 16s rDNA sequencing in a large validation screen with some 204 genera showing discordant results from different identification methods [58]. The method has since found utility for evaluation within the Ochrobactrum genus. The utility of automated rep-PCR (DiversiLab™ system, BioMèrieux, France) and MALDI-TOF MS analysis was compared for typing of 23 O. anthropi clinical isolates (bacteraemias) [44]. MALDI-TOF MS evaluation clustered the 23 strains of O. anthropi into a single group containing four distinct subgroups at close distance, indicating a high similarity between the isolates but also its accuracy in identification [44]. The technique of MALDI-TOF MS is gaining widespread usage in clinical situations and is increasingly utilised for Ochrobactrum identification in the clinic [59].
4. Ochrobactrum spp. Virulence

Ochrobactrum spp. are considered to be of low virulence. A study carried out by Yagel et al. into the virulome of Ochrobactrum spp. looked at the genomes of 130 isolates [60]. These isolates were taken from clinical, environmental, animal and plant settings. The study identified a limited number of virulence factors in the majority of these isolates. They found lipid A biosynthesis genes in all genomes analysed. They also found other virulence-associated genes in the majority of isolates such as genes associated with fatty acid biosynthesis (fabZ), carbohydrate metabolism (pgm and cgs), cell wall biosynthesis (wbpL) and biofilm formation (ricA, 95%). Genes for other more widespread Gram-negative virulence-associated proteins were not found in these genomes [60].

5. Ochrobactrum spp. Outbreaks

5.1. Outbreak Identification

All obtainable publications (journal articles, case reports and conference proceedings) discussing Ochrobactrum spp. infections were recovered using the PubMed, Web of Knowledge and Google Scholar search databases from 1980 to April 2020. The terms “CDC group VD1-2”, “Ochrobactrum”, “Ochrobactrum spp.”, “Ochrobactrum anthropi” and “Ochrobactrum intermedium” as well as all species names listed in Table 1 were searched. Any publications that discussed infection were set aside. These papers/abstracts were then read and the required information extracted from them. This information included year, geographic location, patient information (age, sex and any underlying medical conditions), antimicrobial testing, treatment and patient outcomes where available. The references cited from these publications were also checked for any publications/reports that may not have been found during the database searches.

5.2. Outbreak Analysis

The results of the investigations of the literature can be seen in Tables 4 and 5. The tables summarise year, geographic location, patient information (age, sex and any underlying medical conditions), antimicrobial testing, treatment and patient outcome. One hundred seventeen separate instances of Ochrobactrum anthropi infection (277 individual cases) were identified along with a further eleven instances (twelve cases) of Ochrobactrum intermedium, Ochrobactrum oryzae, Ochrobactrum pseudogrignonense, Ochrobactrum pseudointermedium and Ochrobactrum tritici infection. The major breakdown of O. anthropi related conditions were as follows: forty-six instances of bacteraemia (42%) from which three were described as “bloodstream infections” that were usually associated with catheters, fourteen instances of sepsicaemia/sepsis/septic shock (12%) and two further instances of biliary sepsis (2%), nine instances of endophthalmitis, eight instances of peritonitis, four instances of pneumonia (8%) and two instances each of endocarditis (2%). Other infections included two cases of keratitis (2%), four of various types of abscess (neck, pelvic, pancreatic and retropharyngeal) (3%) and one instance each of “hand infection” and brain empyema (1%). There have also been multiple reported instances of Ochrobactrum spp. infection that have caused two or more conditions. These include bacteraemia and necrotising fasciitis, bacteraemia and pneumonia, sepsicaemia and peritonitis and two instances of septic shock and endocarditis. Ten cases of death associated to Ochrobactrum spp. infection (all O. anthropi) have also been reported in the literature, four with sepsis/sepsicaemia (one with endocarditis), two with peritonitis and one each with a bloodstream infection, pyrogenic infection, endocarditis and infection of transjugular intrahepatic portosystemic shunt.

6. Factors linked with Ochrobactrum spp. Infection

6.1. Underlying Conditions/Illness

The bulk of Ochrobactrum related infections (Tables 4 and 5) had an associated underlying disorder or disease that increased patient susceptibility to infection. Multiple patients, who were
afflicted with a variety of different cancers or those with kidney failure (caused by diabetes mellitus), contracted *Ochrobactrum*-related bacteraemia/septicaemia due to a catheter/undergoing dialysis. These demonstrate how *Ochrobactrum* acts as an opportunistic pathogen in immunocompromised individuals. Infections were both hospital and community acquired. This is of interest as opportunistic pathogens such as *Ochrobactrum* spp. are mostly contracted in clinical environments. It was also interesting that a high level of instances of infection, 23 separate instances, occurred where patients had no underlying health conditions.

6.2. *Pseudo--Outbreaks*

To date, six pseudo-outbreaks have been described with *Ochrobactrum* spp. (Table 4 and Table 5). These may be challenging as they may lead to unessential/unneeded treatments such as needless courses of antibiotics or patient interventions (e.g., the removal of indwelling devices including various catheter types) and can waste both time and resources in both the clinical laboratory and treatment ward settings. Pseudo-outbreaks have many possible causes including contaminated water or materials used in the clinical testing laboratory or contaminated medical solutions such as saline. Montaña et al. described how *O. anthropi* was the reason for a pseudo-outbreak in a general treatment ward in an Argentinean hospital due to contaminated collection tubes [61]. No symptoms connected with bacterial infection were observed in any patients, even though *O. anthropi* was identified in microbiological testing. The recovered bacteria were carbapenem-resistant.
Table 4. Incidences of *Ochrobactrum anthropi* infection from 1980 to 2020. Main characteristics of the case reports.

| Author (Ref)       | Year | Sex/Age   | Country | Co-morbidity                          | Type of Infection                  | Susceptible to*                  | Resistance to*                  | Treatment                               | Outcome                           |
|--------------------|------|-----------|---------|---------------------------------------|------------------------------------|----------------------------------|----------------------------------|----------------------------------------|-------------------------------------|
| Appelbaum and Campbell [62] | 1980 | M/75 years old | USA     | COPD, MI, CVA                         | Pancreatic abscess                 | Gentamicin, TMP-SMZ              | Amikacin, Chloramphenicol, Tetracycline, Tobramycin | Gentamicin                           | Died of respiratory failure          |
| Kish [63]          | 1984 | F/21 years old | USA     | Astrocytoma                           | Bacteraemia (catheter related)     | Amikacin, Gentamicin, Imipenem, Moxalactam, Gentamicin, Tetracycline, TMP-SMZ, Amikacin, Gentamicin | Chloramphenicol, Netilmicin, Rifampin, Tobramycin | TMP-SMZ, Gentamicin                  | Complete Recovery                    |
| Barson et al. [20] | 1987 | M/14 years old | USA     | Puncture wound of the foot            | Osteochondritis                    | Imipenem, Moxalactam, Gentamicin, Rifampin Tetracycline, TMP-SMZ | Chloramphenicol, Netilmicin, Tobramycin | TMP-SMZ, Gentamicin                  | Complete Recovery                    |
| Van Horn [64]      | 1989 | F/23 years old | USA     | Hodgkin’s disease, had undergone bone marrow transplantation | Bacteraemia (catheter related), Urinary Tract Infection | Amikacin, Norfloxacin, Tetracycline, TMP-SMZ | Ampicillin, Aztreonam, Carbenicillin, Cefoperazone, Cefoxitin, Ceftazidime, Cephalothin, Chloramphenicol, Gentamicin, Mezlocillin, Piperacillin, Ticarcillin, Tobramycin, Norfloxacin (400 mg orally twice a day), TMP-SMZ (320/1600 mg orally every 6 h), Amikacin (500 mg intravenously every 12 h) | Norfloxacin, TMP-SMZ, Gentamicin, Vancomycin, Ceftazidime Followed by Amikacin and TMP-SMZ, Ciprofl oxacin, Gentamicin, Imipenem | Complete Recovery                    |
| Cieslak et al. [65] | 1992 | F/3 years old | USA     | Retinoblastoma                        | Bacteraemia (catheter related)     | Amikacin, Ciprofl oxacin, Gentamicin, Imipenem, Polymyxin E, TMP-SMZ, Amikacin, Aztreonam, Cefoxitin, Ceftazidime, Ceftriaxone, Cephalothin, Mezlocillin, Rifampin, Tobramycin, Tobramycin Amoxicillin, Amoxicillin–clavulanate, Azlocillin, Aztreonam Cefuroxime, Cefotaxime, Cefoxitin, Ceftazidime, Ticarcillin Trimethoprim | Vancomycin and Ceftazidime Followed by Amikacin and TMP-SMZ, Ciprofl oxacin, Gentamicin, Imipenem | Ampicillin, Aztreonam, Cefoxitin, Ceftazidime, Ceftriaxone, Cephalothin, Mezlocillin, Rifampin, Tobramycin, Tobramycin Amoxicillin, Amoxicillin–clavulanate, Azlocillin, Aztreonam Cefuroxime, Cefoxitin, Ceftriaxone, Ceftazidime, Ticarcillin Trimethoprim | Complete Recovery                    |
| Gransden et al. [66] | 1992 | Multiple (7 cases) | UK     | Multiple                               | Sepsis (catheter related)          | Amikacin, Ciprofl oxacin, Gentamicin, Imipenem, TMP-SMZ, Tobramycin | Ciprofl oxacin, Gentamicin, Imipenem | Ciprofl oxacin, Gentamicin, Imipenem | 5 complete Recovery, 2 deaths unrelated to infection |
| Brivet et al. [67] | 1993 | F/74 years old | France  | Alcoholism                             | Necrotising fasciitis, bacteraemia and | Amikacin, Ceftazidime, Cefotaxime, Ciprofl oxacin, Imipenem, Pefloxacin, Amoxicillin, Amoxicillin–clavulanate acid, Carbenicillin, Amoxicillin–clavulanate acid and amikacin. Followed by Imipenem | Amoxicillin, Amoxicillin–clavulanate acid and amikacin. Followed by Imipenem | Amoxicillin, Amoxicillin–clavulanate acid and amikacin. Followed by Imipenem | Complete Recovery                    |
| Authors                  | Year | Country       | Diagnosis                | Treatment                                                                 |
|-------------------------|------|---------------|--------------------------|---------------------------------------------------------------------------|
| Kern et al. [68]         | 1993 | USA           | Leukaemia                | Bacteraemia (catheter related) Ciprofloxacin, TMP-SMZ Cephalothin, Colimycin, Piperacillin |
| Klein & Eppes 1993 [69]  | 1993 | USA           | Leukaemia                | Bacteraemia (catheter related) Ciprofloxacin, Ceftriaxone, Gentamicin, Imipenem, TMP-SMZ, Tobramycin |
| Ainsor et al. 1994 [70]  | 1994 | Denmark       | Crohn’s disease, Gastric ulcer | Septicaemia Peritonitis (catheter related) Ciprofloxacin, Gentamicin, Imipenem, Tobramycin |
| Ezzedine et al. 1994 [71]| 1994 | Austria       | Leukaemia                | Bacteraemia in rabbit anti-thymocyte globulin (RATG) infusion vials Amikacin, Imipenem, Ofloxacin |
| Haditsch et al. 1994 [72]| 1994 | Austria       | Leukaemia                | Bacteraemia Amikacin, Polymyxin B, Imipenem, Norfloxacin, Tetracycline |
| Braun et al. 1996 [73]   | 1996 | Germany       | Cataract surgery         | Endophthalmitis after cataract surgery Amikacin, Ciprofloxacin, Imipenem, Tetracycline |
| Chang et al. 1996 [74]   | 1996 | USA           | Neurosurgery Patients    | Meningitis Ciprofloxacin, Gentamicin, Imipenem–cilastatin, Tetracycline |
| Cieslak et al. 1996 [75] | 1996 | USA           | Hypertension, hypothyroidism, Renal insufficiency, Pyogenic Infection | N/A | N/A | Died |
| Study/Year | Sex  | Age/Year(s) | Country | Primary Diagnosis | Cause of Infection | Initial Antibiotics | Additional Treatments | Outcome |
|------------|------|-------------|---------|------------------|--------------------|---------------------|----------------------|---------|
| Cieslak et al. [75] | M | 66 years old | USA | Small cell carcinoma | Pyogenic Infection | Aztreonam, Ceftazidime, Vancomycin After failure TMP-SMZ | Complete Recovery |
| Cieslak et al. [75] | M | 29 years old | USA | None | Pyogenic Infection | Cephradine | Complete Recovery |
| Ramos et al. [76] | F | 26 years old | Spain | Cancer | Bacteraemia (catheter related) | Ciprofloxacin (oral for 10 days) | Complete Recovery |
| Ramos et al. [76] | F | 62 years old | Spain | Cancer | Bacteraemia (catheter related) | Gentamicin and Catheter removal | Complete Recovery |
| Berman et al. [77] | F | 74 years old | USA | Pneumonia | Endophthalmitis with indwelling catheters for venous access | Ciprofloxacin (Oral 500 mg twice daily for 2 weeks) | Complete Recovery |
| Christenson et al. [78] | Multiple (3 Cases) | USA | Various | Meningitis (pericardial allograft tissue) | Ciprofloxacin, Gentamicin, Imipenem, Tetracycline | Removal of tissue allograft implants | Complete Recovery |
| Earhart et al. [79] | F | 40 years old | USA | Rheumatic heart disease | Infection of retained pacemaker leads | Ciprofloxacin, Rifampin Vancomycin, TMP-SMZ for 6 weeks Followed by Ciprofloxacin TMP-SMZ for 4 1/2 months | Complete Recovery |
| Gill et al. [80] | M | 45 years old | USA | Coronary artery disease | Intravenous line infection | None Administered | Complete Recovery |
| Torres et al. [81] | N/A | Spain | AIDS | Bacteraemia | None | None | N/A |

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| Authors                  | Year | Age     | Gender | Country | Diagnosis            | Infections and Antimicrobials                                                                 | Outcome               |
|------------------------|------|---------|--------|---------|----------------------|---------------------------------------------------------------------------------------------|-----------------------|
| Yu et al. [82]         | 1998 |         |        | China   | Various              | Bacteraemia (3 catheter related) Amikacin, Ceftriaxone, Cefoperazone, Gentamicin, Imipenem | Aminoglycoside        |
| Jelveh & Cunha 1999 [6]| 1999 | M/33    | Month  | USA     | Osteomyelitis        | Bacteraemia Gentamicin Levofloxacin, TMP-SMZ Amikacin, Ciprofloxacin, Gentamicin, Meropenem | N/A                   |
| Hay & Lo 1999 [83]     | 1999 | F/Neona |        | UK      | Neonate Meningitis   | Amikacin, Ciprofloxacin, Gentamicin, Tobramycin, TMP-SMZ Amikacin, Cefmetazole, Cefbuperazone, Gentamicin Imipenem, Levofloxacin, Minocycline, Tobramycin Amikacin, Ciprofloxacin, Gentamicin, Meropenem, Tobramycin, Cefpodoxime Flomoxef | Gentamicin            |
| Inoue et al. 1999 [84]| 1999 | M/64 Yr |        | Japan   | None                 | Endophthalmitis Amikacin, Cefmetazole, Cefbuperazone, Gentamicin, Imipenem, Levofloxacin, Tobramycin, Amikacin, Cefpodoxime Flomoxef | Aminoglycoside        |
| Manfredi et al. 1999 [85]| 1999 | M/41 years |        | Italy   | HIV Septicaemia      | Aztreonam, Ceftazidime, Tobramycin Meropenem (3 g/day) | Complete Recovery     |
| Manfredi et al. [85]   | 1999 | M/35 years |        | Italy   | HIV Septicaemia      | Aztreonam, Ticarcillin–Clavulanate, Tobramycin | Complete Recovery     |
| Mastroianni et al. [86] | 1999 | M/47 years |        | Italy   | None                 | Bacteraemia Cephalosporins, Imipenem, Tobramycin | Aminoglycoside        |
| Saavedra et al. [87]   | 1999 | M/4 Yr  |        | Spain   | Neuroblastoma Bacteraemia (catheter related) | N/A Amikacin, TMP-SMZ Imipenem (14 days) | Complete Recovery     |
| Reference                        | Year | Location | Age/Status | Diagnosis/Complications                                                                 | Bacteremia/Antibiotics                                                                 | Treatment                                                                 | Outcome                                                                 |
|---------------------------------|------|----------|------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Stiakaki et al. [88]            | 1999 | Greece   | Cancer     | Bacteraemia (7 cases—catheter related)                                                  | β-lactam antibiotics                                                                  | Imipenem, Ciprofloxacin or catheter removal (2 cases)                      | Complete Recovery                                                       |
| Chertow 2000 [89]               | 2000 | USA      | Renal Failure | Bacteraemia (catheter related-Haemodialysis)                                           | Aminoglycosides, Ciprofloxacin, Quinolones                                            | Penicillins, Cephalosporins, TMP-SMZ                                      | Complete Recovery                                                       |
| Deliere et al. [90]             | 2000 | France   | Leukaemia  | Sepsis (catheter related)                                                               | Ciprofloxacin, Colistin Imipenem, Rifampicin                                          | Ciprofloxacin (500 mg daily) and Tobramycin (40 mg intravenously)         | Complete Recovery                                                       |
| Esteban et al. [91]             | 2000 | Spain    | Diabetic nephropathy | Peritonitis in CAPD patient                                                            | Amikacin, Gentamicin, Imipenem, Meropenem, TMP-SMZ                                   | Gentamicin (1 mg/kg 8-hourly)                                             | Complete Recovery                                                       |
| Mahmood et al. [92]             | 2000 | Pakistan | Asthmatic and non-insulin dependent diabetic | Infective Endocarditis and Septic Embolization | Ciprofloxacin, Gentamicin, Imipenem, Meropenem, Ofloxacin, TMP-SMZ                | Ampicillin, Cefotaxime, Piperacillin-Tazobactam, Ticarcillin              | Died (Unrelated to infection)                                            |
| Peltroche-Llacahuang a et al. [93] | 2000 | Germany | End-stage renal disease | Peritonitis in CAPD patient                                                            | Amikacin, Ciprofloxacin, Colistin Gentamicin, Imipenem, Meropenem, Ofloxacin, TMP-SMZ | Ampicillin, Cefotaxime, Piperacillin-Tazobactam, Ticarcillin              | Complete Recovery                                                       |
| Shelly and Mortensen [94]       | 2000 | USA      | None       | Infection                                                                              | Ampicillin, Gentamicin                                                                | Cefuroxime, Ceftriaxone, TMP-SMZ                                          | Cefazolin Followed by Ampicillin-Subactam                                | Complete Recovery                                                       |
| El-Zimaity et al. [95]          | 2001 | UK       | None       | Pseudobacteraemia                                                                     | N/A                                                                                    | N/A                                                                       | N/A                                                                     | N/A                                                                    |
| Greven et al. [96]              | 2001 | USA      | N/A        | Chronic postoperative endophthalmitis                                                   | N/A                                                                                    | N/A                                                                       | N/A                                                                     | N/A                                                                    |
| Daxboeck et al. [97]            | 2002 | Austria  | Chronic renal failure resulting from diabetic nephropathy                              | Bacteraemia (haemodialysis patients)                                                  | Amikacin, Ciprofloxacin, Gentamicin, Imipenem                                        | β-lactam antibiotics, TMP-SMZ                                              | One patient recovered, one died due to MI                                 |
| Author et al. | Year | Case Details | Location | Antibiotics | Outcome |
|--------------|------|--------------|----------|-------------|---------|
| Galanakis et al. [98] | 2002 | Multiple (11 Cases—All less than 7 years old) | Greece | Bacteraemia | Amikacin, Ciprofloxacin, Gentamicin, Imipenem, Naldixic acid, Ofloxacin, Perflaxin, Netilmicin, Norfloxacine, Streptomycin, TMP-SMZ, Tobramycin, Ampicillin, Amoxicillin, Amoxicillin–Clavulanic acid, Aztreonam, Cefalothin, Cefoxime, Cefotaxime, Cefuroxime, Piperacillin, Piperacillin–Tazobactam, Ticarcillin, Ticarcillin–Clavulanate | N/A |
| Stiakaki et al. [99] | 2002 | Multiple (11 Cases) | Greece | Bacteraemia (catheter related) | Aminoglycosides, Colistin, Imipenem, Quinolones, TMP-SMZ | Various different treatments in all 11 cases | N/A |
| Wheen et al. 2002 [100] | 2002 | F/62 years old | New Zealand | Osteomyelitis (vertebral) | Aminoglycosides, Amoxicillin, Cephalosporins, Fluoroquinolones, TMP-SMZ | Ceftriaxone (intravenously for 6 weeks) followed by Ciprofloxacin (orally for 6 weeks) | Complete Recovery |
| Gascón et al. [101] | 2003 | M/3 years old CA | Spain | Bacteraemia | Aminoglycosides, Ciprofloxacin, Imipenem, TMP-SMZ | Gentamicin TMP-SMZ | Complete Recovery |
| Hill [102] | 2003 | N/A | UK | Pseudobacteraemia | N/A | N/A | N/A |
| Kettaneh et al. [17] | 2003 | F/30 years old | France | Septic Shock | Amikacin, Gentamicin, Imipenem, Netilmicin, Perflaxin, Tobramycin, TMP-SMZ | Gentamicin infusion (infusion of 240 mg once), Ofloxacin (200 mg infusion twice a day for 11 days) | Complete Recovery |
| Oliver [48] | 2003 | 30 years old | USA | Infection | N/A | N/A | N/A |
| Name                  | Year | Age/Gender | Location | Disease/Medication                        | Antimicrobial Therapy                                                                 | Outcome                           |
|----------------------|------|------------|----------|-------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------|
| Romero Gomez et al.  | 2004 | F/65 years | Spain    | Hypertension and rheumatic heart disease | Aminoglycosides, Meropenem, Quinolones                                                | Complete Recovery                 |
| Oliver et al.        | 2005 | M/30 years | USA      | Bacteraemia (gunshot wound)               | Aztreonam, Cefepime, Cefotaxime, Ceftazidime, Ceftiaxone, Piperacillin, Piperacillin–Tazobactam | Complete Recovery                 |
| Cho et al.           | 2006 | F/69 years | Korea    | Hypertension (associated with medicinal plants) | Colistin, Imipenem, Meropenem, Tetracycline                                           | Imipenem Complete Recovery       |
| Ozdemir et al. [18]  | 2006 | F/42 years | Turkey   | Endocarditis and septic shock             | Amikacin, Ciprofloxacin, Gentamicin, Imipenem, β-lactams (Excluding Carbapenases)      | Meropenem (500 mg Twice daily)   |
| Vaidya et al.        | 2006 | M/49 years | USA      | Pelvic Abscess                            | Gentamicin, Imipenem, Levofloxacin, Tetracycline                                      | Vancomycin (500 mg Twice daily)  |
| Aly et al.           | 2007 | F/2 years  |          | Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency | Ciprofloxacin, Levofloxacin, Piperacillin–Tazobactam                                 | Cefotaxime Complete Recovery     |
| Laborca et al.       | 2007 | Multiple   | Chile    | Pseudo-bacteraemia                        | N/A                                                                                  | N/A                              |
| Lee et al.           | 2007 | M/80 years | Korea    | intrahepatic duct carcinoma               | Bacteraemia                                                                          | N/A                              |
| Name et al. | Year | Age/Region | Symptoms | Microorganisms | Treatment | Outcome |
|-------------|------|------------|----------|----------------|-----------|---------|
| Song et al. [110] | 2007 | Multiple (9 Cases) Korea | Chronic pseudophakic endophthalmitis | Ciprofloxacin, Imipenem, Ofloxacin, TMP-SMZ, Amikacin, Ciprofloxacin | N/A | Complete Recovery |
| Yu et al. [111] | 2007 | M/62 years old CA Korea | Liver cirrhosis Peritonitis | Gentamicin, Imipenem, Levofloxacin, Meropenem, TMP-SMZ, Tobramycin | β-lactams | Died |
| Arora et al. [112] | 2008 | M/64 years old India | Hypertension, Diabetes, Coronary artery disease | Ciprofloxacin, Cefoperazone– Sulbactam, Imipenem, Tobramycin | Amikacin, Aztreonam, Cefotaxime, Cefoperazone, Gentamicin, Piperacillin, Ticarcillin | Died |
| Battaglia et al. [113] | 2008 | M/17 years old USA | None | Septic arthritis | N/A | Complete Recovery |
| Javaid et al. [114] | 2008 | M/84 years old UK | Acute renal failure | Bacteraemia (catheter related) | Ciprofloxacin, Meropenem | Complete Recovery |
| Menuet et al. [115] | 2008 | F/17 years old France | Cystic Fibrosis. Diabetes | Pneumonia | Amikacin, Ciprofloxacin, Gentamicin, Imipenem, Isepsamicin, Rifampicin, TMP-SMZ, Tobramycin | Aminoglycosides, Cefazidime, Ceftazidime, Ceftriaxone, Colistin, Ticarcillin, Ticarcillin–Clavulanate, Piperacillin–Tazobactam | Complete Recovery |
| Chiang et al. [116] | 2009 | M/75 years old Taiwan | MI Endophthalmitis (Cataract surgery) | N/A | N/A | Ciprofloxacin | Complete Recovery |
| Study, Year, Region, Age | Clusters | Infection Site | Bacteremia Type | Antibiotics | Duration/Outcome |
|-------------------------|----------|----------------|----------------|-------------|-----------------|
| Duran et al. [117], 2009 | M/Neonate, Turkey | Neonate (meconium peritonitis) | Bacteraemia (catheter related) | Ciprofloxacin, Gentamicin, Imipenem | Died (Unrelated to Ochrobactrum infection) |
| Kim et al. [118], 2009 | F/46 years old, Korea | Ovarian cancer | Bacteraemia (catheter related) | Amikacin, Colistin, Ciprofloxacin, Gentamicin, Netilmicin, Pefloxacin, TMP-SMZ | Complete Recovery |
| Ospina et al. [119], 2009 | F/49 years old, M/51 years old, Colombia | Alcoholism | Bacteraemia | Carbapenem, Amikacin-Sulbactam | Complete Recovery |
| Rihova et al. [120], 2009 | Belgium, Chronic kidney disease | Peritonitis (CAPD patient) | Ciprofloxacin, Imipenem, Meropenem, TMP-SMZ | Amikacin, Ceftazidime, Cefepime, Gentamicin, Piperacllin-Tazobactam | Complete Recovery |
| Soloaga et al. [25], 2009 | M/69 years old, Argentina | Type 2 diabetes | Bacteraemia (catheter related) | Amikacin, Ampicillin, Ceftriaxone, Chloramphenicol, Gentamicin, Ofloxacin, TMP-SMZ, Ciprofloxacin | Complete Recovery |
| Adeyemi et al. [121], 2010 | N/A, Nigeria | HIV | Bloodstream infections | Ceftazidime, Cefotaxime, Nalidixic acid | N/A |
| Quintela et al. [122], 2010 | F/50 years old, Spain | Terminal chronic renal failure | Peritonitis (peritoneal dialysis) | N/A | PD catheter removal |
| Saveli et al. [123], 2010 | M/33 years old, USA | Gout, Alcoholism | Septic arthritis | N/A | Complete Recovery |
| Sepe et al. [124], 2010 | M/71 years old, Italy | Type 2 diabetes | Peritonitis (automated peritoneal dialysis) | N/A | Cefotaxime (1 g), Gentamicin (80 mg intraperitoneal) |
| Starr [125], 2010 | N/A, USA | N/A | N/A | Amikacin, Ciprofloxacin, Gentamicin, Imipenem | N/A |
| Wi & Peck [126], 2010 | Multiple (12 Cases), Korea | Cancer (11 cases) and Liver Cirrhosis (1 case) | Biliary sepsis (8 Cases), peritonitis (1 case), catheter- | Ciprofloxacin, Gentamicin, Imipenem, Meropenem, TMP-SMZ, Amikacin, Ceftriaxone, Cefotaxime, Piperacillin-Tazobactam, | Various Died (11 cases) Died (1 case) |
| Author(s)                          | Year | Age/Gender | Country     | Diagnosis                                      | Infection Type                      | Treatments                                                                 | Outcome                      |
|-----------------------------------|------|------------|-------------|-----------------------------------------------|-------------------------------------|----------------------------------------------------------------------------|------------------------------|
| Woo Nho et al. [127]              | 2010 | M/66 yr    | Korea       | Diabetes mellitus                             | Related infection (3 cases)         | Amikacin, Ciprofloxacin, Colistin, Gentamicin, Minocycline, TMP-SMZ, Tobramycin | Complete Recovery            |
| Yagüe-Muñoz et al. [128]          | 2010 | M/8 yr     | Spain       | Cystic fibrosis                               | Bacteraemia                         | Amikacin, Ciprofloxacin, Colistin, Gentamicin, Imipenem, Levofloxacin, Meropenem, Netilmicin, TMP-SMZ Tobramycin | Complete Recovery            |
| Obando et al. [129]              | 2011 | F/19 yr    | Chile       | Hypothyroidism, end-stage chronic renal failure | Bacteraemia                         | Amikacin, Gentamicin, Imipenem Levofloxacin, Meropenem                     | Complete Recovery            |
| Shivaprakasha et al. [130]        | 2011 | M/75 yr    | India       | Aortic valve replacement                      | Endocarditis (prosthetic aortic valve endocarditis) | N/A                                                                          | Died                         |
| Chan & Holland [131]              | 2012 | F/21 yr    | USA         | Asthma, hypertension, gastric reflex          | Endophthalmitis (Boston type 1 keratoprosthesis implantation) Bloodstream infection (Haemodialysis associated) | N/A                                                                          | Complete Recovery            |
| Shrishrimal [132]                 | 2012 | M/78 yr    | USA         | Diabetes mellitus type 2, peripheral vascular disease | N/A                                | Aminoglycosides, Ciprofloxacin                                             | Complete Recovery            |
| Alparslan et al. [133]            | 2013 | M/12 yr    | Turkey      | End stage renal disease                       | Peritonitis (peritoneal dialysis infection) | N/A                                                                          | Complete Recovery            |
| Study                          | Year | Age          | Country    | Associated Conditions | Primary Diagnosis          | Initial Empirical Therapy                                                                 | Additional Treatments                                                                 | Outcome               |
|-------------------------------|------|--------------|------------|------------------------|---------------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------|
| Chiu & Wang [134]             | 2013 | M/34 years   | Singapore  | None                   | Septic arthritis          | Gentamicin, Meropenem, TMP-SMZ                                                             | Ceftazidime, Piperacillin, Piperacillin–Tazobactam, Aztreonam, Cefazidime, Cefepime, Ciprofloxacin Levofloxacin, Gentamicin, TMP-SMZ | Complete Recovery     |
| Hagiya et al. [51]            | 2013 | M/85 years   | Japan      | Hepatocellular carcinoma, Liver cirrhosis | Bacteraemia | Amikacin, Colistin, Imipenem, Meropenem, Minocycline                                     | Cefcapene pivoxil (Oral)                                                                | Complete Recovery     |
| Kumar et al. [135]            | 2013 | M/45 days    | India      | Neonate (congenital abnormalities) | Septicaemia and pneumonia | Amikacin, Gentamicin, Imipenem, Meropenem, Piperacillin–Tazobactam                       | Meropenem                                                              | Complete Recovery     |
| Mattos et al. [136]           | 2013 | Multiple (12 Cases) | Brazil | Various | Endophthalmitis (Tubing following cataract surgery) | N/A                        | N/A                                                                                      | N/A                                                                                   | Complete Recovery     |
| Mudshingka r et al. [137]     | 2013 | M/Neonate    | India      | Neonate | Septicaemia | Amikacin, Imipenem, Meropenem                                                           | Ceftazidime, Cefepime, Gentamicin                                                    | Died                  |
| Mudshingka r et al. [137]     | 2013 | M/Neonate    | India      | Neonate | Septicaemia | Amikacin, Imipenem, Meropenem                                                           | Ceftazidime, Cefepime, Gentamicin                                                    | Complete Recovery     |
| Naik et al. [138]             | 2013 | M/45 years   | USA        | Hypotensive and Hypoxic | Pneumonia               | Ciprofloxacin, Gentamicin, Meropenem, Tobramycin                                          | Ciprofloxacin, Ceftazidime, Piperacillin–Tazobactam, TMP-SMZ                       | Complete Recovery     |
| Siti Rohani et al. [139]      | 2013 | M/60 years   | Malaysia   | Ischaemic heart disease, diabetes mellitus type 2, hypertension and end stage renal failure | Bacteraemia (catheter related) | Amikacin, Cefepime, Ciprofloxacin, Gentamicin Imipenem, Meropenem, TMP-SMZ             | Ceftazidime, Piperacillin–Tazobactam Polymyxin-B                                      | Complete Recovery     |
| Al-Naami et al. [140]         | 2014 | M/15 years   | Australia  | None                   | Retropharyngeal abscess | Amikacin, Cefepime, Ciprofloxacin, Gentamicin, Imipenem                                  | N/A                                                                                   | Complete Recovery     |
| Hernández-Torres et al. [141]| 2014 | M/73 years   | Spain      | COPD, Hypertension, ischemic heart disease and | Pneumonia | Ciprofloxacin, Doxycycline, Meropenem, Levofloxacin, TMP-                             | Amikacin, Aztreonam, Cephalosporins Piperacillin–Tazobactam                          | Complete Recovery     |
| Authors                        | Year                  | Gender | Age         | Country | Comorbidity                                                                 | Cause of Infection                                                                 | Antibiotics                                                                                   | Outcome                                                                                     |
|-------------------------------|-----------------------|--------|-------------|---------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Hernández-Torres et al. [141] | 2014                  | M/38y  | Spain       | None    | Chronic renal failure                                                      | Bacteraemia (catheter related)                                                          | Amikacin, Aztreonam, Ciprofloxacin, Ceftazidime, Cefepime, Doxycycline Imipenem, Levofloxacin, MEROPENEM, TEICOPOLIN | Complete Recovery                                                                            |
| Hernández-Torres et al. [141] | 2014                  | F/49y  | Spain       | Diabetes mellitus type 2 Adenocarcinoma | Biliary sepsis                                                              | Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, Meropenem Amikacin, Cefepime, Ciprofloxacin, Colistin, Gentamicin, Imipenem, Levofloxacin, Meropenem, Minocycline, Tigecycline, TMP-SMZ, Tobramycin | Amikacin, Ceftazidime, PIPERACILLIN-TAZOBACTAM, Meropenem | Complete Recovery                                                                            |
| Hernández-Torres et al. [141] | 2014                  | M/61y  | Spain       | Liver cirrhosis                           | Transjugular intrahepatic portal systemic shunt device infection            | Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, Meropenem Amikacin, Cefepime, Ciprofloxacin, Colistin, Gentamicin, Imipenem, Levofloxacin, Meropenem, Minocycline, Tigecycline, TMP-SMZ, Tobramycin | Meropenem | Died                                                                                       |
| Hernández-Torres et al. [141] | 2014                  | F/56y  | Spain       | Acute myeloblastic leukaemia               | Catheter-related infection                                                | Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, Meropenem, TMP-SMZ                  | Aminoglycosides, Aztreonam, Cephalosporins, PIPERACILLIN-TAZOBACTAM, Meropenem | Complete Recovery                                                                            |
| Hernández-Torres et al. [141] | 2014                  | 5 Mths | Spain       | None                                           | Pseudobacteraemia                                                         | Amikacin, Carbapenems, Colistin, Doxycycline, TMP-SMZ                                | Meropenem | Complete Recovery                                                                            |
| Khan et al. [142]             | 2014                  | F/53y  | India       | Chronic kidney disease, diabetes mellitus   | Sepsis (catheter related)                                                  | Imipenem, TMP-SMZ                                                                     | Aminoglycosides, β-lactams, Colistin, Quinolones | N/A | Died                                                                                       |
| Menezes et al. [143]          | 2014                  | F/Neona| Brazil      | Neonate with Cystic Fibrosis                  | Bacteraemia (catheter related)                                            | Amikacin, Meropenem, TMP-SMZ                                                           | Cefazidime | N/A | Died                                                                                       |
| Mrozek et al. [144]           | 2014                  | M/28y  | France      | Brain Trauma                                  | Brain empyema                                                              | Carbapenems, Ciprofloxacin, Levofloxacin                                                | Ciprofloxacin, Meropenem (IV for 6 weeks)                                                                 | Complete Recovery                                                                            |
| Study          | Year | Cases/Type                | Country | Age   | Condition                             | Initial Antibiotics                                                                 | Adj. Antibiotics                                                                 | Outcome               |
|----------------|------|---------------------------|---------|-------|----------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------|
| Quirino et al. | 2014 | Multiple (19 Cases)       | Italy   | N/A   | Bacteraemia                            | Amikacin, Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, TMP-SMZ                 | Tazobactam, Tobramycin, TMP-SMZ, Ampicillin, Moxolillin–Sulbactam, Cefazolin, Cefepime, Cefotaxime, Ceftriaxone, Nitrofurantoin, Piperacillin–Tazobactam | N/A N/A               |
| Qasimyar et al. | 2014 | M/Neonate                 | USA     | Neonate | Sepsis (catheter related)             | Amikacin, Levofloxacin, Meropenem, Amikacin, Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, Sulfamethoxazole, Tetracycline Cefepime, Gentamicin, Imipenem, Meropenem, Piperacillin–Tazobactam, Ampicillin–Sulbactam, Aminocillin–clavulanic acid, Aztreonam, Cefazidime, Cefotaxime, Piperacillin, Piperacillin–Tazobactam | Amikacin Meropenem (IV) B-lactams | Complete Recovery     |
| Wu et al.      | 2014 | M/35 years old            | China   | None  | Neck abscess                           | Cefotaxime, Cefazidime, Ceftriaxone                                                  | Levofoxacin                                                      | Complete Recovery     |
| Cenkçi et al.  | 2015 | F/13 months old           | Turkey  | None  | Bacteraemia, pneumonia                 | Cefotaxime, Cefazidime, Ceftriaxone                                                  | Ceftriaxone                                                      | Complete Recovery     |
| Hindilerden et al. | 2015 | N/A                       | N/A     | N/A   | Bacteraemia                             | N/A                                                                                   | N/A                                                              | N/A                  |
| Patra et al.   | 2015 | M/54 years old            | India   | Guillaun Barre Syndrome                | Septicaemia                                                                              | Aminoglycosides, Carbapenems, Aminocillin, Aztreonam, Cefazidime, Cefotaxime, Piperacillin–Tazobactam | Piperacillin–Tazobactam, vancomycin Followed by Meropenam                                      | Complete Recovery     |
| Ashraf         | 2016 | F/58 years old            | USA     | None  | Septic shock, Infective endocarditis   | N/A                                                                                   | N/A                                                              | Piperacillin–Tazobactam, vancomycin Followed by Meropenam                                      | Complete Recovery     |
| Haviari et al. | 2016 | Multiple (3 Cases)        | France  | None  | Bacteraemia (1 case)                   | Aminoglycosides, Carbapenems, Aminocillin, Aztreonam, Cefazidime, Cefotaxime, Ceftriaxone, Ceftriaxone (1 g/day intravenously for 2/3) | Complete Recovery                                          | Complete Recovery     |
| Authors                  | Year | Age   | Gender | Location | Diagnosis                        | Initial Treatment                                                                 | Follow-up Treatment                                                                 | Outcome                      |
|-------------------------|------|-------|--------|----------|-----------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------|
| Jimenez and Antony, 2016 | 2016 | M/40  | USA    |          | Osteomyelitis and liver cirrhosis | Ciprofloxacin, Rifampin, Tigecycline, TMP-SMZ                                       | Ofloxacin (200 mg 2×/day orally for 10/21 days)                                    | Complete Recovery             |
| Kanjee et al, 2016      | 2016 | F/60  | USA    |          | None                              | Amikacin, Levofoxacin                                                                 | Levofloxacin                                                                           | Complete Recovery             |
| Venkateswaran et al.    | 2016 | F/57  | USA    |          | Herpetic keratitis and persistent central neurotrophic ulcer | N/A                                                                                 | Tobramycin                                                                             | Eye evisceration              |
| Gigi et al. [155]       | 2017 | M/18  | Israel |          | Osteomyelitis in the (Foot puncture) | Amikacin, Imipenem, Meropenem, Piperacillin–Tazobactam                              | Ciprofloxacin (Oral 750 mg 2/day) Clindamycin                                       | Complete Recovery             |
| Khasawneh & Yusef, 2017 | 2017 | F/Neonate | Jordan | Neonate | Sepsis (catheter related)        | Ceftazidime, Cefipime, Gentamicin                                                   | Imipenem (25 mg/kg twice daily) Amikacin (15 mg/kg)                                 | Complete Recovery             |
| Rastogi & Mathur, 2017  | 2017 | M/58  | India  |          | Severe head injury                 | Septicaemia with meningitis (catheter related)                                      | Ceftazidime–Tazobactam (1.12 gm) Amikacin (400 mg) (injection every 12 h)         | Complete Recovery             |
| Torres Aguilera et al.  | 2017 | F/88  | Spain  |          | Diabetic and hypertensive, with significant vascular disease | Bacteraemia (catheter related)                                                      | Cefepime–Tazobactam                                                                 | Complete Recovery             |
| Torres Aguilera et al.  | 2017 | M/84  | Spain  | HA       | Diabetic nephropathy               | Bacteraemia (catheter related)                                                      | Initial treatment                                                                  | Complete Recovery             |
| Authors                        | Year | Country | Age | Diagnosis                          | Clinical Features                                      | Pathogen                          | Treatment                                                                                      | Outcomes                                                                 |
|-------------------------------|------|---------|-----|------------------------------------|--------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Cipolla et al. [158]          | 2018 | Argentina | N/A | Bacteraemia                        | Argentina                                             | N/A                              | N/A                                                                                         | N/A                                                                       |
| Hafeez et al. [159]           | 2018 | USA      | M/64 years old | Alcohol abuse, Hypertension | N/A                      | N/A                              | Ciprofloxacin followed by Meropenem                                                   | Complete Recovery |
| Montaña et al. [61]           | 2018 | Argentina | N/A | Pseudobacteraemia                  | Argentina                                             | N/A                              | N/A                                                                                         | N/A                                                                       |
| Zhu et al. [160]              | 2018 | China    | Multiple (11 Cases) | Various | Bloodstream infection (catheter related) | Ciprofloxacin, Levofloxacin, Imipenem, TMP-SMZ | Various                                      | N/A                                                                                         |
| Caroleo et al. [161]          | 2019 | Italy    | Multiple (4 Cases) | Cancer | Catheter-related bloodstream infections | N/A                              | N/A                                                                                         | N/A                                                                       |
| Grabowska-Markowska et al. [162] | 2019 | Poland   | M/13 years old | Neurodegenerative disorder         | Bacteraemia                                           | Imipenem, Meropenem                | Ceftazidime, Pipercillin-Tazobactam, Amoxicillin, Ampicillin, Benzylpenicillin, Cefepime, Ceftazidime, Ceftriaxone, Imipenem, Pipercillin Ampicillin, Amoxicillin, Amoxicillin-Clavulanate, Aztreonam, Cefepime, Cefotaxime, Cefixime, Cefotaxime, Ceftriaxone, Imipenem, Pipercillin Pipercillin, Pipercillin-Tazobactam Ticarcillin–Clavulanate | Complete Recovery |
| Kang et al. [163]             | 2019 | Korea    | F/53 years old | None | Keratitis                           | Ciprofloxacin, Gentamicin                | Gentamicin                                      | Complete Recovery                                                             |
| Roussotte et al. [164]        | 2019 | France   | F/53 years old | Facial oedema                      | Catheter-related infection associated with superior vena cava | Amikacin, Ciprofloxacin, Ertapenem Gentamicin, Imipenem, Meropenem, Moxifloxacin, TMP-SMZ, Tobramycin | Imipenem–Cilastine, Ciprofloxacin Catheter removal | Complete Recovery                                                             |
| Arimuthu and Seong Lim [165]  | 2020 | Malaysia | M/24 years old | Dengue viral fever                | Bacteraemia (catheter related)                       | Ciprofloxacin, Gentamicin, Imipenem, Meropenem, Tigecycline | Ceftazidime, Cefepime, Pipercillin–Tazobactam, Polymyxin B, TMP-SMZ | Complete Recovery                                                             |

Note: HA = Hospitalized, N/A = Not available.
| Authors                        | Year | Age   | Country | Underlying Conditions | Complication | Initial Treatment | Outcome |
|-------------------------------|------|-------|---------|------------------------|--------------|-------------------|---------|
| Arimuthu and Seong Lim [165]  | 2020 | M/64 years old HA | Malaysia | Diabetes, end stage renal disease, Hypertension, Ischemic dilated cardiomyopathy | Bacteraemia (catheter related) | Ciprofloxacin, TMP-SMZ | N/A | Ciprofloxacin | Complete Recovery |
| Bratschi et al. [166]         | 2020 | M/70 years old CA | Switzerland | None | Hand infection | N/A | N/A | Surgical debridement Amoxicillin-clavulanic acid (empirically) Cefepime (2 g 3 times/day intravenously for 15 days) Co-trimoxazole (960 mg 3 times/day orally for 2 weeks) | Complete Recovery |
| Ko et al. [167]               | 2016-2020 | Multiple (5 cases) | Korea | Various (Pneumonia, Hypertension, Diabetes mellitus) | Various | Ciprofloxacin, Levofloxacin, TMP-SMZ Aztreonam, Cefepime, Cefotaxime; Ceftazidime, Piperacillin, Piperacillin-Tazobactam Ticacillin-Clavulanic acid | Complete Recovery in 3 patients Death in 2 patients |

M, Male; F, Female; N/A, Not Available; CA, Community Acquired; HA, Hospital Acquired; TMP-SMZ, Trimethoprim–sulfamethoxazole. *Antibiotic susceptibility testing was carried out using a variety of methods including disk diffusion testing, agar and broth dilution testing and E-testing methods.
7. Treatment of *Ochrobactrum* spp. Infections

Treatment of *Ochrobactrum* spp. infections is often problematic, due to their resistance to different families of antibiotics such as β-lactams (penicillins, cephalosporins and emerging cases of carbapenem resistance). The antibiotic susceptibility profiles of some 103 typed strains of *Ochrobactrum* were analysed using the E-test™ for 19 clinically relevant antimicrobials [46]. In general, strains were highly resistant to β-lactam antibiotics, susceptible to ciprofloxacin, and 97.1% of the strains tested were susceptible to trimethoprim/sulfamethoxazole. This suggests that ciprofloxacin and/or trimethoprim/sulfamethoxazole in combination may be useful for empirical treatment of *Ochrobactrum* infections [46]. In the majority of outbreaks described in Table 4, aminoglycoside, fluoroquinolone, carbapenem or trimethoprim/sulfamethoxazole antibiotics were used in patient treatment. In the majority of cases, these treatments were successful in curing infections. However, as can be seen in Table 4, resistance was observed in various different outbreaks to all these antibiotics. An example of this is reported in a case of *O. anthropi* bacteraemia in a patient in Japan in 2013 where susceptibility testing showed the organism to be resistant to aztreonam, ceftazidime, cefepime, ciprofloxacin, gentamicin, levofloxacin, piperacillin, piperacillin–tazobactam and trimethoprim–sulfamethoxazole [51]. There have been no controlled trials of antibiotic therapies for *Ochrobactrum* spp. infections in humans therefore treatment should be based upon the results of in vitro susceptibility testing on the isolated clinical strains. Resistance to β-lactam antibiotics (cephalosporins, cephemycins and β-lactamase inhibitors) is due to a chromosomal gene (*bla*och) that is similar to the Ambler class C β-lactamase gene. This gene encodes an AmpC-like enzyme that is called OCH [168]. In addition, a plasmid-borne *bla*oxa-181 gene has been found in some *Ochrobactrum intermedium* strains giving resistance to carbapenems [169]. Three *Ochrobactrum* spp. strains isolated from birds in Pakistan harboured aminoglycoside (*aadB, aadA2, aac6-Ib and strA, strB*) β-lactam (*bla*och2 and *carb2*), tetracycline (*tetG*), chloramphenicol (*floR*), sulphonamide (*sulf*) and trimethoprim (*dfrA10*) resistance genes [170].
Table 5. Incidences of *Ochrobactrum* spp. (excluding *Ochrobactrum anthropi*) infection from 1998–2020. Main characteristics of the case reports.

| Author (Ref) | Bacteria                     | Year  | Sex/Age | Country       | Co-Morbidity       | Type of Infection | Susceptible to*                                      | Resistance to*                                      | Treatment                                   | Outcome            |
|--------------|------------------------------|-------|---------|---------------|-------------------|-------------------|--------------------------------------------------|-------------------------------------------------|---------------------------------|--------------------|
| Möller et al. [8] | *Ochrobactrum intermedium*   | 1999  | F/45 years old | The Netherlands | Liver transplant patient | Bacteraemia | Ciprofloxacin, Imipenem, TMP-SMZ | Amoxicillin, Cefuroxime, Cefotaxime, Cefazidime, Colistin, Piperacillin, Polymyxin B, Tobramycin | Imipenem, Tobramycin | Complete Recovery |
| Apisarnthanarak et al. [171] | *Ochrobactrum intermedium*   | 2005  | M/74 years old | Thailand       | Bladder cancer    | Bacteraemia | Aminoglycosides, Carabapemems, Fluoroquinolones, TMP-SMZ | N/A | Ciprofloxacin, Imipenem | Complete Recovery |
| Vaidya et al. [106] | *Ochrobactrum intermedium*   | 2006  | M/49 years old | USA            | None              | Pelvic abscess | Ciprofloxacin, Gentamicin, Nalidixic acid, Ofloxacin, Pefloxacin, Rifampicin | Cefepime, Tobramycin | Levofloxacin, Metronidazole | Complete Recovery |
| Teyssier et al. [36] | *Ochrobactrum pseudintermedium* | 2007  | Multiple (2 cases) | France | ICU patient | Fosfomycin | N/A | N/A | N/A |
| Dharne et al. [172] | *Ochrobactrum intermedium*   | 2008  | M/ | India          | N/A              | Stomach isolate from non-ulcer dyspeptic patient | N/A | N/A | N/A |
| Jacobs et al. [173] | *Ochrobactrum intermedium*   | 2013  | M/34 years old | USA            | None              | Endophthalmitis (metallic intraocular foreign body contamination) | Ciprofloxacin, Levofloxacin, TMP-SMZ | Amikacin, Ampicillin, Ampicillin–Sulbactam, Cefazidime, Ceftriaxone, Gentamicin, Piperacillin–Tazobactam, Tobramycin | Moxifloxacin | Complete Recovery |
| S. No. | Authors and Year | Species | Age (years) | Gender | Country | Underlying Disease(s) | Antibiotics Used | Outcomes |
|--------|------------------|---------|-------------|--------|---------|-----------------------|-----------------|----------|
| 1      | Hirai et al. 2016 [59] Ochrobactrum intermedium | 2016 M/86 years old Japan | N/A Pneumonia (catheter related) | Amikacin, Ciprofloxacin, Imipenem, Levofloxacin, Meropenem, Minocycline Aztreonam, Cefazidime | Ampicillin–Sulbactam followed by Meropenem (2 g/day) | Complete Recovery |
| 2      | Borges et al. [174] Ochrobactrum oryzae | 2016 M/86 years old Brazil | Hypertension, type II diabetes mellitus, dyslipidaemia, end stage renal disease Bloodstream infection | Ciprofloxacin, Imipenem, Meropenem, Polymyxin B | Imipenem | Complete Recovery |
| 3      | Hong et al. [175] Ochrobactrum tritici | 2016 M/70 years old Korea | Cholangiocellular carcinoma, Cholecystitis | N/A | Ceftriaxone, Cefepime, Ticarcillin | Complete Recovery |
| 4      | Bharucha et al. [176] Ochrobactrum intermedium | 2019 M/23 years old UK Undergoing haemodialysis | Endocarditis (catheter related) | Ertapenem, Meropenem, Tigecycline | Ciprofloxacin, Colistin, Fosfomycin | Complete Recovery |
| 5      | Cho et al. [177] Ochrobactrum pseudogrignonense | 2020 M/44 years old Korea | Hypertension, diabetes mellitus, dilated cardiomyopathy | Aztreonam, Piperacillin, Piperacillin–Tazobactam | Vancomycin and Piperacillin–Tazobactam Followed by Meropenem | Complete Recovery |

M, Male; F, Female; N/A, Not Available; CA, Community Acquired; HA, Hospital Acquired; TMP-SMZ, Trimethoprim–sulfamethoxazole. *Antibiotic susceptibility testing was carried out using a variety of methods including disk diffusion testing, agar and broth dilution testing and E-testing methods.

8. Conclusions.
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Ochrobactrum spp. are not presently thought of as major pathogens. Nevertheless, as a result of our literature search, it can be seen that there have been 128 separate outbreaks of Ochrobactrum spp. infections reported. Thus, the consideration that they may be innocuous should in our opinion be reconsidered based on these findings. Although the genus is considered of low virulence and of lower risk compared to other non-fermenting Gram-negative bacteria such as Pseudomonas aeruginosa, we feel it must not be ignored as a potential cause of infections (nosocomial or otherwise) and should be included in routine screening programs in hospitals.

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