Case Report

Clustered multidrug-resistant *Bordetella petrii* in adult cystic fibrosis patients in Ireland: case report and review of antimicrobial therapies

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Introduction: *Bordetella petrii* is an emerging pathogen. Whilst association with cystic fibrosis (CF) has been described previously, this is the first report to our knowledge of multidrug-resistant *B. petrii* incidence in an Irish CF patient population.

Case presentation: Using a case series of four adult CF patients with varying baselines of health, one of whom was asymptomatic, this report attempts correlation of *B. petrii* colonization, by one common strain, with incidence of acute exacerbation of symptoms. As definitive guidelines for antimicrobial sensitivity/resistance do not exist for *B. petrii*, we completed a systematic review of available literature to collate evidence of antimicrobial efficacy against *B. petrii*. Comparison with the isolates in this study indicated *B. petrii* sensitivity to piperacillin/tazobactam and minocycline but resistance to antimicrobials in the macrolide, other β -lactam and fluoroquinolone groups.

Conclusion: To our knowledge, this is the first report of multiple CF patients sharing a strain of *B. petrii*. Furthermore, *B. petrii* may be under-identified in CF patients and should be considered when evaluating exacerbation of CF symptoms.

Keywords: *Bordetella* colonization; cystic fibrosis; multidrug-resistant.

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Introduction

Bordetella petrii is unique among *Bordetella* species as it is capable of independent existence as an environmental facultative anaerobe (Gross *et al.*, 2008). Most of the nine *Bordetella* species are host restricted. *B. pertussis*, *B. parapertussis*, *B. holmesii*, *B. ansorpii*, *B. hinzii* and *B. trematum* are human pathogens (Mattoo and Cherry, 2005; Fry *et al.*, 2007a, b; Ko *et al.*, 2005; Gerlach *et al.*, 2001; Moissenet *et al.*, 2011; Livovsky *et al.*, 2012). *B. bronchiseptica* causes disease in mammals and *B. avium* in birds specifically (Gerlach *et al.*, 2001).

Studies of *B. petrii* are comprised largely of molecular characterization (typically of environmental isolates) (Gross *et al.*, 2010; Zelazny *et al.*, 2013). However, there are a limited number of descriptions involving clinical incidences: mandibular osteomyelitis (Fry *et al.*, 2005), suppurative mastoiditis (Stark *et al.*, 2007) and respiratory infections particularly in patients with bronchiectasis (Le Coustumier *et al.*, 2011) and cystic fibrosis (CF) (Spilker *et al.*, 2008).

Globally, Ireland has the highest prevalence of CF (a recessive autosomal disease associated with increased susceptibility to respiratory infection) with a prevalence of 2.98 per 10 000 of the population compared with prevalence in Europe and the USA of 0.737 and 0.797 per 10 000, respectively (Farrell, 2008). *Bordetella* species have

Abbreviations: bd, twice day⁻¹; i.v., intravenously; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; od, once day⁻¹; p.o., by mouth; tds, three times day⁻¹.

been associated with CF, with *B. petrii* in particular being the species commonly cultured in the sputum of these patients (Spilker *et al.*, 2008). However, the clinical significance of *B. petrii* in CF is unknown. In this report, using a case series of adult CF patients colonized by a single discrete strain of *B. petrii* and with varying baselines of health (one of whom was asymptomatic), we aimed to correlate colonization with incidence of acute exacerbation of symptoms. In addition, as definitive guidelines for antimicrobial sensitivity/resistance do not exist for *B. petrii*, we completed a systematic review of the available literature to collate evidence of antimicrobial efficacy against *B. petrii* and compared this information with the characteristics of the isolate obtained from the four patients in this study with a view to determining effective antimicrobial therapy.

Case report

Four CF patients (three female, mean age 21 years, non-smokers), named A–D, with chronic *B. petrii* colonization were identified in University Hospital, Limerick, Ireland, between March 2009 and December 2012. Retrospective analyses of patient charts and stored sputum samples determined the frequency of hospitalization, episodes of infections, antimicrobial use and patient quality of life scores (Henry *et al.*, 2003) for the year prior to *B. petrii* detection and throughout colonization. Emphasis was placed on the presence/absence of clinical features during colonization, in particular lung function, efficacy of antimicrobial therapy and patient outcome.

Genotypically, patients A and B were heterozygotic for the Δ 508 mutation (within the CF transmembrane conductance regulator causing loss of the amino acid phenylalanine, affecting chloride ion channels in cell membranes and leading to production of thickened mucus), whilst patients C and D were homozygous. All resided in the same county in the midwest of Ireland. Each of the patients had experienced at least one acute hospitalization in the year prior to *B. petrii* detection. As they attended the same outpatient clinic, exposure to one another was possible. The clinic implements a system of segregated clinics according to pathogen status [in particular for *Burkholderia cepacia* complex, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA)]. Each clinic uses single-patient rooms, with healthcare workers rotating through these (i.e. patients remain *in situ* to limit cross-transmission of micro-organisms through contact with other patients, and the healthcare workers adopt strict infection control practices during patient contact). However, in 2003, patients A and D were admitted simultaneously to the same paediatric ward for 1 day. Also in 2008, patients A and C were hospitalized simultaneously but in separate wards. *B. petrii* was initially detected in March 2009.

B. petrii from sputum was preliminarily reported as an undetermined *Bordetella* species. Subsequent identification

of isolates from the four patients was by PCR 16S rRNA gene sequencing and *gyrB* sequence cluster analysis, PFGE and matrix-assisted laser desorption/ionization-time of flight techniques, and indicated the presence of a single discrete *B. petrii* strain. Our group has found that PFGE is capable of differentiating among *B. petrii* isolates (data not shown). Currently, there is no definitive classification of *B. petrii* as sensitive/resistant to specific antimicrobials. In this study, the efficacy of selected antimicrobials against the *B. petrii* isolates (subsequently found to be a single strain) was assessed using Etest (bioMérieux) strips.

Patients A, B, C and D first presented with *B. petrii* in March 2009, March 2010, January 2011 and February 2011, respectively. Durations of intermittent colonization ranged from 8 to 35 months (Table 1). Monomicrobial culture of *B. petrii* was relatively infrequent, with *P. aeruginosa* being the most common co-isolate, although methicillin-sensitive *S. aureus* (MSSA) was found occasionally in three of the four patients, as were *Candida* species (Table 1). Notably, three of the four patients (A, C and D) experienced at least one acute infective exacerbation of CF while simultaneously being positive for *B. petrii*. These patients were treated with antimicrobials directly following detection of *B. petrii*. Patient B was neither admitted to hospital nor treated for infective exacerbation during the course of *B. petrii* colonization. Retrospective analysis of spirometry results for all four patients failed to indicate a correlation between *B. petrii* detection and impaired lung function [measured as forced expiratory volume in 1 s (FEV1)].

In patient A, *B. petrii* was first co-isolated with *Aspergillus fumigatus*. Ten days later, the patient required antimicrobial therapy at home [piperacillin/tazobactam, 4.5 g three times day⁻¹ (tds) intravenously (i.v.), nebulized colomycin [2 million units twice day⁻¹ (bd)] and clarithromycin [500 mg bd by mouth (p.o.)]. Subsequently, *B. petrii* was not detected for 10 months until February 2010 when *B. petrii* re-occurred as a monomicrobial isolate. Patient A was treated with nebulized colomycin (as above) and a 3 week course of oral ciprofloxacin (500 mg bd). In April 2010, treatment for *P. aeruginosa* was nebulized colomycin (as above) and meropenem (2 g tds i.v.), and in May 2010, *B. petrii* was detected for the third time. *Aspergillus fumigatus* was also present. At that time, the patient presented with a 3-day history of haemoptysis and increased volume of sputum. A chest X-ray showed patchy infiltrates. Successful treatment consisted of 2 weeks of nebulized colomycin (as above) and meropenem (as above) and switch therapy with oral co-amoxiclav (625 mg tds). In August 2010 and April 2011, *B. petrii* was again detected, although the patient was asymptomatic on both occasions. *B. petrii* was not detected again until December 2011 but now persisted concomitantly with *Achromobacter xylosoxidans* and *Aspergillus fumigatus*.

In patient B, following first detection, *B. petrii* was identified in 12 of the subsequent 13 sputum samples tested (92 %). Nine of these were polymicrobial, and only

Table 1. Summary of information from patients A–D of the case series

Characteristics	Patient A	Patient B	Patient C	Patient D
Outpatient mean % predicted FEV1	78 %	60 %	37 %	49 %
Inpatient average % predicted FEV1	66 %	–	31 %	43 %
Number of admissions	1/year (2008–2010) 2/year (2011)	1/year (2009–2011)	3/year (2010–2011)	2/year (2010) 4/year (2011)
First diagnosed with <i>B. petrii</i>	Mar 2009	Mar 2010	Jan 2011	Feb 2011
Number of positive specimens	8/28	12/13	3/13	8/8
Last sputum sample with <i>B. petrii</i>	Feb 2012	Jan 2012	Aug 2011	Dec 2011
Duration of Infection	35 months	22 months	8 months	10 months
Number of polymicrobial <i>B. petrii</i> isolates	7	9	13	7
Main co-colonizers	<i>P. aeruginosa</i> , <i>Aspergillus fumigatus</i> , <i>Candida</i> spp., <i>Achromobacter xylosoxidans</i>	<i>P. aeruginosa</i> , <i>Candida</i> spp, MSSA, <i>Cupriavidus metallidurans</i> , <i>Alcaligenes faecalis</i> , <i>Achromobacter xylosoxidans</i>	<i>P. aeruginosa</i> , MSSA, MRSA	<i>P. aeruginosa</i> , MSSA, <i>Haemophilus parainfluenzae</i> , <i>Candida</i> spp.
Number of <i>P. aeruginosa</i> isolates	1	1	3	3
Number of monomicrobial cultures	1	3	0	1
Symptoms with monomicrobial culture	Yes	No	No	Yes

one with *P. aeruginosa*. Other co-colonizers included *Candida* spp., MSSA, *Cupriavidus metallidurans*, *Alcaligenes faecalis* and *Achromobacter xylosoxidans*. No respiratory symptoms were reported and therefore no antimicrobial treatment was offered.

In contrast, patient C was positive for *B. petrii* on only 3 of 13 samplings (23 %) since first detection. On each occasion, *P. aeruginosa* was also identified, and the patient required treatment for infective exacerbation of CF. In January 2011, treatment comprised tobramycin [10 mg kg⁻¹ once day⁻¹ (od) i.v.] (dependent on trough levels), flucloxacillin [2 g four times day⁻¹ (qds) i.v.] and piperacillin/tazobactam (4.5 g tds i.v.), which effectively eradicated *B. petrii* until June 2011, at which time *P. aeruginosa* was also cultured. The patient was admitted for 4 days of i.v. hydrocortisone treatment with a course of ciprofloxacin (500 mg bd p.o.). However, the patient clinically deteriorated after cessation of treatment and merited further antimicrobials for 2 weeks in July: a repeat course of ciprofloxacin (as above) with linezolid (600 mg bd p.o.). In August 2011, patient C was again admitted for acute infective exacerbation coinciding with *B. petrii*, *P. aeruginosa* and MRSA being isolated from the sputum. Symptoms included a history of 6 kg weight loss over the prior 5 weeks, 2 weeks of shortness of breath at rest, a productive cough with yellow sputum and pyrexia.

Treatment comprised ceftazidime (2 g tds i.v.) for 7 days, teicoplanin (6 mg kg⁻¹ i.v.) for 8 days following double dosage for the first 24 h and tobramycin (10 mg kg⁻¹ od i.v.) (dependent on trough levels) for 11 days, followed by nebulized colomycin (2 million units bd) and 6 days of meropenem (2 g tds i.v.). On discharge, patient C required ventilatory support, but *B. petrii* had been effectively eradicated.

Patient D was admitted due to acute infective exacerbations of CF in May, September and November 2011 coinciding with detection of monomicrobial *B. petrii*. Antimicrobial treatment in May comprised meropenem (2 g tds i.v.), tobramycin (10 mg kg⁻¹ od i.v.) (dependent on trough levels) and linezolid (600 mg bd p.o.); the latter was cycled with flucloxacillin (2 g qds i.v.) plus meropenem (as above) and tobramycin (as above) for the subsequent exacerbation in September. During the hospitalization in December 2011, patient D developed a right pneumothorax (>50 %). Eight days later, additional antimicrobials were administered, specifically, vancomycin (15 mg kg⁻¹ bd i.v.), piperacillin/tazobactam (4.5 g tds i.v.) and azithromycin (500 mg od p.o.) with ciprofloxacin (500 mg bd p.o.) to treat *B. petrii*, *P. aeruginosa* and *Candida* sp. These proved ineffective, and 4 days later, patient D died due to cardiorespiratory failure.

Discussion

Since its discovery in 2001 (von Wintzingerode *et al.*, 2001), publications relating to *B. petrii* have focused largely on the molecular and biochemical aspects of the organism (Zelazny *et al.*, 2013). A systematic PubMed search ['*Bordetella*'(Mesh), Limits '01 January 2001 to 01 August 2013'] initially yielded 1471 results, but only five publications reported incidence of *B. petrii* in humans; as referenced above, three were case reports detailing clinical symptoms associated with colonization (mandibular osteomyelitis, chronic suppurative mastoiditis and an acute infective exacerbation in a patient with a background history of bronchiectasis) and two described methods of isolating *B. petrii* from biological material.

In a previous study describing a patient with bronchiectasis, *B. petrii* colonization lasting 13 months was described as 'long-lasting persistence' (Le Coustumier *et al.*, 2011). In this study, we determined that duration of colonization was between 8 and 35 months (a conclusion based on PFGE profiling of isolated cultures rather than comparison of each individual isolate with type strains), and therefore was 'long lasting' but, due to recurrent isolation despite repeated antimicrobial therapy, 'recalcitrant' may be a more accurate term.

As with previous studies in which varying media were used to culture *B. petrii* [fastidious anaerobe agar, Columbia blood agar and MacConkey agar, horse blood, and MacConkey and chocolate agar, as well as chocolate PolyViteX, bromocresol purple and selective *Haemophilus* agar (chocolate bacitracin); Stark *et al.*, 2007], we found that conventional microbiology techniques for identification of *B. petrii* were unsuccessful and, indeed, often misidentified the bacterium. However, molecular techniques were effective.

In performing analyses for this study, we determined that, from the adult CF patient population of 45 in Limerick, *B. petrii* had colonized four patients (9 %). In contrast, none of the 81 paediatric CF patients have been positive for *B. petrii*, supporting the rationale that *B. petrii*, as an environmental isolate, is emerging as an opportunistic pathogen in patients with altered microflora due to repeated, long-term exposure to antimicrobials (Zelazny *et al.*, 2013; Gross *et al.*, 2008; von Wintzingerode *et al.*, 2002). However, the concept of emergent pathogens should be considered in the context of better diagnostic techniques and their influence on reported incidences.

In the four patients described here, *B. petrii* was monomicrobial in only 16 % of positive samples, and was found in conjunction with known pathogens in 68 % of microbiological processing of sputa (e.g. *P. aeruginosa* was detected in 30 %) and with non-pathogens (*Alcaligenes faecalis*, *Aspergillus fumigatus* and *C. metallidurans*) in 10 %. Owing to the complex nature of CF infections with the tendency of bacteria to co-exist as biofilms within the lungs of CF patients, as well as varying

baselines of patient health, it is difficult to definitively state the clinical significance of *B. petrii* in this case series. However, two of the patients were symptomatic during monomicrobial colonization by *B. petrii*, and one patient was symptomatic during co-colonization by *B. petrii* and *Aspergillus fumigatus*, a species with limited evidence of invasive pathogenicity in CF. Conversely, however, patient B experienced persistent asymptomatic colonization for 22 months, and the presence of *B. petrii* could not be correlated with variations in lung function for any of the four patients.

The cases reported here illustrate the recalcitrance of *B. petrii* and its ability to recur. Previously published papers, describing clinical involvement of *B. petrii*, have failed to identify the sources of infection, and no guidelines exist as yet regarding the antimicrobial susceptibility of *B. petrii*. Antimicrobial MICs in the literature are the only guidance for effective treatment of *B. petrii*, and so this study brings together for the first time (Table 2) MICs for the first *B. petrii* environmental isolate and available information for all published clinical isolates and the multiple isolates of the Limerick strain from this study (completed following Clinical and Laboratory Standards Institute guidelines). In summary, susceptibility testing using disc diffusion tests showed apparent sensitivity of *B. petrii* to erythromycin, gentamicin, ceftriaxone and piperacillin/tazobactam, with resistance to amoxicillin, co-amoxiclav, tetracycline, clindamycin, ciprofloxacin and metronidazole (Fry *et al.*, 2005). However, *in vivo* antimicrobial treatments did not mirror results under laboratory conditions and, specifically, the VITEK2 Compact system has been criticized as inappropriate for the susceptibility testing of *Bordetella* species (Le Coustumier *et al.*, 2011). In practice, clarithromycin has been used preferentially for *B. petrii*. However, studies have shown resistance to this antibiotic *in vitro*, and when administered to patients for differing durations – 6 weeks (Fry *et al.*, 2005) and 8 weeks (Stark *et al.*, 2007) – improvement of symptoms was observed but in conjunction with the emergence of resistance. Indeed, positive patient outcome was subsequently attributed to ancillary treatment (Fry *et al.*, 2005). Amoxicillin and metronidazole have been administered with no resolution of symptoms (Fry *et al.*, 2005), whilst co-amoxiclav has improved symptoms but not eradicated *B. petrii* colonization (Le Coustumier *et al.*, 2011). In the patients reported here, *B. petrii* was sensitive to piperacillin/tazobactam and minocycline but resistant to erythromycin and aztreonam (Table 2). Worryingly, the Limerick *B. petrii* isolate was resistant to antimicrobials in the macrolide, most of the β -lactam and the fluoroquinolone groups, and can therefore be considered multidrug-resistant.

Overall, this paper advances our knowledge surrounding *B. petrii* in the clinical setting, and represents the first report to our knowledge of multiple patients colonized by a single *B. petrii* strain, highlights problematic *B. petrii* identification and indicates that colonization may be underestimated in the CF population. Furthermore, *B. petrii*

Table 2. Summary of MIC values (mg l^{-1}) for *B. petrii* from all known sources*

Drug	Le Coustumier <i>et al.</i> (2011)				von Wintzingerode <i>et al.</i> (2001) (environmental isolate)	Fry <i>et al.</i> (2005)	Stark <i>et al.</i> (2007)	Summarized conclusions of Le Coustumier <i>et al.</i> (2011)	Current study (MWRH, 2012) [†]
Penicillin	>32	>32	>32	>32	>32	>32	ND	All resistant	
Amoxicillin	>256	>256	>256	>256	8	6	+clav: 4	All resistant	
Piperacillin	16	12	12	256	0.25	ND	ND		
Piperacillin/ tazobactam	16	48	24	256	0.38	2	<4	Sensitive (Fry <i>et al.</i> , 2005)	0.125–1
Cefotaxime	>32	>32	>32	>32	>32	>32	Ceftriax: >64	All resistant	
Ceftazidime	48	256	>256	2	4	32	16	All resistant	
Ertapenem	>32	>32	>32	0.02	0.047	>32	ND	High MIC	
Imipenem	3	4	8	1	0.75	>32	ND	High MIC	
Meropenem	12	>32	12	0.02	0.047	>32	<0.25	High MIC	0.064–>32
Doripenem	32	>32	>32	0.09	0.125	ND	ND	High MIC	
Gentamicin	1	1	1.5	12	3	4	4	Intermediate	4–16
Tobramycin	1	1	1	64	4	16	2	Intermediate	4–96
Amikacin	8	16	16	64	48	6	8	Intermediate	
Levofloxacin	16	24	24	2	0.25	ND	ND	High MIC	
Ciprofloxacin	>32	>32	>32	4	0.38	>32	2	High MIC	8–>32
Moxifloxacin	12	12	12	1.5	0.032	ND	ND	High MIC	
Minocycline	0.75	0.75	0.75	0.5	0.125	ND	ND	Sensitive	0.25–2
Tigecycline	0.75	1	1	0.25	0.023	ND	ND	Sensitive	
Cotrimoxazole	0.5	0.5	0.5	0.01	0.006	8	ND	Sensitive	
Fosfomycin	4	8	8	6	12	ND	ND	Sensitive	
Quinupristin/ dalbapristin	>32	>32	>32	>32	>32	ND	ND	All resistant	
Rifampin	>32	>32	>32	>32	>32	>32	ND	All resistant	
Daptomycin	>256	>256	>256	>256	>256	ND	ND	All resistant	
Linezolid	>256	>256	>256	>256	>256	ND	ND	All resistant	
Clindamycin	>256	>256	>256	>256	>256	6	ND	All resistant	
Fucidic acid	>256	>256	>256	>256	>256	ND	ND	All resistant	
Erythromycin									>256

ND, Not determined.

* Adapted from data from the Centres for Disease Control and Prevention (Fry *et al.*, 2005; Le Coustumier *et al.*, 2011; Stark *et al.*, 2007; von Wintzingerode *et al.*, 2001) and the four patients in this study.[†]MWRH, Mid-Western Regional Hospital, Limerick, Ireland.

was present in all cases of CF exacerbation in the patients colonized, and was found to be multidrug-resistant, with piperacillin/tazobactam being the only effective common antimicrobial therapy.

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