Familial cluster of *Inquilinus limosus* infection among three brothers with cystic fibrosis

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ARTICLE INFO	ABSTRACT
	Inquilinus limosus is an uncommon, poorly understood bacterium capable of infecting the respiratory tracts of people with cystic fibrosis. The transmission, clinical relevance and changes in antimicrobial resistance of *I. limosus* over time are unclear due to the low frequency of identification. We report three co-habiting brothers with cystic fibrosis who developed chronic *I. limosus* infection and document the clinical and microbiological features of the infections. Clinical evolution after *Inquilinus* infection varied but was associated with an initial decline in lung function. Familial clustering of this rare pathogen raises the possibility of cross-infection as a potential mechanism of transmission of Inquilinus between CF patients.

1. Introduction

Inquilinus limosus is a poorly understood Gram negative bacterium capable of causing respiratory infection in people with cystic fibrosis (CF). Infection by *I. limosus* is uncommon, with an incidence of 2.8% in CF patients [1]. Recent evidence suggests that *Inquilinus* infection is associated with poorer clinical outcomes [2,3]. However, the transmissibility of *Inquilinus* remains unclear. Only one familial cluster of *Inquilinus* has been reported and the clinical details of each sibling were not provided [3]. We describe a unique case of chronic *I. limosus* infection in three co-habiting brothers with CF.

2. Case series

Written consent for publication of this report was obtained from the patients. All three British Asian brothers were diagnosed with CF at neonatal screening and are homozygous for the R709X (c.2125C>T, p. Arg709X) CFTR mutation. At the time of the first *Inquilinus* isolate, all siblings had exocrine pancreatic insufficiency and were taking nebulised DNase, prophylactic oral azithromycin and nebulised antibiotics as detailed below. All *Inquilinus* samples were isolated from sputum using *Burkholderia cepacia* selective agar and identified by MALDI-TOF. Antibiotic susceptibility was tested by disk-diffusion technique and interpreted using the European Committee on Antimicrobial Susceptibility Testing guidelines for *Pseudomonas* [4].

2.1. Case 1

The youngest sibling is a 19-year-old male. Airway cultures through childhood were positive for *Pseudomonas aeruginosa* and he was maintained on continuous nebulised colistin. Sputum culture was first positive for *Inquilinus limosus* at the age of 10 years, on the same date that case 2 first yielded *Inquilinus*. The initial sample was co-infected with *Pseudomonas* spp. and later samples were co-infected with *Aspergillus fumigatus, Pseudomonas aeruginosa* and *Paenibacillus amylolyticus*. The subsequent 9 years involved intermittent *Inquilinus* identification with 8 further isolates (9/19 respiratory samples were *Inquilinus*-positive, Fig. 1A). Case 1 did not receive intravenous (IV) antibiotics in the twelve months before or after first growth of *Inquilinus*. Susceptibility patterns were consistent with recent reports [3], with most isolates resistant to piperacillin-tazobactam, tobramycin, aztreonam and colistin sulfate and susceptible to ertapenem, meropenem and ciprofloxacin (Fig. 1B). Infection was associated with a decline in the ppFEV1 and ppFVC compared to twelve months prior (ppFEV1 from 60.9% to 46.9%, ppFVC from 61.2% to 52.2%). Lung parameters improved twelve months after the first isolate (ppFEV1 64.1%, ppFVC 61.2%) and fluctuated at a higher baseline than pre-*Inquilinus* levels. The patient's weight at the time of the first isolate was lower than twelve months prior (75th percentile from 80th percentile), but weight increased on transition to adult services.

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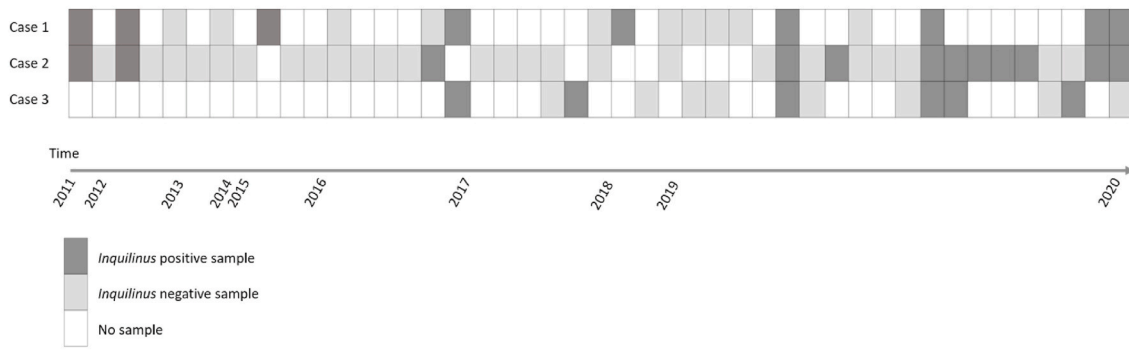
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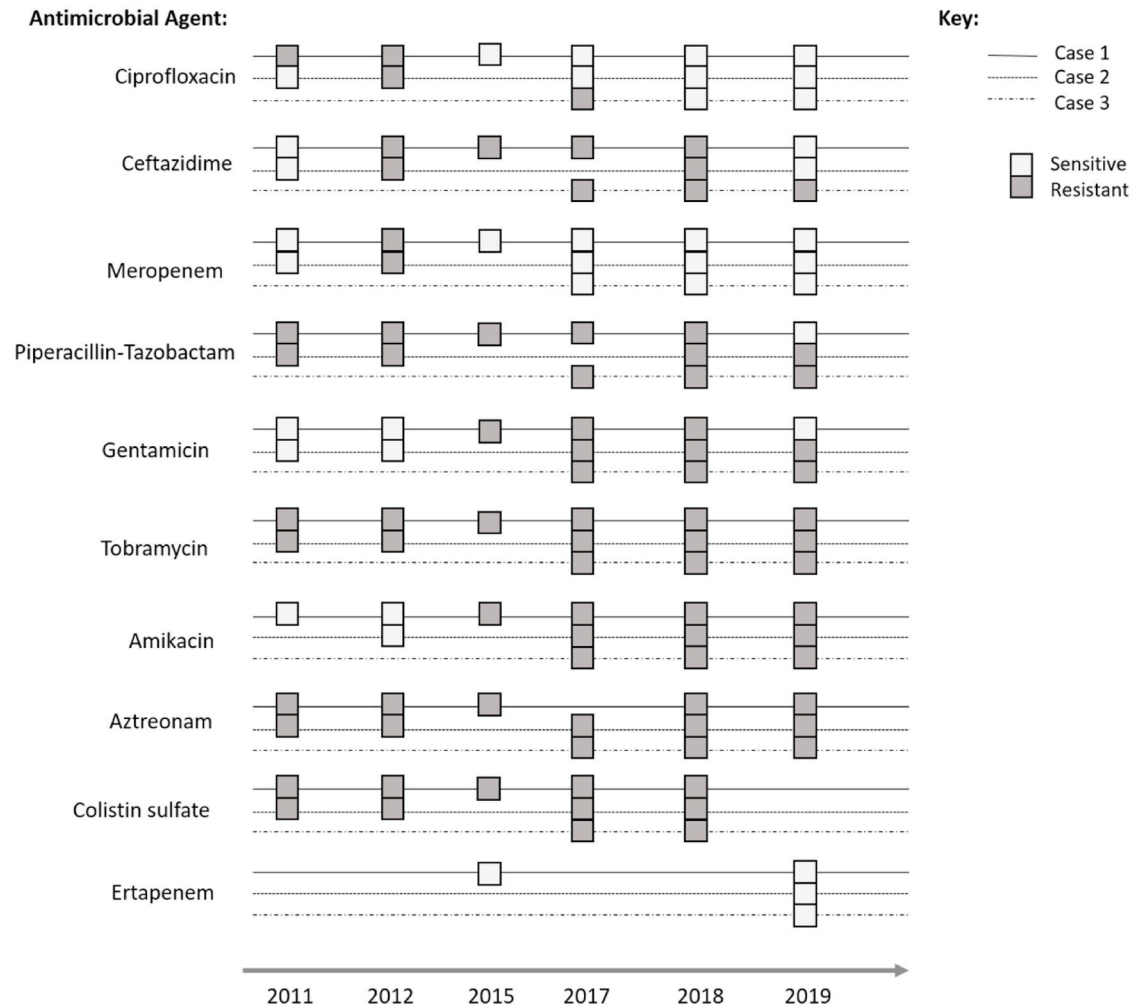
Fig. 1. Pattern of positive *Inquilinus* isolates (A) and antimicrobial susceptibility profiles (B) in each sibling over time. In A, each vertical column reflects a 1 month period where ≥1 sibling produced a respiratory sample. Concordance between siblings is reflected by simultaneous *Inquilinus*-positive samples in ≥1 sibling in a given 1 month period.

2.2. Case 2

The middle sibling is a 22-year-old male. Airway cultures through childhood were positive for *Pseudomonas aeruginosa* and he was established on nebulised colistin, before switching to an alternate month regimen of nebulised tobramycin and colistin at age 15. Sputum culture was first positive for *Inquilinus limosus* 13 years of age, on the same date that case 1 first yielded *Inquilinus*. The initial sample was co-infected with *Pseudomonas aeruginosa* and later samples were co-infected with *Aspergillus fumigatus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Case 2 received 10 days of intravenous antibiotics in the twelve months following first *Inquilinus* growth. The subsequent 9 years involved intermittent *Inquilinus* identification with 11 further isolates (12/37 respiratory samples were *Inquilinus*-positive). Antimicrobial susceptibility patterns of isolates from case 2 were near-identical to isolates from case 1 throughout the follow-up (Fig. 1B). Infection was associated with an initial decline in ppFEV1 and ppFVC compared to twelve months prior (ppFEV1 from 77.4% to 72.9%, ppFVC from 78.7% to 70%). Lung parameters remained reduced twelve months after initial infection (ppFEV1 65.0%, ppFVC 66.5%). During follow-up, ppFEV1 steadily declined to 61% in 2019. Weight percentile did not decline at the time of the first isolate and rose steadily throughout follow-up.

2.3. Case 3

The eldest sibling is a 25-year-old male with a history of low bone mineral density and distal intestine obstruction syndrome. Airway cultures through childhood were positive for *Staphylococcus aureus*, *Aspergillus fumigatus* and *Pseudomonas aeruginosa*. Sputum culture was first positive for *Inquilinus limosus* at 22 years of age, 6 years after *Inquilinus* was first identified in his siblings. At the time of the first isolate, sputum was co-infected with *Staphylococcus aureus*, *Aspergillus fumigatus* and mucoid *Pseudomonas aeruginosa*. Follow-up over a 37-month period revealed intermittent *Inquilinus* identification with 5 further isolates (6/14 respiratory samples were *Inquilinus*-positive). Case 3 was established on alternate month nebulised tobramycin and colistin but did not receive any intravenous antibiotics in the twelve months before or after the first *Inquilinus* growth. Antimicrobial susceptibility patterns of isolates from case 3 were near-identical to isolates from cases 1 and 2 throughout the follow-up (Fig. 1B). At the time of the first isolate, the ppFEV1 and ppFVC were 43.0% and 59.0% respectively, compared with 46.0% and 57.0% twelve months prior. Lung parameters rose over the following twelve months (ppFEV1 52.0%, ppFVC 63.0%). Body mass index was lower at the time of infection than twelve months prior (21.7 kg/m^2 from 22.8 kg/m^2) and subsequently fluctuated at a reduced baseline.

3. Discussion

While one sibling pair of *Inquilinus* infection has been recorded [3], this is the first report detailing the clinical and microbiological features of infection across siblings. Our cases all had significant lung disease at the first growth of *Inquilinus* (ppFEV1<75%) and lung function was lower than 12 months prior (mean absolute fall of 11.8% ppFEV1 and 7.4% ppFVC). This deterioration in lung function at first growth of

Inquilinus is out of proportion to the average ppFEV1 change for this age group [5]. Future studies are needed to determine whether any association with lung function decline is causative and whether this is amenable to correction with antibiotic therapy.

Colistin use has previously been hypothesised to select for *Inquilinus* [1]. We found all three siblings took nebulised colistin before *Inquilinus* acquisition. However, it is unclear why the first isolate from case 3 occurred six years after his siblings. All siblings were co-habiting and the lung function of case 3 was lower than his siblings when they first acquired *Inquilinus*. Larger cohort studies are needed to determine independent risk factors for infection.

The transmissibility and environmental sources of *Inquilinus* are unclear [2]. In this report, the youngest siblings yielded their first isolates on the same date and case 3 yielded his first isolate within one month of case 2 re-culturing *Inquilinus* (Fig. 1A) after a gap of over 4 years. This concordance may suggest either inter-sibling transmission or simultaneous acquisition from a common source. *Inquilinus* genotyping could not differentiate these possibilities. No clear source of *Inquilinus* was apparent but environmental testing was not performed. Nevertheless, the low prevalence of infection suggests a low exposure of CF patients to environmental sources. During the study period, only one other patient yielded respiratory *Inquilinus* isolates at our centre. No epidemiological links were identified between this patient and the siblings detailed in this report. Larger studies are needed to determine the primary mechanism of *Inquilinus* transmission. However, the low prevalence of infection and the concordance of infection between siblings described herein adds weight to the argument of cross-infection.

In conclusion, we present a unique case series of chronic *I. limosus* infection in three co-habiting brothers with CF and propose that the possibility of cross-infection requires further investigation as a potential mechanism of transmission.

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Declaration of competing interest

All authors declare no potential conflicts of interest related to the publication.

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