




## ORIGINAL ARTICLE

# Sputum microbiology data and related clinical outcomes among adult Aboriginal Australians with bronchiectasis

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**Key words**

bacterial infections, clinical outcomes, exacerbations, fungal infections, microorganism, pulmonary.

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**ABSTRACT**

**Background:** Sputum microbiology is an integral aspect of managing patients with bronchiectasis. Adult Aboriginal Australians have a high bronchiectasis disease burden; however, as yet there is sparse literature detailing the sputum microbiology profile in this population.

**Aims:** To assess the sputum microbiology profile among Aboriginal patients aged ≥18 years with chest computed tomography-confirmed bronchiectasis in the Top End Northern Territory of Australia.

**Method:** All available sputum samples processed in a single laboratory service with established protocols for examining and reporting sputum microbiology results between 2011 through 2020 were assessed in relation to demographics, lung function parameters, chest radiology, inhaled pharmacotherapy, hospital admissions restricted to respiratory conditions and all-cause mortality.

**Results:** Four hundred twenty-eight patients (median age 47 years, 56% female) had sputum cultures available to assess. *Haemophilus spp.* was the most common (64%), followed by yeast/*Candida spp.* (53%) and *Pseudomonas spp.* (36%). Polymicrobial cultures were noted in 92% of patients. There were significant geographic differences on a region-wise and community-wise basis. Patients with yeast/*Candida spp.* and *Pseudomonas spp.* recorded more hospitalisations (median 7 (interquartile range (IQR) 3–14) and 8 (IQR 4–16)). In multivariate models, both yeast/*Candida spp.* (odds ratio (OR) 2.63 (95% confidence interval (CI) 1.68–4.14)) and *Pseudomonas spp.* (OR 1.95 (95% CI 1.25–3.04)) were associated with increased odds for mortality. Other than higher *Pseudomonas spp.* isolated with the use of inhaled corticosteroids, no significant association was observed either with lung function or chest radiology.

**Conclusion:** Adult Aboriginal Australians with bronchiectasis harbour a significant microorganism load that may play a role in overall morbidity and mortality.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DR, Darwin rural; DU, Darwin urban; EA, Arnhem land; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; ICU, intensive care unit; IQR, interquartile range; KR, Katherine region; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; NT, northern territory; OR, odds

ratio; RDH, royal Darwin hospital; SABA, short-acting beta agonist; SAMA, short-acting muscarinic agent; TEHS, Top End Health Service

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**Conflict of interest:** None.

## Introduction

Bronchiectasis is a chronic progressive respiratory disease, with the clinical hallmarks of cough, sputum production and respiratory infections associated with bronchial dilatation.<sup>1</sup> It is often the final common pathway of multiple aetiologies (infectious and non-infectious) and concurrent pathophysiological processes resulting in a spectrum of clinical presentations.<sup>2</sup> Chronic respiratory tract infections play a pivotal role in the pathogenesis and pathophysiology of bronchiectasis.<sup>3</sup> There are significant geographical variations, with a substantial burden of bronchiectasis in countries and populations with a high incidence of respiratory infections.<sup>4,5</sup>

The northern territory (NT) is a sparsely populated territory of the Australian mainland, with a population of 233 000 in 2021, of which 26.3% self-identify as Aboriginal and/or Torres Strait islander (the highest proportion in Australia).<sup>6</sup> The age-standardised burden of respiratory disease among adult Aboriginal Australians in the NT is 2.7 times higher compared to non-Aboriginal Australians.<sup>7,8</sup> Although the true incidence of bronchiectasis in Aboriginal Australian adults is unknown, especially in rural/remote communities,<sup>9</sup> it has been shown to be higher than non-Aboriginal Australians.<sup>10</sup>

Lower respiratory tract infections and associated hospital admissions are substantially higher for Aboriginal Australians, including patients with bronchiectasis.<sup>11,12</sup> Commensal organisms may become pathogenic in individuals with bronchiectasis due to mucous thickening, impaired mucociliary clearance and dysregulated immunity.<sup>2</sup> The initial stimulation and persistent inflammation associated with bronchiectasis (including exacerbations) could be due to bacteria, mycobacteria, viruses and/or fungi.<sup>2</sup> Common bacterial organisms associated with bronchiectasis include *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus*.<sup>1,3,13,14</sup> Infections are often polymicrobial, especially in children.<sup>4</sup> Exacerbations and hospitalisation are associated with higher airway bacterial loads, with organisms undergoing adaptations to facilitate immune evasion.<sup>15</sup>

Among adult Aboriginal Australians with bronchiectasis, the limited available data indicate that the most common pathogens isolated from sputum cultures are *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*.<sup>10</sup> Studies from Central Australia have also shown strong associations between bronchiectasis and human T-cell leukaemia virus-1 infection.<sup>16</sup> Bronchiectasis-related outcomes are significantly worse for Aboriginal Australians than their non-Aboriginal counterparts, with death at a significantly younger age (almost 20 years earlier).<sup>17,18</sup>

Despite ample evidence to suggest that adult Aboriginal Australians have a higher burden of bronchiectasis, knowledge surrounding the significance of sputum microbiology to outcomes among adult Aboriginal Australian patients is lacking. This study aims to assess the relationship between sputum microbiology and relevant clinical parameters, hospital admissions and mortality among an adult Aboriginal Australian cohort diagnosed to have bronchiectasis over a 10-year period (2011–2020) from the Top End Health Service (TEHS) region of the NT of Australia.

## Methods

### Setting and study participants

This study was conducted at the respiratory and sleep division based at the Royal Darwin Hospital (RDH), and Darwin Private Hospital, within the TEHS. Participants were Australian Aboriginal patients aged ≥18 years identified to have bronchiectasis via International Statistical Classification of Diseases (ICD) 10th Revision code J47, coded at separation from an in-patient admission across the three hospitals in the TEHS region and confirmed with chest computed tomography (CT) scan between 2011 and 2020.<sup>17</sup>

### Ethics

This study is a part of a larger project examining various aspects of bronchiectasis disease profiles among the adult Aboriginal Australian population residing in the TEHS health districts and was approved by the human research ethics governance/committee of the TEHS, NT and Menzies school of health research (Reference: HREC; 2019–3547).

### Sputum microbiology data

All available sputum microbiology results between 2011 through 2020 were retrieved via patients' electronic medical records, irrespective of ambulatory out-patients' settings or during hospital admissions. Sputum cultures were undertaken as per the discretion of treating medical practitioners. All sputum samples were processed in a single microbiology/pathology service based in the TEHS region: "Territory Pathology Service" with standard established protocols. All sputum culture reports were scrutinised for the quality of the sample and excluded if indicative of poor quality/contaminated samples. Patient sputum microbiology data were analysed in two ways for this study: (i) on the patient level, if patients were observed to have multiple sputum examinations, any cultured microorganisms were counted only once, irrespective of whether it was cultured

**Table 1** Sputum microbiology data by sex

Sputum microbiology	Total (N = 428)	Female (n = 238)	Male (n = 190)
<i>Haemophilus spp.</i>	272 (63.6%)	145 (60.9%)	127 (66.8%)
<i>Yeast/Candida spp.</i>	227 (53%)	117 (49.2%)	110 (57.9%)
<i>Streptococcus spp.</i>	160 (37.4%)	88 (37%)	72 (37.9%)
<i>Pseudomonas spp.</i>	155 (36.2%)	81 (34%)	74 (38.9%)
<i>Moraxella spp.</i>	130 (30.4%)	78 (32.8%)	52 (27.4%)
<i>Staphylococcus spp.</i>	84 (19.6%)	44 (18.5%)	40 (21.1%)
<i>Mycobacterium</i>	53 (12.4%)	20 (8.4%)	33 (17.4%)*
<i>Aspergillus spp.</i>	45 (10.5%)	26 (10.9%)	19 (10%)
Non- <i>Aspergillus</i> fungi	39 (9.1%)	20 (8.4%)	19 (10%)
<i>Klebsiella spp.</i>	31 (7.2%)	14 (5.9%)	17 (8.9%)
<i>Burkholderia spp.</i>	22 (5.1%)	12 (5%)	10 (5.3%)
Others	424 (99.1%)	236 (99.2%)	188 (98.9%)

Differences between females and males tested via univariate logistic regression.

\*Indicates significant difference with Romano-Wolf *P*-value <0.05. *spp.*, species.

multiple times; and (ii) on the hospital admission level, all available sputum culture results within respiratory-related hospital admissions (ICD code J) were assessed individually, irrespective of whether they were from the same patient across multiple admissions. Information pertaining to viral pathogens were not examined.

### Sputum microbiology and clinical data assessment

Sputum results were pragmatically categorised into 11 distinct categories as per common microorganisms encountered in day-to-day clinical practice (Table S1). Sputum microbiology results were assessed against demographics, residence location (by TEHS region and community), smoking status, body mass index, lung function parameters (LFPs; spirometry), comorbidities, inhaled pharmacotherapy use, immunoglobulin levels, chest CT findings, hospital admission rates (restricted to ICD J presentations), need for intensive care unit (ICU) admission and overall all-cause mortality (followed until April 2023). A subgroup analysis was undertaken to assess the sputum microbiology data during acute hospitalisation during exacerbation of respiratory airway disease (ICD code J) during the study window.

### Statistical analysis

Differences in demographic and clinical variables between females and males with sputum cultures were tested via univariate quantile regression (continuous parameters) or logistic regression (categorical parameters), with Romano-Wolf (RW) adjustment for

multiple hypothesis testing. Pairwise correlations between sputum culture categories and lobar involvement were tested via Pearson pairwise correlation coefficient ( $R^2$ ), with *P*-values adjusted via Bonferroni correction. Univariate and multivariate quantile regression models were utilised to explore the effect of sputum categories on the number of hospitalisations for patients across the study period, with the multivariate models adjusted for age, sex, urban residence, chronic obstructive pulmonary disease (COPD) and hypertension, inhaled pharmacotherapy prescription (short-acting beta agonist (SABA), short-acting muscarinic agent (SAMA), long-acting beta agonist (LABA), long-acting muscarinic agent (LAMA), inhaled corticosteroids (ICSs)) and bilateral radiological extent with models reported as beta coefficients (95% confidence intervals (CIs)). Univariate and multivariate logistic regression models were utilised to explore the association between sputum categories and mortality, adjusting for the same factors as the quantile regression models, and reported as odds ratios (ORs) and 95% CIs. All regression models were adjusted for multiple hypothesis testing via RW correction with 250 bootstrap replications. All analyses were conducted in STATA IC 15 (College Station, Texas) and alpha was set to  $P < 0.05$  throughout.

## Results

### Demographics and clinical data

Of the 459 patients identified to have bronchiectasis, 428 had either outpatient or during respiratory-related hospital admission sputum culture available to be included for analysis (Table S2). The median age was 47 years (interquartile range (IQR) 40–56 years), with 56% female, and 7% residing in urban areas. Of the 428 patients, 387 had at least one hospital admission (median five admissions, IQR 2–10) for a total of 3474 hospital admissions. Of the 387 patients with a hospital admission, 315 had a sputum culture recorded within at least one hospital admission, with 3157 admissions recording a sputum culture in total.

### Sputum microbiology results

*Haemophilus* species (*spp.*) were the most commonly cultured (64%), followed by yeast/*Candida spp.* (53%), *Streptococcus spp.* (37%), *Pseudomonas spp.* (36%) and *Moraxella spp.* (30%) (Table 1). Mycobacteria were more common among males than females (17.4 vs 8.4%,  $P = 0.04$ ). Most patients (92.3%) had two or more micro-organism species cultured. *Haemophilus spp.* with *Streptococcus spp.* were

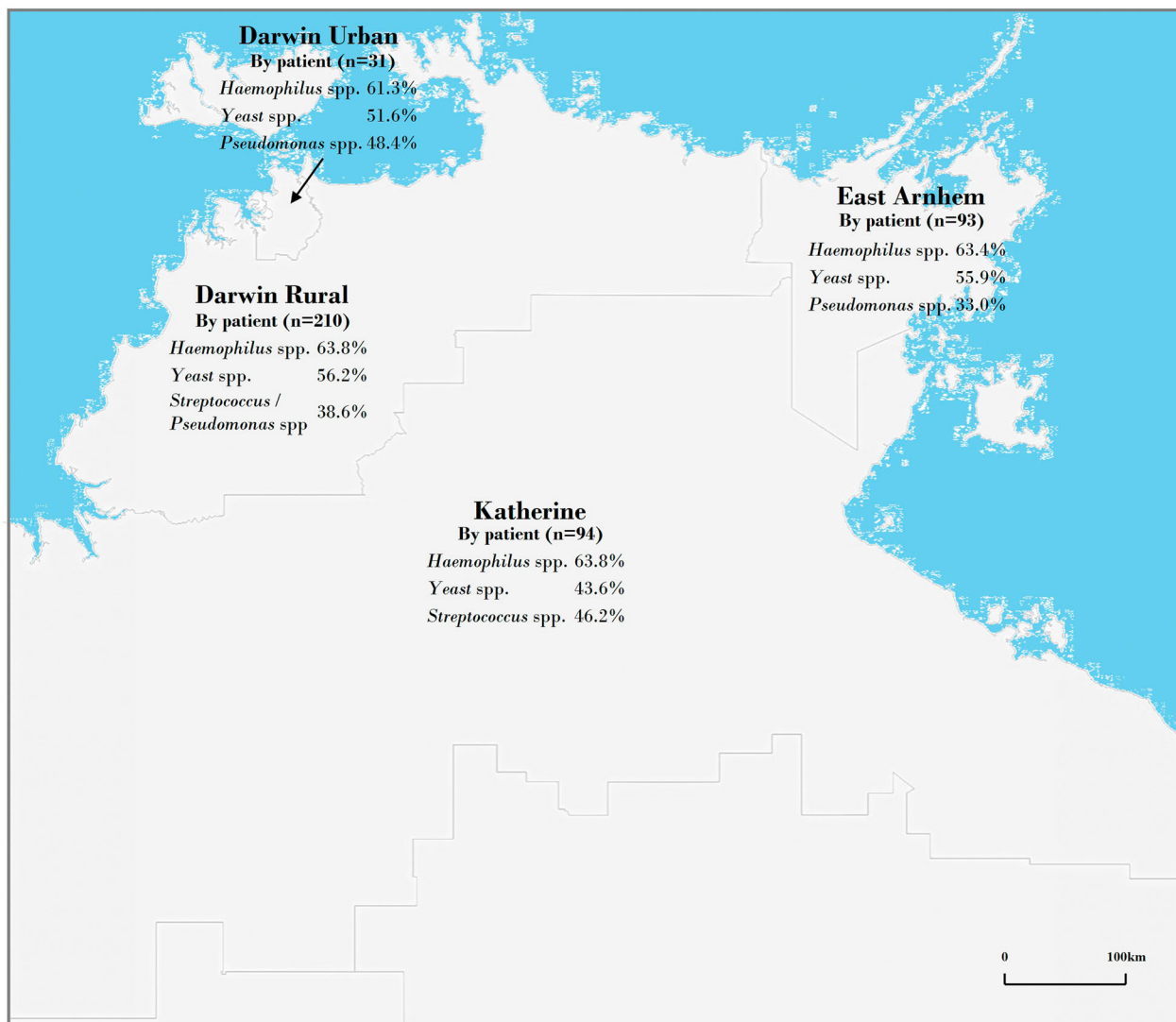
cultured together in 134 patients (31.3%;  $R^2 = 0.324$ ,  $P < 0.001$ ) and *Moraxella* spp. with *Streptococcus* spp. in 80 (18.7%;  $R^2 = 0.330$ ,  $P < 0.001$ ), with both pairings showing the strongest Pearson pairwise correlations (Fig. S1). *Haemophilus* spp. and yeast spp. were the most common co-cultures identified (153 patients, 35.8%;  $R^2 = 0.085$ ,  $P = 1.000$ ); however, Pearson pairwise correlation was not significant (Table S3).

### Relationship of sputum microbiology by patients' geographic location

*Haemophilus* spp. prevalence was stable across the four health districts (range 61.3%–63.8%) (Fig. 1). However,

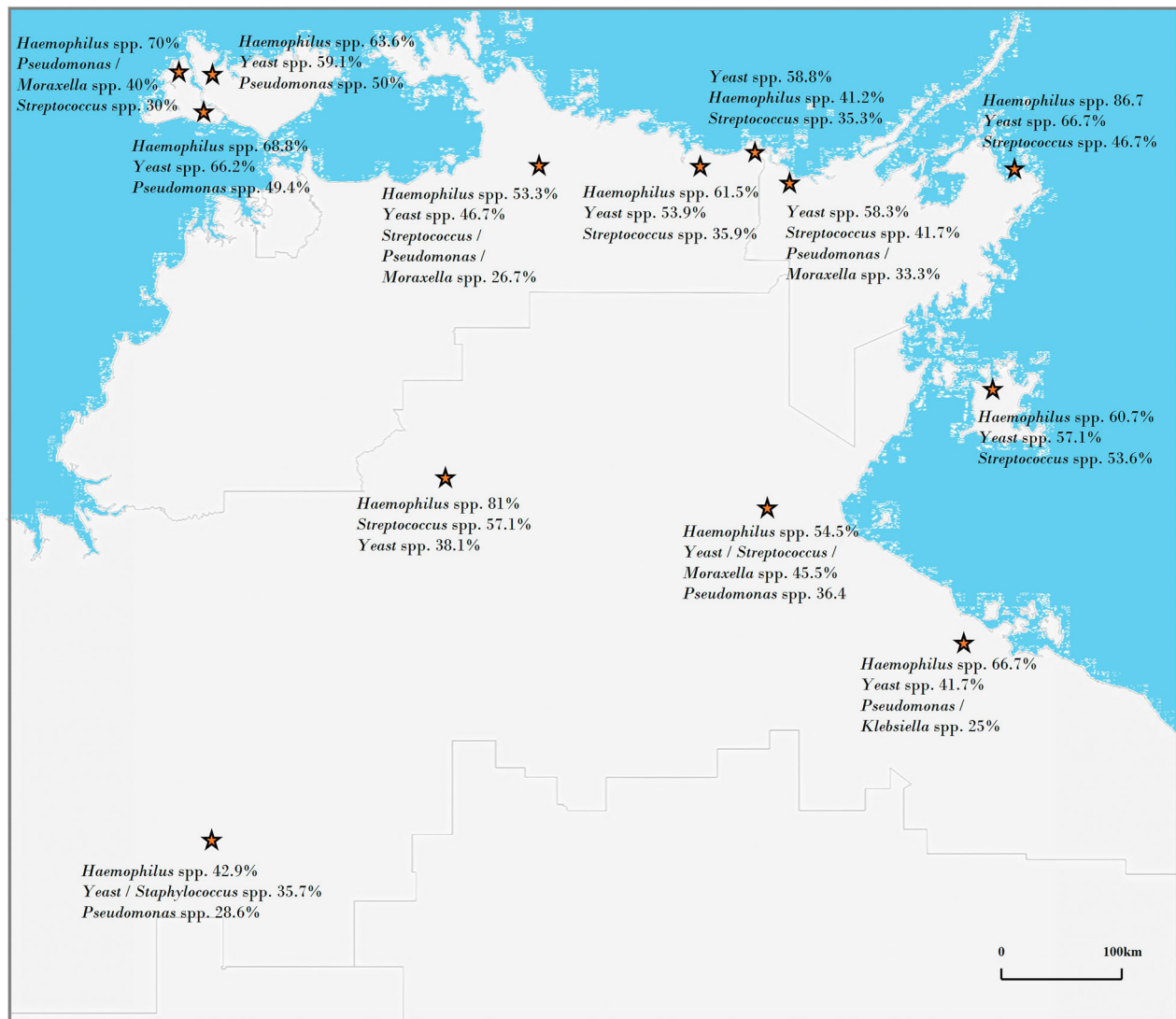
*Streptococcus* spp. prevalence ranged from 22.5% (Darwin Urban) to 46.2% (Katherine). *Pseudomonas* spp. was more common in the Darwin urban region (48.4%), with little variation between other regions (range 30.1%–38.6%).

On a community-by-community basis (including only those with >10 bronchiectasis cases), *Haemophilus* spp. was the most cultured organism in 11 of 13 communities (range 43%–87%), with yeast/*Candida* spp. being the most cultured in the remaining two of 13 (58% and 59%) (Fig. 2). Yeast/*Candida* spp. were the second most common in nine of 13 communities (range 36%–67%), with *Streptococcus* spp. the second most common in three of 13 (36%, 42% and 57%).



**Figure 1** Relationship of sputum microbiology by patients' geographic location in the Top End Health Service districts showing the three most frequently cultured micro-organisms. spp., species.





**Figure 2** Relationship of sputum microbiology by patients' geographic location in the Top End Health Service districts showing approximate community locations with >10 cases and the three most frequently cultured micro-organisms. spp., species.

### Sputum microbiology data during exacerbation and hospital admissions

A total of 3157 sputum samples were recorded during acute hospital admissions (*Mycobacterium* data were not captured for each hospital admission) with females having a fewer number of admissions with sputum recorded than males (median 5 (IQR 2–10) vs 6 (IQR 23)). *Haemophilus* spp. were the most common (6.7%), followed by yeast/*Candida* spp. (6.1%) and *Pseudomonas* spp. (6%) (Table 2). Males recorded more *Pseudomonas* spp. (7.1% vs 4.6%, RW  $P = 0.015$ ), while females recorded more *Staphylococcus* spp. (2.1% vs 1.2%). Differences in sputum microbiology by geographic region were noted, but failed to reach statistical significance (Fig. S2).

### Sputum microbiology relationship to hospital admission and mortality data — regression analysis

*Pseudomonas* spp. (4.88 (95% CI 3.20–6.56)), *Moraxella* spp. (4.07 (95% CI 2.39–5.76)), yeast/*Candida* spp. (3.67 (95% CI 2.14–5.2)), *Staphylococcus* spp. (3.6 (95% CI 1.91–5.30)), *Streptococcus* spp. (3.46 (95% CI 1.82–5.09)), *Aspergillus* spp. (3.05 (95% CI 0.26–5.85)) or *Haemophilus* spp. (2.76 (95% CI 1.09–4.44)) were associated with significantly increased hospitalisations. The increase in hospitalisations with *Pseudomonas* spp. was significantly larger than that associated with *Haemophilus* spp. ( $P = 0.023$ ), yeast spp. ( $P = 0.013$ ) and *Staphylococcus* spp. ( $P = 0.038$ ). After RW adjustment, the significance of

**Table 2** Sputum cultures within hospital admissions by sex

Sputum microbiology	Recorded during hospital admissions (n = 3157)	Female (n = 1450)	Male (n = 1707)	RW P-value
<i>Haemophilus spp.</i>	212 (6.7%)	96 (6.6%)	116 (6.8%)	0.968
<i>Yeast/Candida spp.</i>	192 (6.1%)	98 (6.8%)	94 (5.5%)	0.659
<i>Pseudomonas spp.</i>	188 (6%)	66 (4.6%)	122 (7.1%)	0.015*
<i>Streptococcus spp.</i>	108 (3.4%)	48 (3.3%)	60 (3.5%)	0.968
<i>Moraxella spp.</i>	88 (2.8%)	43 (3%)	45 (2.6%)	0.968
<i>Staphylococcus spp.</i>	51 (1.6%)	31 (2.1%)	20 (1.2%)	0.214
Non- <i>Aspergillus</i> fungi	20 (0.6%)	8 (0.6%)	12 (0.7%)	0.968
<i>Aspergillus spp.</i>	19 (0.6%)	9 (0.6%)	10 (0.6%)	0.968
<i>Klebsiella spp.</i>	12 (0.4%)	4 (0.3%)	8 (0.5%)	0.960
<i>Burkholderia spp.</i>	3 (0.1%)	2 (0.1%)	1 (0.1%)	0.659

\*Indicates significance at Romano-Wolf (RW)  $P < 0.05$  via univariate logistic regression. *spp.*, species.

all associations were fully attenuated. In multivariate logistic models, *yeast/Candida spp.* (OR 2.63 (95% CI 1.68–4.14)), *Pseudomonas spp.* (OR 1.95 (95% CI 1.25–3.04)) and *Staphylococcus spp.* (OR 1.72 (95% CI 1–2.95)) were associated with increased odds of mortality (Fig. 3). The association with *yeast/Candida spp.* remained significant (RW  $P$ -value = 0.006) and *Pseudomonas spp.* was borderline significant (RW  $P$ -value = 0.062) after RW adjustment.

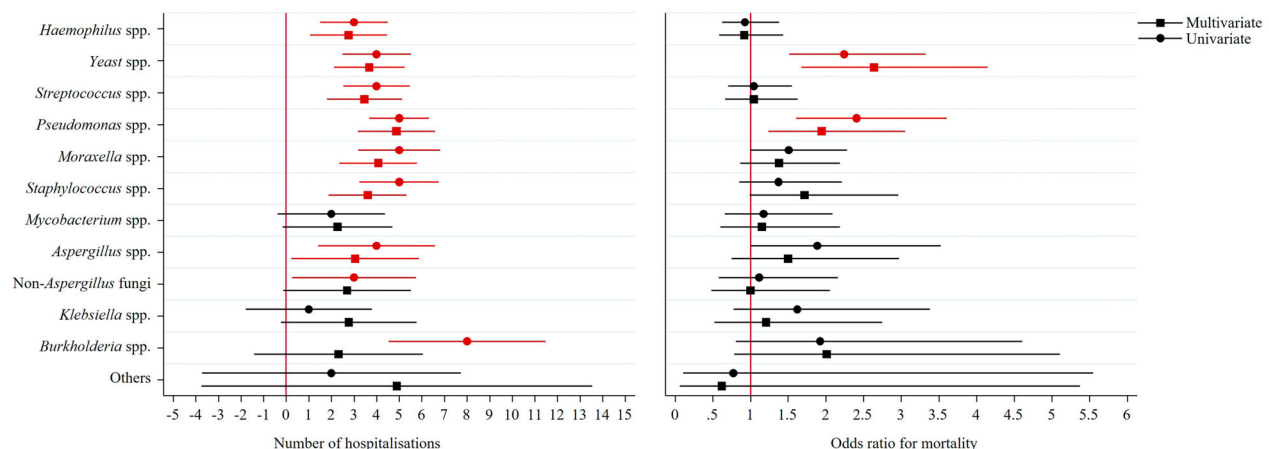
### Clinical outcomes in relation to sputum microbiology

Patients with *yeast/Candida spp.* or *Pseudomonas spp.* displayed increased prevalence of COPD (*yeast/Candida spp.* 91.6 vs no *yeast/Candida spp.* 77.1%,  $P = 0.055$  and *Pseudomonas spp.* 93.5 vs no *pseudomonas spp.* 79.9%,  $P = 0.121$ ) (Table S4). A greater proportion of patients with *yeast/Candida spp.* or *pseudomonas spp.* recorded at

least one hospitalisation (*yeast/Candida spp.* 96.9 vs no *yeast/Candida spp.* 83.1%,  $P = 0.048$  and *Pseudomonas spp.* 97.4 vs 86.4%,  $P = 0.163$ ). Among those who recorded one or more hospitalisation, patients with *yeast/Candida spp.* or *Pseudomonas spp.* recorded more hospitalisations than patients without (*yeast/Candida spp.* 7 (IQR 3–14) vs 3 (IQR 2–6),  $P = 0.055$  and *Pseudomonas spp.* 8 (IQR 4–16) vs 3 (IQR 2–7),  $P = 0.028$ ). Those with *yeast/Candida spp.* also recorded a greater proportion with an ICU visit (42.3 vs 13.2%,  $P = 0.014$ ).

### Relationship of sputum microbiology data to chest CT findings, spirometry, immunoglobulin levels and inhaled pharmacotherapy use

Most patients had lower lobe and bilateral involvement; however, Pearson pairwise correlation was weak between all micro-organisms and CT findings.



**Figure 3** Coefficients plot for univariate and multivariate effects of sputum cultures upon hospitalisations, and mortality. Coloured lines indicate those which retained significance following Romano-Wolff multiple hypothesis testing adjustment at  $P < 0.05$ . *spp.*, species.

Though LFPs were low in this sample, there were no differences between any specific micro-organism. Most patients recorded high IgA and IgG values (77% and 78% respectively), but there were no significant differences in immunoglobulin absolute values by presence of any micro-organism. SABA (62.6%) and LABA (61.9%) were the most common inhaled medications, followed by ICS (55.6%), LAMA (47.4%) and SAMA (7.5%). More patients using SABA or ICS recorded *Pseudomonas spp.* compared to patients not using SABA or ICS (SABA 42.2 vs 26.3% ( $P = 0.037$ ) and ICS 43.3 vs 27.4% ( $P = 0.037$ )) (Table 3).

## Discussion

To the best of the authors' knowledge, this is the first study to demonstrate sputum microbiology data in an adult Aboriginal Australian population with bronchiectasis, and has illustrated the following:

- 1 *Haemophilus spp.* is the most common organism.
- 2 Polymicrobial cultures are frequent, with *Haemophilus spp.* and yeast/*Candida spp.* commonly co-cultured.
- 3 Geographical variations in the sputum microbiology exist.
- 4 *Pseudomonas spp.* or yeast/*Candida spp.* increase hospitalisation rates and all-cause mortality.

One of the major clinical manifestations of bronchiectasis is a vicious cycle of recurrent lower airway infections and worsening airway function due to ongoing chronic airway inflammation, leading to lower quality of life, higher hospitalisation rates and mortality.<sup>19,20</sup> Extensive research has been undertaken to study the sputum microbiology profiles and related clinical outcomes among patients with bronchiectasis across various ethnic populations

globally.<sup>21,22</sup> However, among adult Indigenous patients, despite evidence to suggest a higher burden of respiratory disorders, including higher health care utilisation rates, hospital admission rates and mortality,<sup>12,23</sup> data pertaining to respiratory microbiology/microbiome are sparse and mostly restricted to children and young adults.<sup>24,25</sup>

Our results show sputum microbiology profiles similar to what has been reported from geographical regions such as Africa, the Indian-subcontinent and low-income countries.<sup>26–28</sup> We also observed polymicrobial isolates were frequent, especially with concurrent isolation of *Haemophilus spp.* and *Streptococcus spp.*, *Moraxella spp.* and *Streptococcus spp.*, and *Haemophilus spp.* and yeast/*Candida spp.* The implications of polymicrobial isolates in the study cohort are not exactly known, as this study was retrospective in nature and acute hospital admission details against sputum microbiology data were not examined prospectively. However, it is reasonable to speculate that this will have substantial implications in the management of patients with acute exacerbations and in the choice of empirical anti-microbial therapy among Aboriginal Australian patients.<sup>29</sup> Moreover, there were regional and community-wise differences in the micro-organism isolated. Knowledge of the most prevalent micro-organisms in a given community/region can guide early interventions with appropriate antibiotics during exacerbations, thereby reducing the need for hospitalisation and associated health care cost. However, the significance of some of the isolates is not entirely clear, as the isolated organisms may be mere commensal. In the recent past there has been significant interest in the research communities assessing the respiratory microbiome among patients with bronchiectasis.<sup>30,31</sup>

In this study, a significant proportion of participants had fungi cultured, including *Aspergillus spp.*, yeast/

**Table 3** Pharmacotherapy recorded for patients by micro-organism finding

Sputum microbiology	SABA (n = 268)	P-value	SAMA (n = 32)	P-value	LABA (n = 265)	P-value	LAMA (n = 203)	P-value	ICS (n = 238)	P-value
<i>Haemophilus spp.</i>	177 (66%)	0.963	19 (59.4%)	1.000	165 (62.3%)	1.000	133 (65.5%)	1.000	145 (60.9%)	1.000
Yeast/ <i>Candida spp.</i>	152 (56.7%)	0.805	20 (62.5%)	1.000	156 (58.9%)	0.171	118 (58.1%)	0.805	138 (58%)	0.549
<i>Streptococcus spp.</i>	108 (40.3%)	0.927	14 (43.8%)	1.000	107 (40.4%)	0.927	85 (41.9%)	0.902	95 (39.9%)	1.000
<i>Pseudomonas spp.</i>	113 (42.2%)	0.037*	11 (34.4%)	1.000	110 (41.5%)	0.220	88 (43.3%)	0.220	103 (43.3%)	0.037*
<i>Moraxella spp.</i>	92 (34.3%)	0.549	11 (34.4%)	1.000	89 (33.6%)	0.902	65 (32%)	1.000	78 (32.8%)	1.000
<i>Staphylococcus spp.</i>	64 (23.9%)	0.244	10 (31.3%)	0.915	59 (22.3%)	0.915	47 (23.2%)	0.915	53 (22.3%)	0.951
<i>Aspergillus spp.</i>	32 (11.9%)	1.000	6 (18.8%)	0.951	34 (12.8%)	0.805	21 (10.3%)	1.000	30 (12.6%)	0.951
Mycobacteria	30 (11.2%)	1.000	3 (9.4%)	1.000	36 (13.6%)	1.000	22 (10.8%)	1.000	31 (13%)	1.000
Non- <i>Aspergillus</i> fungi	27 (10.1%)	1.000	2 (6.3%)	1.000	26 (9.8%)	1.000	21 (10.3%)	1.000	22 (9.2%)	1.000
<i>Klebsiella spp.</i>	19 (7.1%)	1.000	1 (3.1%)	1.000	17 (6.4%)	1.000	12 (5.9%)	1.000	17 (7.1%)	1.000

\*Indicates  $P$ -value  $< 0.05$ .

Values are displayed as median (interquartile range).  $P$ -value obtained via multivariate quantile regression, following Romano-Wolf adjustment.

ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; SABA, short-acting beta agonist; SAMA, short-acting muscarinic agent; *spp.*, species.

*Candida* and non-*Aspergillus* fungi. Moreover, isolation of yeast/*Candida* spp. was associated with higher hospital admission rates and all-cause mortality. Again, the clinical relevance of this remains unclear, as the fungal load may be related to prior exposure to broad-spectrum antimicrobials. Moreover, we observed the concurrent presence of other microorganisms alongside yeast/*Candida* spp. (192 patients with yeast/*Candida*, during the same hospital admission also had concurrent sputum cultures positive for *Haemophilus*: seven (3.7%); *Pseudomonas*: six (3.1%); *Staphylococcus*: six (3.1%); and *Streptococcus*: three (1.6%)). Similarly, in a previous prospective, observational study, *Candida* spp. was attributed as the causative agent in community-acquired pneumonia and these patients were noted to demonstrate the concurrent presence of *S. pneumoniae*, *S. aureus*, or *Pseudomonas*.<sup>32</sup>

The significance of fungal isolates among patients with bronchiectasis has generally received little attention in the past, although this is gaining interest.<sup>33,34</sup> Studies have illustrated that differing social determinants and environmental exposures between populations may place non-Caucasian populations at higher risk of fungal infections than Caucasian populations.<sup>35</sup> Furthermore, indigenous peoples globally typically experience disadvantage with several social determinants, such as inadequate housing, household overcrowding, indoor air pollution, childhood chronic infections and poor access to health care and so forth.<sup>36,37</sup> Hence, growth of fungal species from sputum samples in Aboriginal Australian patients with bronchiectasis may require greater scrutiny.

Our study mirrored what has been demonstrated in previous reports, with the presence of *Pseudomonas* spp. being associated with poor outcomes.<sup>38</sup> A previous study from this region<sup>10</sup> had demonstrated a higher prevalence of *Pseudomonas* spp. cultured in non-Aboriginal patients in comparison to Aboriginal Australian patients with bronchiectasis; however, we did not have data to directly compare the outcomes between Aboriginal Australian and non-Aboriginal patients. Although isolation of *Staphylococcus* spp. was not associated with higher hospital admission rates as compared to patients demonstrating *Pseudomonas* spp. or yeast/*Candida* spp., the presence of *Staphylococcus* spp. showed a borderline significant association with all-cause mortality. Aboriginal Australians are reported to have higher rates of *Staphylococcus* spp. bacteraemia than non-Aboriginal Australians, including community-associated methicillin-resistant *Staphylococcus aureus*.<sup>39</sup> It is plausible that *Staphylococcus* spp. may have contributed to severe lower respiratory tract infection/pneumonia in our study cohort in the backdrop of having bronchiectasis.<sup>40</sup> Our study also showed that bronchiectasis is higher in females

compared to males.<sup>41</sup> This may be attributed to a higher prevalence of underlying connective tissue diseases and influence of hormones in females.<sup>42,43</sup> In our study, we observed a marginally higher number of males with cultured Mycobacteria, in contrast to previous studies that have demonstrated an association between non-tuberculous mycobacteria and a female preponderance.<sup>44</sup>

Although we did not observe any correlation between inhaled pharmacotherapy and any studied outcomes, including hospitalisation rates and mortality, the use of ICSs was observed to be higher among patients with cultured *Pseudomonas* spp. It is difficult to conclude whether the use of ICSs influenced higher *Pseudomonas* spp. infection rates, including higher hospitalisation rates and mortality.

Immunoglobulin deficiencies are well established to be associated with bronchiectasis and to perpetrate ongoing respiratory tract infections.<sup>19</sup> However, rather than deficiency, we noticed higher immunoglobulin levels, especially for IgA and IgG. This finding may be reflective of continued chronic inflammatory responses to infections among our patients,<sup>45</sup> hence indirectly reflecting a persistent and chronic respiratory inflammatory process secondary to bronchiectasis.

Sputum microbiology profiles and related clinical outcomes in adult Aboriginal Australian patients with bronchiectasis diverge, at least in some respects, from what is conventionally known in other non-Indigenous populations. This is likely related to social determinants of health for Indigenous persons, as well as other complex health determinants, including differing aetiological factors and co-morbidities. There is also heterogeneity of bronchiectasis disease manifestations within the population and geographic regions. Hence, future prospective studies are needed to better understand sputum microbiology characteristics, including respiratory microbiome profiles not only among Aboriginal Australians but also Indigenous peoples globally.

## Limitation

This study's outcomes pertain to Aboriginal Australian people residing in the TEHS region of Australia and the results cannot be generalised to the wider Aboriginal Australian population or to Indigenous people globally. All available sputum microbiology data were collected during the study window between 2011 and 2020 across various time points. Hence, we were not able to correlate accurately the sputum data with the related clinical outcomes, rather it was represented as overall outcomes. We did not collect treatment details during hospital admissions or during exacerbations. Nor did we examine



data on viruses (such as detection via polymerase chain reaction) and acknowledge their potential significance in bronchiectasis exacerbations. Moreover, we did not have lung function data or immunoglobulin data for all patients, which may have induced bias in these sections. Furthermore, the mortality data presented are all-cause related and as such we do not know whether the mortality was directly related to sputum microbiology results. Nevertheless, this is the first study to represent sputum microbiology data in an adult Aboriginal population with bronchiectasis from the top end NT making pathways for prospective studies for the future.

## Conclusion

This study demonstrated heterogeneity in the sputum microbiology profile among adult Aboriginal Australian patients within the TEHS region. *Haemophilus spp.* was the most common microorganism and polymicrobial cultures were also common. *Pseudomonas spp.* and yeast/*Candida spp.* significantly increased hospitalisation rates and all-cause mortality. Immunoglobulin levels are high, potentially indicating persistent chronic respiratory inflammatory processes. Further prospective studies are warranted to better understand the respiratory microbiome among indigenous patients with bronchiectasis.

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## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

**Supplementary Figure 1** Pearson pairwise correlations for sputum microbiology results.

**Supplementary Figure 2** Differences in sputum microbiology by geographic region.

**Supplementary Table 1** Categorisation of sputum cultures in the study participants.

**Supplementary Table 2.** Demographic and clinical profile of included patients by gender.

**Supplementary Table 3.** Co-occurrence of sputum cultures within patients with bronchiectasis.

**Supplementary Table 4.** Demographic and clinical details for patients who recorded either non-*Aspergillus* fungi or *Pseudomonas spp.* culture, compared with those who did not.

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