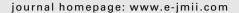


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ORIGINAL ARTICLE

Bacteremia caused by *Pantoea agglomerans* at a medical center in Taiwan, 2000–2010

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KEYWORDS

16S rRNA gene sequence analysis; Antimicrobial susceptibilities; Bacteremia; Pantoea agglomerans Background/Purpose: There are only three case reports of adult patients with spontaneous Pantoea agglomerans bacteremia in the English literature. The aim of this study was to investigate clinical and microbiologic characteristics patients of *P agglomerans* bacteremia.

Methods: We studied all adult patients with P agglomerans bacteremia at a medical center from 2000 to 2010. The isolates were identified using two commercial identification systems. Results: Of the 18 patients identified, 72% (n = 13) had active gastroesophageal disease treated with antacids. Two-thirds of patients had indwelling central lines and advanced cancers. None of the removed catheter tips yielded P agglomerans and line persistence was not associated with adverse outcomes. Initial disease severity was low, hypotension was uncommon and no patient died of bacteremia. Recurrence of bacteremia occurred in one patient with deep-seated infection. 16srRNA gene sequencing identified only half of the isolates as P agglomerans. The remaining nine isolates were Enterobacter species for six, Pantoea ananatis for two, and Exiguobacterium profundum for one. There were no significant differences between the characteristics of the subgroup molecularly identified as P agglomernas and the overall group characteristics. Eleven (61%) of the 18 isolates were susceptible to cefazolin, six (33%) susceptible to fosfomycin (MIC \leq 64 mg/ml). Two isolates had colistin MICs \geq 4 mg/ml.

Conclusion: Bacteremia caused by *P agglomerans* is associated with gastroesophageal reflux disease and receipt of antacids. 16srRNA gene sequencing should not be used as the sole basis for its identification and we have highlighted the need for another molecular-based technique

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to conclusively characterize *P agglomerans*.

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Introduction

Pantoea agglomerans, previously known as Erwinia herbicola or Enterobacter agglomerans, is a facultative anaerobic gram-negative bacillus frequently associated with plants. It is the most clinically significant species of the highly diverse genus of Pantoea, yet its role as a human pathogen continues to be questioned due to infrequent reports of spontaneously occurring P agglomerans infections and uncertainties in taxonomic identification.^{1–3}

P agglomerans has been isolated from the blood in the context of outbreaks caused by the use of contaminated intravenous products and medical equipment. 4-6 However, there are only three reports of adults with sporadic bacteremia (not outbreak-related) due to P agglomerans in the English literature. 7-9 Given the commercial and scientific interests in this species as a biocontrol agent for a variety of plant diseases 10,11 as well as a source of an anticancer lipopolysaccharide with immune enhancing activity, 12,13 its clinical significance is of relevance not only to physicians, but also to scientists and stakeholders. In the past, few clinical reports have incorporated 16S rRNA gene sequence information for the identification of P agglomerans. 1,2

In this study, we investigated clinical and microbiologic characteristics patients of sporadic *P agglomerans* bacteremia at our university hospital in Taiwan over the last decade.

Materials and methods

Hospital setting

The National Taiwan University Hospital, is a 2500-bed, academically affiliated medical center providing both primary and tertiary care in Taipei, Taiwan. All patients seen at the hospital with clinical specimen positive cultures for Pantoea species from January 2000 to December 2010 were retrieved from our microbiology laboratory database. Of these patients, we selected cases whose blood cultures were positive for *P agglomerans*.

Bacterial identification

In this study, identification of the preserved isolates of *P agglomerans* was performed by using two commercial identification systems: Enterotube II (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) and Phoenix Identification System PMIC/ID-30 (Becton Dickinson Diagnostic Systems).

The 16S rRNA gene sequencing analysis was also performed for all preserved *Pantoea agglomerans* isolates. ¹⁴ The amplification products, obtained by polymerase chain reaction (PCR) with primers 8FPL (5'-AGAGTTTGA

TCCTGGCTCAG-3') and 1492RPL (5'-GGTTACCTTGTTACGA CTT-3'), were sequenced, and the sequences were compared to known 16S rRNA gene sequences in the GenBank database of the National Centre for Biotechnology Information by using the Basic Local Alignment Search Tool (BLAST) algorithm. The species with the best match and their accession numbers were obtained.¹⁴

Antimicrobial susceptibilities

Antimicrobial susceptibilities were determined by the agar dilution method for ampicillin, amoxicillin-clavulanic acid, cefazolin, cefmetazole, cefotaxime, ceftazidime. piperacillin-tazobactam, ertapenem, imipenem, ciprofloxacin, gentamicin, amikacin, colistin, and fosfomycin according to the Clinical and Laboratory Standards Institute (CLSI) criteria for Enterobacteriaceae. 15 There were no minimum inhibitory concentrations (MICs) interpretive criteria of colistin for Enterobacteriaceae. 15 Tigecycline MICs were determined by broth microdilution and interpreted by the guidelines recommended by the U.S. Food and Drug Administration for Enterobacteriaceae (susceptible, MICs of $<2 \mu g/ml$). Quality control tests were performed using Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853.

Clinical characteristics of patients

A retrospective review of the medical records of cases with blood isolates unanimously identified as *P agglomerans* by biochemical methods was performed using a standard computerized form. Baseline demographic and clinical characteristics were recorded. The composite measure for chronic health status was measured by the Charlson's comorbidity index.¹⁶ Initial disease severity was assessed using the Pitt bacteremia score.¹⁷ Outcome measures included time to defervescence, time to microbiological eradication, and time to hospital discharge.

To investigate the clinical implications of possible resolution problems at the species level with 16S rRNA gene sequencing data, we analyzed clinical or microbiological differences between patients whose strains were typed as *P agglomerans* by 16S rRNA gene sequence compared to the entire study population.

Results

Overall, a total of 307 clinical isolates from 237 patients, including 105 (34.2%) blood isolates from 59 (24.9%) patients were identified as *Pantoea* species by traditional biochemical tests during the 10-year study period (Fig. 1). Since taxonomic misidentifications are common for *P agglomerans*, we re-tested the archived blood isolates. Phenotypically, there were 25 patients with 28 isolates

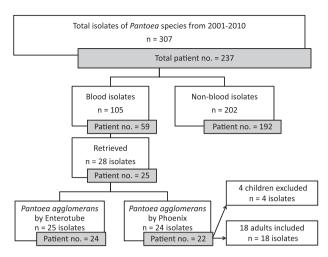


Figure 1. Flow diagram of cases identification and enrollment.

identified conventionally; there were 24 patients with 25 isolates of *P* agglomerans identified by Enterotube II and 22 patients with 24 isolates Phoenix system. Good agreement was observed between the two commercial systems, with all 22 patients identified to be *P* agglomerans by the automated Phoenix system also being identified as *P* agglomerans by the Enterotube II. All patients contributed one isolate of *P* agglomerans each. Only one patient contributed three blood isolates collected at different times spanning a period of 1 year.

Of the 22 individuals with blood isolates that were unanimously phenotypically *P agglomerans*, we excluded four pediatric cases and analyzed the eighteen patients aged 18 years and above with *P agglomerans* bacteremia. These patients were disseminated in space and time (see Table 1). Nine (50%) patients were subsequently identified as *P agglomerans* by 16S rRNA gene sequencing, seven with 99%—100% maximal identity, and two with 94%—96% similarity. The closest matches on GenBank, all with at least 99% maximal identity, for the remaining nine patients were *Enterobacter* species for four patients (33.3%), *Enterobacter hormaechei* for two patients (22.2%), *Pantoea ananatis* for another two patients (22.2%), and *Exiguobacterium profundum* for one patient (5.6%).

The baseline demographics and clinical characteristics of these eighteen patients are summarized in Table 1. The patient and microbiological characteristics of the subgroup molecularly identified as *P agglomerans* are compared to the entire cohort in Tables 2 and 3.

Of the 18 patients, 11 (61.1%) were male and the median age was 57 years of age. Approximately two-thirds of patients had underlying malignancy; six (33.3%) with advanced solid organ malignancy (all stage IV disease) and five (27.8%) with hematologic malignancies. Thirteen patients (72.2%) had symptoms of gastroesophageal reflux disease and were receiving antacids at onset of bacteremia. Twelve patients (66.6%) had indwelling central venous catheters at bacteremia onset, with an even distribution between nontunneled (n = 6) and tunneled lines with reservoir ports (n = 6). The median Charlson's comorbidity index was moderately high at four (range, n = 6). ABO blood-group A (44.4%), rather than blood Group

O (33.3%) was the most frequent blood group among these patients. In the general Taiwanese population, these proportions are reversed with Group O (44%) being more common than Group A (26%).¹⁸

The majority of cases were classified as primary bloodstream infections (66.6%) CDC/NHSN criteria for infections in the acute care settings were followed.¹⁹ There were three cases of bacteremia secondary to intra-abdominal infections (16.7%), two cases secondary to soft tissue infections (11.1%), and one secondary to pneumonia (5.6%).

The median onset of bacteremia was 1 week following admission, but ranged from the day of admission to seven weeks later. Initial disease severity as assessed by the Pitt Bacteremia Score was low, with a median score of 1. Indeed, eight patients had Pitt scores of zero; five had transient hypotension (27.8%) and only one patient required intensive care. Fever (72.2%) and gastrointestinal symptoms (44.4%) were common as were the laboratory findings of anemia (77.8%) and abnormal leucocyte count with an equal likelihood of leucopenia (38.9%) or leukocytosis (38.9%). Most patients (55.6%, n=10) had two or more sets of blood cultures positive for P agglomerans. Seven patients had P agglomerans growing in only one of two sets of blood culture drawn in total.

Among the 18 P agglomerans isolates (only the first pretreatment isolate from the patient with recurrent bacteremia was tested), 10 (56%) isolates were susceptible to ampicillin, 11 (61%) susceptible to cefazolin (MIC \leq 2 μ g/ ml), and six (33%) susceptible to fosfomycin (MIC \leq 64 μ g/ ml) (Table 4). Two isolates had colistin MICs of $\geq 4 \mu g/ml$ (4 and >128 µg/ml, respectively). Thus, the vast majority of patients (88.9%) received effective empirical antibiotics and treatment was successful in all cases both in terms of clinical and bacteriological cure. There were two unrelated in-hospital deaths, one due to progressive lymphoma (4 months after P agglomerans bacteremia) and the other due to subsequent sepsis due to methicillin-resistant Staphylococcus aureus (MRSA) infection (3 months later). There was only one case with recurrent P agglomerans bacteremia after an interval of 11 months, in whom the focus was septic arthritis.

In the subgroup analysis of patients whose 16S rRNA gene sequencing was most closely matched to Pagglomerans, we found no significant differences between the clinical and microbiological characteristics of this subgroup compared to the overall group (Table 3). Of note, in one individual with more than one blood isolates available for 16S rRNA gene sequencing, the accession numbers and molecular identities using this gene were incongruous within the same host and did not match antimicrobial susceptibility patterns (data not shown). Particularly, the patient with recurrent bacteremic septic arthritis had three sequential blood isolates matched to three different accession numbers; the first isolate was obtained in December 2004, susceptible to all antibiotics tested and identified as P agglomerans (FJ756348.1), the second blood isolate was alternatively identified as Enterobacter species in late November 2005 (EU078564.1) but shared acquired resistance to ampicillin and cefazolin with the last isolate (obtained 5 days later in early December 2005) identified as 94% P agglomerans (FJ999930.1). Although pulse-field gel electrophoresis

	Year	Age M/F	Underlying Comorbidities	Onset day	Infection Site	Medication history	Clinical presentation	Concomitant pathogen	16S rRNA ID, (accession number)	Outcomes
1	2000	66 F	Stroke, heart failure, diabetes mellitus	1	SSTI	Nil	Left leg necrotizing fasciitis	Group B Streptococcus	99% E. hormaechei (EF428236.2)	Died 82 days later
2	2001	56 M	Lymphoma stage III, GERD	20	Primary BSI	Antacid, chemotherapy	Epigastralgia, fever after endoscopy	Nil	99% Enterobacter spp. (FN908870.1)	Discharge
3	2001	57 M	Depression, GERD	1	Primary BSI	Antacid	Headache and fever due to neurosyphilis	Nil	99% P agglomerans (HM130693.1)	Discharge
4	2003	55 M	Alcoholic liver cirrhosis, Child C, GERD	1	IAI	Antacid	Abdominal pain and diarrhea	Nil	99% E profundum (HM584043.1)	Discharge
5	2003	74 M	Hepatocellular carcinoma stage IV, diabetes mellitus	21	Primary BSI	Nil	Out-of-hospital cardiac arrest	Nil	99% P ananatis (GU339282.1)	Discharge
6	2003	73 F	Depression	5	Primary BSI	Antacid	Suicide attempt with corrosive esophagitis	P aeruginosa K oxytoca	99% E hormaechei (EF428236.2)	Discharge
7	2004	32 F	Cervical cancer stage IV, HBV active carrier	1	IAI	Antacid, chemotherapy	Seizure and chills due to brain metastases	Nil	94% P agglomerans (AY941841.1)	Discharge
8	2004	74 M	Lymphoma stage IV, heart failure	24	Primary BSI	Antacid, chemotherapy	Fever and chills after chemotherapy	Nil	99% P agglomerans (GU477762.1)	Died 118 days late
9	2004	39 M	Depression, septic arthritis	21	Septic arthritis	Antacid	Right hip pain	Candida albicans A baumannii	96% P agglomerans (FJ756348.1)	Discharge
10	2005	48 F	Polymyositis, diabetes mellitus	54	Primary BSI	Antacid, steroid	Meningism due to cryptococcosis	Nil	99% P agglomerans (FJ999930.1)	Discharge
11	2005	74 F	Acute myeloid leukemia	8	Primary BSI	Antacid, chemotherapy	Post-chemotherapy fever, abdominal pain	Nil	99% <i>Enterobacter</i> spp. (AM396909.1)	Discharge
12	2006	46 M	Acute hepatitis secondary to HBV	12	IAI	Nil	Jaundice, vomiting, abdominal fullness	Nil	99% P ananatis (DQ777968.1)	Discharge
13	2006	43 M	Esophageal cancer IV, aortic pseudoaneurysm	3	Primary BSI	Antacid, chemotherapy	Post-chemotherapy fever and dysphagia	Nil	99% Enterobacter spp. (FN908870.1)	Discharge
14	2007	72 F	Biliary pancreatitis, GERD	1	IAI	Antacid	Epigastralgia	S parasanguis	100% P agglomerans (HM130696.1)	Discharge
15	2008	74 F	Lymphoma stage IV, Grave's disease, GERD, HBV/HCV co-infection	12	Primary BSI	Antacid, steroid	Fever after biopsy of abdominal tumor	S maltophilia	99% P agglomerans (FJ593000.1)	Discharge
16	2009	57 M	Hypertension, MGUS CKD stage IV, gout	22	Primary BSI	Steroid	Fever after dialysis for acute renal failure	Nil	99% P agglomerans (GU991862.1)	Discharge
17	2009	67 M	Bladder cancer stage IV	1	LRTI	Nil	Fever, vomiting, aspiration pneumonia	Nil	99% Enterobacter spp.(FN908870.1)	Discharge
18	2010	52 M	Breast cancer stage IV, GERD	1	Primary BSI	Antacid, chemotherapy	Chills after systemic chemotherapy	A baumannii	99% P agglomerans (JN585671.1)	Discharge

BSI = primary bloodstream infection including catheter associated bacteremia; CKD = chronic kidney disease; GERD = gastroesophageal reflux disease; HBV/HCV = hepatitis B virus/hepatitis C virus; ID = identification; IAI = intra-abdominal infection; LRTI = lower respiratory tract infection; M/F = male/female; MGUS = monoclonal gammopathy of unknown significance; SSTI = skin and skin structure infection.

	Total patients $(n = 18)$	P agglomerans by 16S rRNA $(n = 9)$	Other species by 16S rRNA $(n = 9)$
Age, median years (range)	57.0 (32.0-74.9)	57.0 (32.0-74.4)	66.3 (43.9–74.9)
Men, % (<i>n</i>)	61.1 (11)	55.6 (5)	66.7 (6)
Average body mass index, median kg/m ² (range)	22.8 (11.7-33.9)	22.3 (11.7-33.9)	23.1 (18.6-26.8)
Admission to onset, median days (range)	6.5 (0-54)	12 (0-54)	5.0 (0-21)
ABO blood group, % (n)			
A blood type	44.4 (8)	44.4 (4)	44.4 (4)
B blood type	11.1 (2)	22.2 (2)	0 `´
O blood type	33.3 (6)	22.2 (2)	44.4 (4)
Underlying disease, % (n)			
Peptic ulcer disease	72.2 (13)	66.7 (6)	77.8 (7)
Active malignancy	61.1 (11)	66.7 (6)	55.6 (5)
Hematologic cancers	27.8 (5)	33.3 (3)	22.2 (2)
Solid organ cancers	33.3 (6)	33.3 (3)	33.3 (3)
Chronic viral hepatitis	44.4 (8)	33.3 (3)	55.6 (5)
Cerebrovascular accident	22.2 (4)	11.1 (1)	33.3 (3)
Diabetes mellitus	16.7 (3)	11.1 (1)	22.2 (2)
Congestive heart failure	16.7 (3)	11.1 (1)	22.2 (2)
Autoimmune or connective tissue disease	11.1 (2)	22.2 (2)	0
Chronic obstructive pulmonary disease	5.6 (1)	11.1 (1)	0
End-stage renal disease	5.6 (1)	11.1 (1)	0
Charlson's index, median (range)	4 (1-9)	3 (1-8)	4 (1-9)
Risk for <i>Pantoea agglomerans</i> bacteremia, % (n)			
Receipt of antacid	72.2 (13)	88.9 (8)	55.6 (5)
Receipt of steroid	33.3 (6)	55.6 (5)	11.1 (1)
Chemotherapy within 4 wks	33.3 (6)	33.3 (3)	33.3 (3)
In-situ central venous catheter	66.7 (12)	77.8 (7)	55.6 (5)
Tunneled CVC	33.3 (6)	22.2 (2)	44.4 (4)
Non-tunneled CVC	33.3 (6)	55.6 (5)	11.1 (1)
Sites of infection, % (n)			
Primary bloodstream infection	66.7 (12)	77.8 (7)	55.6 (5)
Catheter-associated	44.4 (8)	66.7 (6)	22.2 (2)
Intra-abdominal infection	16.7 (3)	11.1 (1)	22.2 (2)
Soft-tissue infection	11.1 (2)	0	22.2 (2)
Pneumonia	5.6 (1)	0	11.1 (1)

would be necessary to confirm these isolates were of the same strain, reinfection at each point with a different strain of *P agglomerans* was less likely due to the rarity of this pathogen in an otherwise immunocompetent host in whom the primary site of infection was the same throughout.

Discussion

In this single-center cohort study of 18 adults with P agglomerans bacteremia, we demonstrated that P agglomerans is a pathogen of low virulence even in immunocompromised hosts. Our report is unique for collecting the largest series of P agglomerans bacteremic cases that have occurred outside the context of iatrogenic outbreaks and neonatology. $^{4-6,20}$

Two of the three published adult cases of *P agglomerans* septicemia have occurred in debilitated patients; one with colon cancer and the other with acute myeloid leukemia.^{7,9}

Consistent with these reports, the majority of our patients also suffered from advanced malignancy (Table 2).

In addition, we found a strong association between spontaneously occurring bacteremia and upper gastrointestinal symptoms alongside antacid receipt. Given that the ABO blood Group A is well known to be associated with certain gastrointestinal tract disorders including esophageal adenocarcinoma²¹ and gastric carcinoma associated with pernicious anemia,²² overrepresentation of blood Broup A individuals among this cohort (44.4%) compared with the general Taiwanese population (26%)¹⁷ and the prominence of anemia (77.8%), reinforces the association between gastroesophageal disease and transient bacteremia with *P agglomerans*.

As *Pantoea* species are commonly found on plants, they may be introduced by ingestion of vegetables or fruits, with the opportunity for gastrointestinal translocation in the presence of gastroesophageal mucosal lesions and/or in the absence of protective stomach acidity. Whether blood group A phenotypes reflect a genetic susceptibility to *P*

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	Total patients $(n = 18)$	P agglomerans by 16S rRNA ($n = 9$)	Other species by $16S \text{ rRNA } (n = 9)$
Symptoms and signs	()		
Pitt bacteremia score, median (range)	1 (0-5)	1 (0-5)	1 (0-4)
Temperature, median (range), °C	38.7 (36.7–39.8)	38.2 (36.7–39.8)	38.9 (36.6–40.4)
Mean arterial pressure, median (range)	79.8 (35.7–102.0)	77.0 (35.7–101.7)	81.3 (43.3–102)
Fever, % (<i>n</i>)	72.2 (13)	66.7 (6)	77.8 (7)
Gastrointestinal symptoms, % (n)	44.4 (8)	22.2 (2)	66.7 (6)
Shock, % (n)	27.8 (5)	33.3 (3)	22.2 (2)
Laboratory findings at bacteremia onset, % (n)			
Leukocytosis	38.9 (7)	44.4 (4)	33.3 (3)
Leukopenia	38.9 (7)	33.3 (3)	44.4 (4)
Thrombocytopenia	50.0 (9)	22.2 (2)	77.8 (7)
Anemia	77.8 (14)	66.7 (6)	88.9 (8)
Two or more sets of positive cultures	55.6 (10)	55.6 (5)	55.6 (5)
Drug susceptibility, % (n)			
Ampicillin resistant	50.0 (9)	33.3 (3)	66.7 (6)
Treatment and clinical outcome, % (n)			
Defervescence within 48 hrs	84.6 (11/13)	83.3 (5/6)	85.7 (6/7)
Recurrence of bacteremia ^a	5.6 (1)	11.2 (1)	0
Initial appropriate antibiotic treatment	88.9 (16)	88.9 (8)	88.9 (8)
Antibiotic duration, median d (range)	14 (7 - 25)	14 (9 - 18)	14(7-25)
Clinical treatment success	100 (18)	100 (9)	100 (9)
Length of stay, median d (range)	29.5 (6-211)	42 (13 – 211)	28 (6-79)
28-d mortality	0	0	0
Hospital mortality	11.1 (2)	5.6 (1)	5.6 (1)

agglomerans infection directly and not by way of association with gastric intestinal metaplasia is presently speculative and warrants further elucidation.

By contrast to previous reports of sporadic *P agglomerans* bacteremia secondary to compartmentalized infection, e.g., cases of septic arthritis, synovitis,

osteomyelitis, endophthalmitis and peritonitis related to penetrating injuries with vegetative material such as plant thorns, ^{23–26} the majority of our cases had primary bloodstream infections; by definition not secondary to a localized foci. Although often associated with the presence of intravascular catheters, these infections did not appear to

		Susceptible (%)			
	Range	MIC ₅₀	MIC ₉₀		
Ampicillin	≤0.03−128	8	128	10 (56)	
Amoxicillin-clavulanate	≤0.03−8	4	4	18 (100)	
Cefazolin	0.25-64	2	8	11 (61)	
Cefmetazole	0.06-16	4	8	18 (100)	
Cefotaxime	≤0.03−0.5	0.12	0.5	18 (100)	
Ceftazidime	≤0.03−1	0.25	0.5	18 (100)	
Piperacillin-tazobactam	≤0.03−4	2	4	18 (100)	
Ertapenem	≤0.03−0.06	≤0.03	≤0.03	18 (100)	
Imipenem	≤03-0.5	0.12	0.5	18 (100)	
Ciprofloxacin	≤0.03-0.25	≤0.03	≤0.03	18 (100)	
Gentamicin	0.25—1	0.25	0.5	18 (100)	
Amikacin	0.5-2	1	2	18 (100)	
Colistin	0.25 to >128	0.5	1	b	
Fosfomycin	16 to >256	128	>256	6 (33)	
Tigecycline	<0.03-0.25	0.12	0.12	18 (100)	

^a Minimum inhibitory concentrations (MICs) of the 18 isolates to tigecycline were determined by the broth microdilution method and to other 13 agents were determined by the agar dilution method.

^b MIC susceptibility breakpoint is not available.

be directly related to the catheter by tip culture or differential time to positivity. This is in line with the prior reported case with acute myeloid leukemia, whose infection also did not appear to be line-related. Furthermore, persistence of the catheter was not associated with adverse outcomes or relapses. Therefore, we propose the gastrointestinal tract rather than the intravenous catheter to be the more common portal of entry in these patients.

As far as we know, there is only one case of *P agglomerans* pneumonia in a heart-lung transplant recipient in the English literature. ²⁷ Likewise the respiratory tract was the least common site of infection in our series. Although more sporadic infections were reported to be community acquired, the aforementioned heart-lung transplant recipient was a case of nosocomial pneumonia. Similarly, one-half of the patients in this current series acquired *P agglomerans* infection after the first week of hospitalization and were not classically cases from the community. Hence, *Pantoea* species may be ubiquitous in both the community and hospital environment.

Resolution problems at the genus and/or species level with 16S rRNA gene sequencing data have been reported by phylogenetic scientists for *Pantoea*. ²⁸ In this clinical study, we agree that the 16S rRNA gene does not offer additional discriminatory value for classifying this species although previous studies have attempted to use it as a confirmatory identification tool. ^{7,28} However, a limitation of this study was the lack of type strains of *Pantoea agglomerans* for alignment comparisons with our isolates' 16s rRNA gene sequences.

The miscellaneous genotypes found for the phenotypically homogenous group suggests that currently, *P agglomerans* may represent a complex of closely related organisms rather than a single organism. The amount of diversity within *P agglomerans* and its population structure remains unclear. Another possibility is that there is intragenomic heterogeneity of the 16S rRNA gene among *Pantoea* species that would preclude the use of this technology for species identification. However, due to the lack of major inter- and intra-individual differences regardless of 16S rRNA gene-based identification, further delineation by sophisticated molecular methods may not be so much a clinical priority as an academic interest.

Like other published cases, we showed that P agglomerans is not infrequently isolated in conjunction with established pathogens in polymicrobial infections. P agglomerans is known to compete successfully with the indigenous flora of a variety of microenvironments, and it is suggested that this may occur through the production of potent antimicrobial agents. 2,13,29 Since P agglomerans is often isolated from patients with cancers, we were curious to whether this immunomodulatory agent also has anticancer properties. Literature review revealed that immunopotentiator from P agglomerans 1 (IP-PA1) ameliorates chemotherapy-induced immunosuppression. 29,30 In vitro experiments showed that IP-PA1 activated nuclear factorkappa B (NF-κB) and ameliorated doxorubicin induced growth inhibition of macrophages³⁰ whilst in vivo experiments showed that IP-PA1 improved survival of melanomabearing, doxorubicin treated mice.³⁰

Hence from the antibacterial and anticancer molecules that *P agglomerans* secretes, this species may not be simply the villainous emerging opportunistic human pathogen that previous case reports have depicted. Rather it may be a symbiotic commensal or innocent bystander since serious morbidity and mortality appears not a common feature in our cohort.

This "friend or foe" distinction carries not only therapeutic but also important biosafety implications. In the United States, Pantoea species are largely regarded as "friends" and are currently approved by the U.S. Environmental Protection Agency (EPA) to be used as microbial pesticides. In Europe, this species have currently been classified as biosafety level two organisms. However due to the resoundingly assuring good prognosis associated with these infections, we hope that our cohort study and literature review will help dispel excessive concerns and broaden perspectives on both the potential harm and benefits of *P agglomerans*.

In conclusion, this report indicated a high association between spontaneous *P agglomerans* bacteremia and upper gastrointestinal disease, antacid therapy, and ABO blood Group A. However, comparison data of appropriate control populations, including all patients with bacteremia, are needed to make these conclusions. The prognosis is excellent even in immunocompromised hosts. 16S rRNA gene sequencing should not be used as the sole basis for its identification and we have highlighted the need for another molecular-based technique to conclusively characterize *P agglomerans*.

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