

Outbreak of *Pandoraea commovens* Infections among Non-Cystic Fibrosis Intensive Care Patients, Germany, 2019–2021

Tassilo Kruijs, Peter Menzel, Rolf Schwarzer, Solveigh Wiesener, Felix Schoenrath, Frank Klefisch, Miriam Stegemann, Frieder Pfäfflin

Pandoraea spp. are gram-negative, nonfermenting rods mainly known to infect patients with cystic fibrosis (CF). Outbreaks have been reported from several CF centers. We report a *Pandoraea* spp. outbreak comprising 24 non-CF patients at a large university hospital and a neighboring heart center in Germany during July 2019–December 2021. Common features in the patients were critical illness, invasive ventilation, antimicrobial pretreatment, and preceding surgery. Complicated and relapsing clinical courses were observed in cases with intraabdominal infections but not those with lower respiratory tract infections. Genomic analysis of 15 isolates identified *Pandoraea commovens* as the genetically most similar species and confirmed the clonality of the outbreak strain, designated *P. commovens* strain LB-19-202-79. The strain exhibited resistance to most antimicrobial drugs except ampicillin/sulbactam, imipenem, and trimethoprim/sulfamethoxazole. Our findings suggest *Pandoraea* spp. can spread among non-CF patients and underscore that clinicians and microbiologists should be vigilant in detecting and assessing unusual pathogens.

The widespread use of matrix-associated laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, 16s rRNA sequencing, and whole-genome sequencing (WGS) have improved diagnostic accuracy. However, in using those methods, microbiologists and clinicians can be confronted with uncommon gram-negative, nonfermenting bacteria. Those microorganisms originate from the environment,

and their pathogenic potential is often unclear. When they are cultured from a clinical specimen, determining whether such a finding represents a true pathogen or a contaminant can be difficult.

One example is the genus *Pandoraea*, which was described in 2000 when researchers reclassified several *Burkholderia*- or *Ralstonia*-like organisms cultured from specimens of patients with cystic fibrosis (CF) (1). *Pandoraea* spp. are found in soil and water habitats, where the bacteria contribute to soil formation and cycling of elements necessary for plant growth. By 2022, at least 29 species had been identified within the genus, 19 of which were detected in clinical samples, most often from CF patients (2). Those species are *P. anapnoica*, *P. anhela*, *P. aquatica*, *P. apista*, *P. bronchicola*, *P. capi*, *P. captiosa*, *P. cepalis*, *P. commovens*, *P. communis*, *P. faecigallinarum*, *P. iniqua*, *P. morbifera*, *P. nosoerga*, *P. norimbergensis*, *P. pneumonica*, *P. pnomenusa*, *P. pulmonicola*, and *P. sputorum* (2).

Pandoraea spp. can trigger inflammatory responses and interleukin 6 and 8 elevation in cultures of lung epithelial cells and bacteria from some isolates are capable of crossing lung epithelial cell monolayers (3,4). In an in vivo model for killing *Galleria mellonella* larvae, virulence of some *Pandoraea* strains was comparable to that of *Burkholderia cenocepacia* (3,4). Various other virulence and resistance factors found in other pathogens also can be found in *Pandoraea* spp. (5,6).

Knowledge on the clinical significance of *Pandoraea* spp. is based on case reports and case series. *Pandoraea* spp. can chronically colonize lungs of CF patients and evolve over time by sequential mutations, leading to an adaptation to the CF host niche (7–10). Worsening lung function in CF patients has been linked to *Pandoraea* spp. colonization, but because CF patients often carry multiple other relevant pathogens, causality between

Author affiliations: Labor Berlin Charité Vivantes GmbH, Berlin, Germany (T. Kruijs, P. Menzel, R. Schwarzer); German Heart Center Berlin, Berlin (S. Wiesener, F. Schoenrath); Paulinenkrankenhaus, Berlin (F. Klefisch); Charité–Universitätsmedizin Berlin, Berlin (M. Stegemann, F. Pfäfflin)

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Pandoraea spp. colonization and clinical deterioration is not always clear (9,11,12). The potential of *Pandoraea* spp. to cause acute illnesses has been exemplified by bloodstream and other life-threatening infections in CF patients and patients who received solid organ transplantation (7,13–15).

Single cases of *Pandoraea* spp. infections in patient populations other than those with CF or solid organ transplantation have been documented. Cases have occurred among persons without apparent immunodeficiency, causing illnesses such as nosocomial pneumonia, including infections associated with COVID-19, as well as localized hemodialysis catheter infections, prosthetic valve endocarditis, and skull base osteomyelitis (16–22). Nosocomial acquisition and antimicrobial pretreatment seem to be common features among affected patients (16–22).

Pandoraea outbreaks have been documented in CF centers in Denmark and France, each comprising 6 patients (9,12). One in-depth analysis described a large *P. apista* cluster affecting 18 CF patients serviced at the pediatric and adult CF centers in a city in Scotland and 1 other patient from south England (6). We report a *Pandoraea* spp. outbreak during July 2019–December 2021 at a large university hospital and the directly neighboring heart center in Berlin, Germany, involving 24 non-CF patients colonized or infected with a novel *P. commovens* strain.

Methods

Patient Data

We retrospectively extracted patient data from hospital records. Data included length of hospital stay, time to isolate *Pandoraea* spp., antimicrobial drug treatment, intensive care unit (ICU) admission, renal dialysis, solid organ transplantation, underlying conditions exemplified by the Charlson Comorbidity Index (CCI) scores, and patient outcome. We classified patients as either colonized or infected according to the judgment of 2 infectious disease consultants. Detection of *Pandoraea* spp. from otherwise sterile sites, such as blood, or from intraabdominal specimens was considered as infection. Culture from nonsterile sites (e.g., respiratory samples) was considered colonization if further assessment of antibiotic prescriptions, physicians' notes, laboratory values, and radiology and pathology findings did not reveal evidence of infection. For the diagnosis of pneumonia, ≥ 1 of the following criteria had to be met: new or progressive infiltrate, new or worsening respiratory signs and symptoms, or rising inflammatory markers and assessment of pneumonia by the treating physician. For difficult cases, 2 clinicians

discussed and then agreed on a classification for each case (Appendix, <https://wwwnc.cdc.gov/EID/article/29/11/23-0493-App1.pdf>).

Microbiology

All microbiological investigations were performed by Labor Berlin–Charité Vivantes GmbH in accordance with German Quality Standards for the Microbiological Diagnosis of Infectious Diseases (<https://www.dghm.org>). To detect aerobic bacteria, we plated clinical specimens on conventional solid media, then incubated in ambient air and 5% CO₂ enriched atmosphere at 37°C. We read plates after 24 h and 48 h incubation. We tested suspicious gram-negative microorganisms on oxidase and catalase activity and identified microorganisms by using the VITEK 2 System (bioMérieux, <https://www.biomerieux.com>), VITEK MALDI-TOF mass spectrometry (bioMérieux), or both. Per our clinical routine, we performed antimicrobial susceptibility testing of *Pandoraea* spp. by using the VITEK 2 AST GN-233 card, GN-248 card, or both. In addition, we subjected several isolates to further genomic analyses. For those isolates, we performed broth microdilution by using MICRONAUT-S test plates (MERLIN Diagnostika GmbH, <https://www.merlin-diagnostika.de>), and tested the following antimicrobial agents: piperacillin, piperacillin/tazobactam, temocillin, ceftazidime, cefepime, ceftolozane/tazobactam, ceftazidime/avibactam, meropenem, imipenem, ertapenem, aztreonam, aztreonam/avibactam, ciprofloxacin, levofloxacin, gentamicin, tobramycin, amikacin, trimethoprim/sulfamethoxazole (TMP/SMX), fosfomycin, colistin, minocycline, and tigecycline. We used MIC strips (Liofilchem, <https://www.liofilchem.com>) to solve discrepancies or to test antimicrobial agents that failed or were not included in VITEK 2 or MICRONAUT-S panels. Were interpreted results according to non-species-related pharmacokinetic/pharmacodynamic (PK/PD) breakpoints published by the European Committee on Antimicrobial Susceptibility Testing (23).

We also conducted environmental investigations for a point source of *P. commovens*. For environmental investigations, we probed respiratory tubes, nebulizers, suction catheters, washing gloves, toothbrushes, nutrition solutions, inhalation solutions, oral medications such as painkillers in solution, eye and nasal ointments, and eye drops.

Genomic Sequencing and Analysis

For exact species identification and determination of clonality, we subjected 15 clinical outbreak isolates to WGS, by using either the Nextera Flex (Illumina, <https://www.illumina.com>) or QIASeq FX

(QIAGEN, <https://www.qiagen.com>) library preparation kits, according to the manufacturers' protocols. In brief, we extracted and enzymatically fragmented 10–100 ng of DNA by using DNeasy PowerSoil Pro Kit (QIAGEN). We added indexed adapters and amplified libraries in limited-cycle PCRs. After clean-up, we quantified, normalized, and pooled sequence-ready libraries before sequencing by using 2× 250 cycles paired-end sequencing on a MiSeq (Illumina).

To close the genome, we performed nanopore sequencing on genomic DNA from isolate LB-19-202-79 from our outbreak on GridION (Oxford Nanopore Technologies, <https://nanoporetech.com>) using an R9.4 flow cell (Oxford Nanopore). We prepared the sequencing library by using the SQK-LSK109 Ligation Sequencing Kit (Oxford Nanopore), according to the manufacturer's protocol. We performed basecalling by using Guppy version 5.0.11 (Oxford Nanopore) on the SUP accuracy setting in GridION.

After adapter-trimming the Illumina sequencing reads by using fastp version 0.20.0 (24), we performed de novo genome assemblies by using SPAdes assembler version 3.15.5 (25). For the assembly of nanopore sequencing reads, we tried several protocols using ont-assembly-snake version 1.0 (P. Menzel, unpub. data, <https://doi.org/10.20944/preprints202208.0191.v1>) and eventually chose the protocol that showed the least differences with *P. commovens* strain LMG 31010 (National Center for Biotechnology Information [NCBI] RefSeq accession no. GCF_902459615.1). For that protocol, we used Filtong (<https://github.com/rrwick/Filtong>) to quality-filter nanopore reads that passed the basecalling quality filter to the top 500 megabases and assembled reads using Flye version 2.9 (26). Then, we polished the initial assembly with the ONT reads by using Racon version 1.4.20 (27) and Medaka version 1.4.3 (<https://github.com/nanoporetech/medaka>) and polished the Illumina reads by using Polypolish version 0.5.0 (28). We rotated the final assembly to start at the *dnaA* gene.

We screened the genome assembly of LB-19-202-79 against all available *Pandoraea* spp. assemblies in the NCBI RefSeq database (29) as of July 21, 2022, by using mash-screen version 2.3 (30). We calculated average nucleotide identity (ANI) between genome assemblies by using FastANI version 1.33 (31). We used andi version 0.12 (32) to calculate pairwise genetic distances between the assembled genomes, from which we constructed a phylogenetic tree comprising the isolate assemblies and the closest *Pandoraea* spp. by using the neighbor joining method of the ape package version 5.6 (33).

We uploaded the genome assembly to GenBank for annotation by using the NCBI Prokaryotic Genome Annotation Pipeline (34). The uploaded assembly was then automatically annotated by the Bacterial and Viral Bioinformatics Resource Center (BV-BRC) pipeline (<https://www.bv-brc.org>).

Ethics, Consent, and Permissions

The study was approved by the internal review board of Charité-Universitätmedizin Berlin (registry no. EA4/145/21). The need for informed consent was waived because the study was retrospective.

Results

During July 2019–December 2021, we registered phenotypically identical *Pandoraea* spp. isolates in specimens from 24 patients, which is 8 times the number of all *Pandoraea* spp. detected at our laboratory in the 3 previous years (2016–2018). The cases clustered at Charité Campus Virchow Klinikum (CVK) and Deutsches Herzzentrum Berlin (DHZB), 2 neighboring institutions that are on the same grounds; staff and patients regularly move between the 2 institutions. Thirteen patients were treated at DHZB and 9 were treated at CVK. One other patient was treated at Charité Campus Benjamin Franklin and 1 at Unfallkrankenhaus Berlin, a major trauma center; both of those institutions are in different districts of the city. A total of 7 ICUs, 3 at DHZB and 4 at Charité CVK, and 3 regular wards were affected by the outbreak. Cases were first observed at Charité CVK, then the outbreak shifted after a patient was transferred to 2 ICUs at DHZB. Since late August 2019, nearly all isolates have been recovered on those 2 ICUs (Figure 1). Environmental investigations performed at those ICUs in September 2019 did not reveal any point source.

Patient Information and Outcomes

Among the 24 patients whose cultures grew *Pandoraea* spp., the median age was 67 (range 45–81) years; 50% were male and 50% female. Clinical data were available on 23 patients. Median time from admission to *Pandoraea* spp. detection was 22 days; 22 (96%) of the 23 patients were treated in ICUs. Patients had numerous underlying conditions, and the median CCI was 6 (range 0–13). All patients had received antimicrobial drug treatment during their hospital stays before *Pandoraea* spp. detection, 65% had undergone surgery, and 65% received mechanical ventilation (Table 1).

We considered 12 patients colonized and 10 patients infected. For 2 cases, we were unable to make a classification. All 10 of the infected patients were on mechanical ventilation, compared with only 4 (33%)

SYNOPSIS

colonized patients. Among infected patients, 8 had lower respiratory tract infections and 2 had intraabdominal infections. In 5 infected patients, *Pandora* spp. was part of a polymicrobial culture, and in the other 5 infected patients, no other pathogens were detected. *Pandora* spp. infections were treated with imipenem in 8 patients and meropenem in 2 patients. TMP/SMX was administered as stepdown therapy in 1 patient after initial treatment with imipenem. All respiratory tract infections resolved, whereas the 2 patients with intraabdominal infections had complicated clinical courses that involved several surgical interventions and protracted administration of various antimicrobial agents in both cases (Appendix).

Among the 10 infected patients, 4 died during hospitalization. None of those deaths were judged to be directly related to the *Pandora* spp. infections (Table 2, <https://wwwnc.cdc.gov/EID/article/29/11/23-0493-T2.htm>).

Microbiology Results

During July 2019–December 2021, *Pandora* spp. was cultured from 43 clinical specimens, including throat

swabs, respiratory secretions, bile, ascites, intraabdominal specimens, and wound swabs. Numerous blood cultures were collected from 19 of the 24 patients. However, *Pandora* spp. was only detected in 1 blood culture from a patient with a complicated intraabdominal infection. *Pandora* spp. isolates grew readily after overnight culture on commercial solid media, such as Columbia blood or MacConkey agars. Single colonies appeared pale to grayish, displayed weak oxidase activity, and were catalase negative. Neither a mucoid phenotype nor small colony variants were observed.

Using the VITEK 2 GN ID card, identification was possible only to the genus level. In 4 of 17 tested isolates, a reliable discrimination between *Pandora* spp. and *Bordetella hinzii* could not be made by VITEK 2. In the remaining 13 isolates, we identified *Pandora* spp. with probabilities ranging from 95% to 99%. All 36 isolates tested by VITEK MALDI-TOF mass spectrometry were identified as *P. sputorum* with a score of 99.9. We were able to perform WGS to differentiate *P. commovens* from *P. sputorum* on isolates from patients 7, 9–11, and 14–24, as described in the next

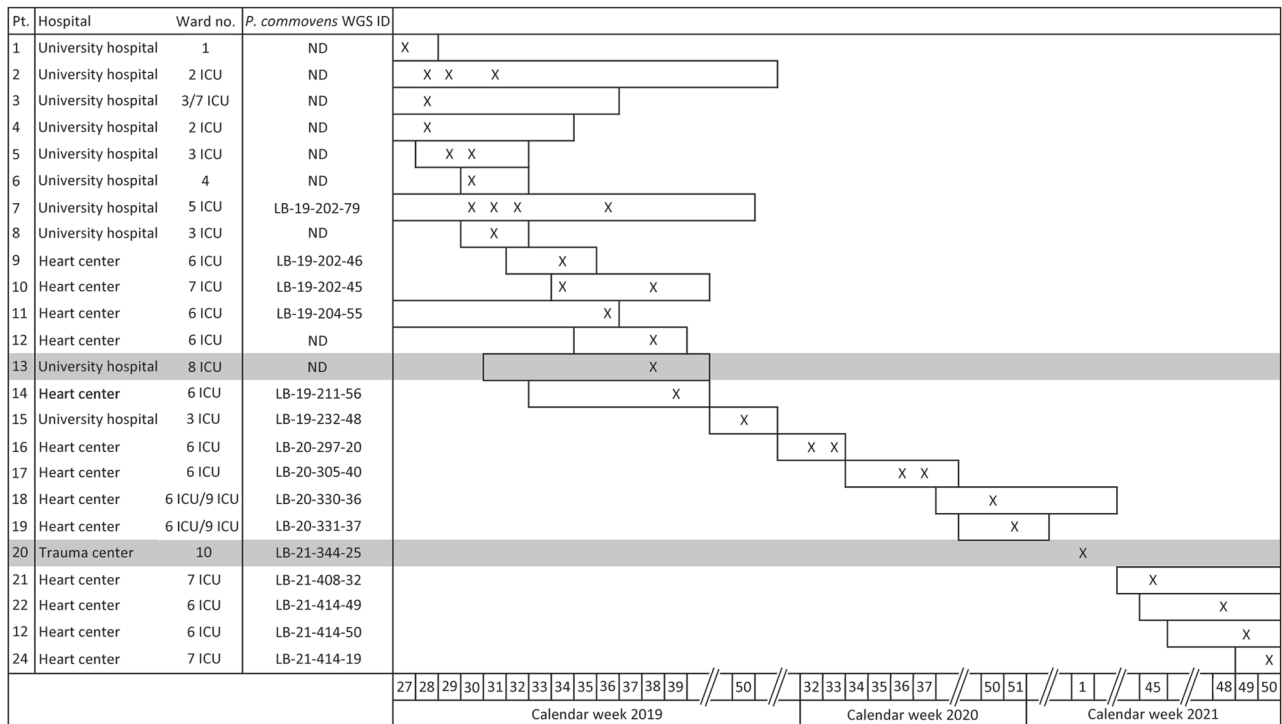


Figure 1. Timeline of an outbreak of *Pandora* *commovens* among non-cystic fibrosis intensive care patients, Germany, 2019–2021. The cases clustered at Charité Campus Virchow Klinikum (university hospital) and Deutsches Herzzentrum Berlin (heart center), 2 neighboring institutions that are on the same grounds and staff and patients regularly move between the 2 institutions. Wards 1–7 are located at the same grounds; wards 8 and 10 are located in facilities elsewhere in Berlin (indicated by grey background). X symbols indicate calendar weeks with detection of *P. commovens*; horizontal bars in timelines indicate length of stay. ICU, intensive care unit; ND not done; Pt., patient; WGS ID, whole-genome sequencing identification number corresponding to the numbering in phylogenetic tree (Figure 2).

section. Because of the local and temporal relationship, identical colony morphology and antimicrobial susceptibilities, we assumed that the correct species identification was *P. commovens* in all patients reported in this outbreak and that *P. sputorum* was a misidentification resulting from limitations in the VITEK mass spectrometry database.

We performed susceptibility testing on 35 isolates. For susceptibility testing methods, agreement between VITEK 2 and MICRONAUT-S broth microdilution plates was good for most tested antimicrobial agents. According to EUCAST PK/PD breakpoints, MICs obtained for ampicillin/sulbactam and imipenem were consistently found to be susceptible at standard dosing levels. MICs for TMP/SMX were ≤ 20 mg/L in all tested isolates. Cephalosporins including ceftazidime/avibactam, ceftolozane/tazobactam, and cefiderocol tested resistant, as did fluoroquinolones, aminoglycosides, tetracyclines, and colistin (Table 3).

Discrepancies between VITEK 2 and microdilution were apparent for piperacillin and piperacillin/tazobactam; higher MICs were detected using VITEK 2 (range 16 to ≥ 128 mg/L for both) than with microdilution (range ≤ 4 to 32 mg/L for piperacillin and ≤ 1 to 2 mg/L for piperacillin-tazobactam). MICs for meropenem and ertapenem were also higher in VITEK 2 (range 4–8 mg/L and 1 to ≥ 8 mg/L, respectively) than in microdilution (range 1–4 mg/L and ≤ 0.5 to 1 mg/L, respectively).

Genomic Characterization and Phylogeny

We screened the genome assemblies from 15 isolates from our outbreak against genomes in RefSeq. We found the genome assembly GCF_902459615.1 of *P. commovens* strain LMG 31010 to be the most similar, then *P. sputorum* strain ATCCBAA64, and *P. oxalati-orans* strain DSM 23570. The average genome-wide nucleotide identity between isolate LB-19-202-79 and GCF_902459615.1 was 99.5% and identity between LB-19-202-79 and *P. sputorum* GCF_900187205.1 was 94.1%. Thus, we designated our strain as *P. commovens* strain LB-19-202-79. The phylogenetic tree derived from the pairwise phylogenetic distances showed that all our isolates are closely related to each other and distinct from *P. commovens* strain LMG 31010 and other *Pandoraea* spp. (Figure 2). We concluded that the outbreak isolates were from a single origin.

The assembly of isolate LB-19-202-79 (NCBI BioSample no. SAMN30015177) from nanopore sequencing data yielded 1 circular chromosome of 5.9-megabase length (GC content 57%; GenBank accession no. CP102780) and 1 plasmid of 80.7 kb length (GC content 63%, 2 copies; GenBank accession no. CP102779).

Table 1. Patient characteristics in an outbreak of *Pandoraea commovens* among non-cystic fibrosis intensive care patients, Germany, 2019–2021*

Characteristics	Value†	IQR
Sex		
M	12 (50)	NA
F	12 (50)	NA
Age, y	67 (45–81)	61–69
Length of stay, d	51 (0–131)	32–105
Discharged alive	17 (74)	NA
Time to detect <i>P. commovens</i> , d	22 (0–131)	11–45
Intensive care unit admission	22 (96)	NA
Invasive ventilation	15 (65)	NA
Renal replacement therapy	7 (30)	NA
Surgery	15 (65)	NA
Antimicrobial drug therapy		
During hospitalization	23 (100)	NA
During previous 3 mo	14 (82)	NA
Immunosuppressed	5 (22)	NA
Charlson Comorbidity Index	6 (0–13)	3–6
Vascular disease or disorder		
Myocardial infarction	4 (17)	NA
Congestive heart failure	14 (61)	NA
Peripheral vascular disease	3 (13)	NA
Cerebrovascular accident	3 (13)	NA
Chronic lung disease	6 (26)	NA
Peptic ulcer disease	1 (4)	NA
Moderate to severe liver disease	3 (13)	NA
Moderate to severe CKD	9 (39)	NA
Diabetes mellitus	5 (22)	NA
Diabetes mellitus with end-organ damage	4 (17)	NA
Cancer		
Solid tumor	2 (9)	NA
Leukemia	2 (9)	NA
Lymphoma	2 (9)	NA

*Data reflect 23 cases, except for sex, median age, and median length of hospitalization (n = 24). CKD, chronic kidney disease.

†Values are no. (%) or median (range).

A search of the plasmid sequence against the NCBI BLAST nucleotide database (<https://blast.ncbi.nlm.nih.gov>) revealed several alignments to the plasmid of *Burkholderia aenigmatica* strain CMCC(B)23010 (GenBank accession no. CP091649.1), totaling ≈ 22 kb and $\approx 99.9\%$ sequence identity. That strain is a member of the *Burkholderia cepacia* complex and was originally isolated from water purified for pharmaceuticals. Apart from that, we only found alignments to transposase genes in *Klebsiella pneumoniae* plasmids.

The annotation of the LB-19-202-79 chromosome yielded 2 β -lactamase family proteins that are also found in the *P. commovens* strain LMG 31010 genome assembly and have $>99\%$ amino acid identity. The β -lactamase with locus tag NTU39_20675 was identified as an oxacillinase (OXA) 62 family carbapenem-hydrolyzing class D enzyme and now is denoted as allele *bla*OXA-1149 in the NCBI Reference Gene Catalog. The β -lactamase with locus tag NTU39_00730 was identified as a class C β -lactamase. We analyzed the complete resistome

Table 3. Antimicrobial susceptibilities of *Pandoraea commovens* isolates in an outbreak among non-cystic fibrosis intensive care patients, Germany, 2019–2021

Antimicrobial drugs tested	MIC, mg/L	Breakpoints, mg/L	
		Susceptible	Resistant
Ampicillin	>32	<2	>8
Ampicillin/sulbactam	≤2	<2	>8
Piperacillin	8 to >128	≤8	>16
Piperacillin/tazobactam	≤1 to >128	≤8	>16
Temocillin	≥128	IE	IE
Cefotaxime	8–16	<1	>2
Ceftazidime	>64	≤4	>8
Cefepime	≥64	≤4	>8
Ceftolozane/tazobactam	16 to >256	<4	>4
Ceftazidime/avibactam	16 to >256	<4	>8
Cefiderocol	>256	<2	>2
Meropenem	1–8	<2	>8
Imipenem	≤0.25 to 1	<2	>4
Imipenem/relebactam	≤1	<2	>2
Ertapenem	<0.5 to ≥8	≤0.5	>0.5
Aztreonam	32 to >128	<4	>8
Aztreonam/avibactam	≥128	NA	NA
Ciprofloxacin	>4	<0.25	>0.5
Moxifloxacin	≥8	≤0.25	>0.25
Gentamicin	8 to ≥16	<0.5	>0.5
Tobramycin	≥16	≤0.5	>0.5
Amikacin	>64	1	>1
TMP/SXT	≤20	IE	IE
Fosfomycin	128 to >256	IE	IE
Colistin	>16	IE	IE
Minocycline	1–4	IE	IE
Tigecycline	1	≤0.5	>0.5
Doxycycline	≥16	IE	IE

*MIC results are from susceptibility testing of 35 *Pandoraea* spp. isolates. The table comprises results of different test methods VITEK 2 (bioMérieux, <https://www.biomerieux.com>), MICRONAUT-S broth microdilution (MERLIN Diagnostika GmbH, <https://www.merlin-diagnostika.de>), and MIC strips (Liofilchem, <https://www.liofilchem.com>). IE, insufficient evidence, no breakpoints available; NA, not applicable; TMP/SXT, trimethoprim/sulfamethoxazole.

†According to pharmacokinetic/pharmacodynamic (non-species related breakpoints from European Committee on Antimicrobial Susceptibility Testing Clinical Breakpoint Tables version 11.0, 2021 (<http://www.eucast.org>).

comprising all genes associated with antimicrobial resistance as determined by the BV-BRC genome annotation (Appendix Table). The complete genome annotation is available at BV-BRC (accession no. 2508289.5; <https://www.bv-brc.org/view/Genome/2508289.5>).

Discussion

We describe a large *Pandoraea* spp. outbreak comprising 24 non-CF patients. In contrast to earlier outbreaks that took place uniformly among CF patients (6,9,12), none of the patients in this outbreak had CF. However, all but 1 patient were treated in an ICU immediately before or during the time when *P. commovens* was isolated. All patients had received antimicrobial drugs before *P. commovens* isolation, and all likely acquired the pathogen in the hospital. Most of the patients had undergone surgery or were on mechanical ventilation, and their overall CCI was high (median 6, range 0–13). Those

observations align with earlier case reports on *Pandoraea* spp. infections among non-CF patients (16–21).

As described by others (35), we experienced difficulties in correctly identifying the species of the outbreak strain. In several cases, *P. commovens* was misidentified as *B. hinzii* by biochemical means. Because *P. commovens* was not identified as a separate species before November 2019 (2), VITEK MALDI-TOF mass spectrometry analysis misidentified the outbreak strain as *P. sputorum*.

Pandoraea spp. can harbor multiple antimicrobial resistance and biodegradation genes, enabling the pathogen to persist in the hospital environment (6). Our resistome analyses and the course of this outbreak that lasted for 2.5 years suggest that *P. commovens* LB-19-202-79 is equipped with such an armament.

Pandoraea spp. exhibit resistance to most antimicrobial agents, including penicillins, cephalosporins, fluoroquinolones, aminoglycosides, and colistin, but frequently are susceptible to imipenem and TMP/SMX (14,36,37). Resistance is mediated by different efflux pumps and β -lactamases with a carbapenem-resistant phenotype observed in isolates carrying OXA-62 or a homologue to OXA-153, both carbapenem-hydrolyzing oxacillinases. OXA-62 hydrolyzes meropenem more efficiently than imipenem, but expanded-spectrum cephalosporins are only poor substrates (5,6,38). Among the β -lactamase family proteins detected in our strain, one was identified as an OXA-62 family carbapenem-hydrolyzing class D β -lactamase, now denoted as OXA-1149. However, all our *P. commovens* isolates were susceptible to imipenem but showed elevated MICs (1–8 mg/L) for meropenem, corresponding to susceptible to increased exposure according to EUCAST PK/PD non-species related breakpoints. The high-level resistance of *P. commovens* to all cephalosporins might at least in part be mediated by the expression of a class C β -lactamase (39). Although all 8 patients with respiratory tract infections recovered with a single course of antimicrobial drugs, the 2 patients with *P. commovens* intraabdominal infections had relapsing courses of disease. *Pandoraea* spp. are environmental bacteria and can thrive in wet settings, such as an abdominal area undergoing multiple surgeries. Under such circumstances, armed with a class D carbapenemase, *P. commovens* LB-19-202-79 might withstand even prolonged targeted antimicrobial treatment, as noted in patient 7 (Appendix).

The assessment of the clinical significance of detection of *P. commovens* in the patients in this outbreak was not always straightforward, especially in cases where *Pandoraea* spp. was cultured from respiratory secretions. Some cases could easily be classified

as colonization, such as when only throat swab samples were positive and patients had no other signs and symptoms of infection. However, *P. commovens* was part of polymicrobial cultures in some patients, and its role in those cases was difficult to estimate. *P. commovens* was the only relevant pathogen that could be detected in 5 of 8 patients with nosocomial pneumonia; however, it was only detected in low to intermediate quantities. Those cases were classified as infections because patients had nosocomial pneumonia, which cleared after administration of targeted antimicrobial drug treatment for *P. commovens*. The pathogenicity of *P. commovens* in the 2 patients with complicated intraabdominal infections seemed evident. *P. commovens* was the predominant pathogen and was repeatedly isolated from different materials, even from blood culture in 1 case.

The first limitation of this study is that we were not able to sequence all *Pandora* spp. isolates from the outbreak. Some uncertainty remains about whether all isolates belonged to the outbreak strain *P. commovens* LB-19-202-79. However, given the identical phenotypic features and the temporal and spatial relationship, we assume the same strain was responsible for all

cases. Second, we were not able to find an environmental source. Third, detection of *Pandora* spp. could not easily be classified as colonization or infection in several patients; however, that is a well-known dilemma when low-virulent pathogens are cultured from non-sterile sites, such as the respiratory tract.

In conclusion, our sequence analysis highlights the advantage of bacterial WGS for exact species identification and typing of outbreak isolates. On the basis of these findings, we conclude that *Pandora* spp. are not only capable of spreading among CF patients, as described before, but also to non-CF patients. The bacteria can also cause outbreaks on ICUs, in particular affecting patients with a history of intensive antimicrobial pretreatment, multiple abdominal surgeries, and mechanical ventilation. This outbreak report underscores the critical role of vigilance among both clinicians and microbiologists when unusual pathogens occur and the need for access to modern molecular sequencing techniques in hospital laboratories.

All sequencing data are available from the NCBI under BioProject no. PRJNA849608.

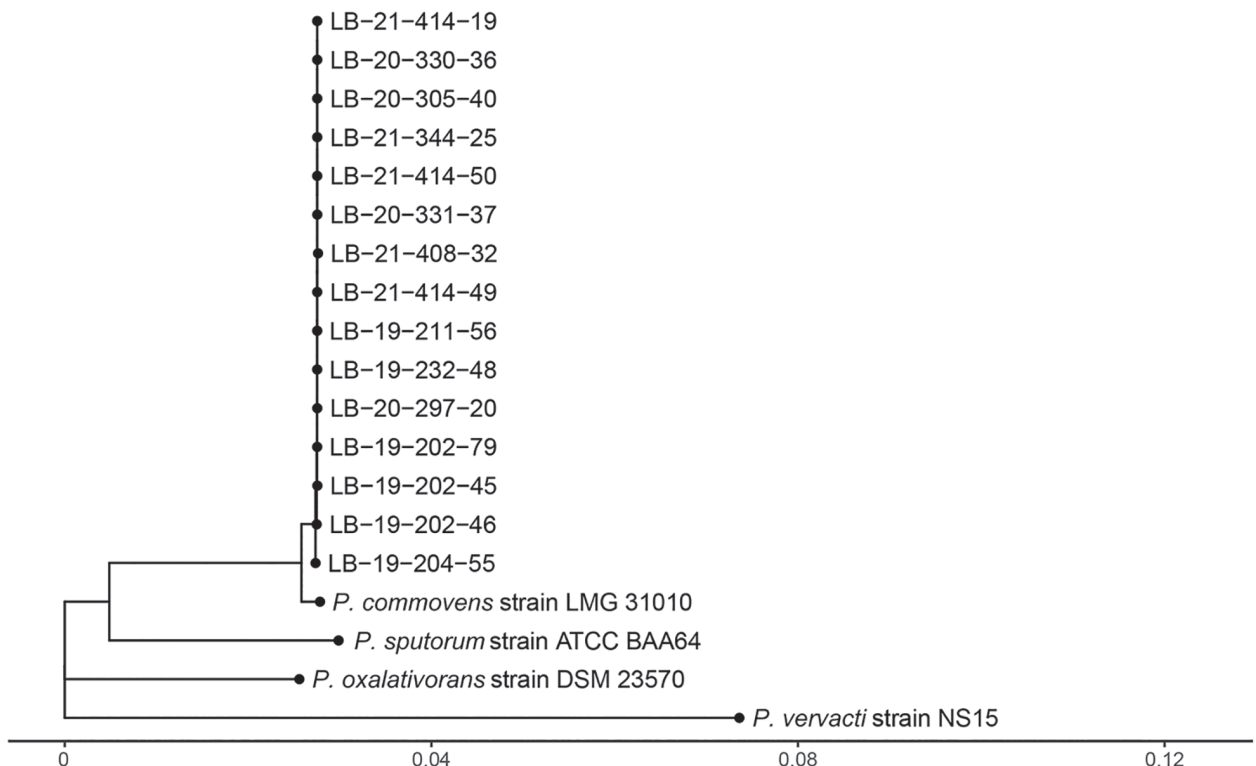


Figure 2. Phylogenetic tree of isolates from an outbreak of *Pandora* *commovens* among non-cystic fibrosis intensive care patients, Germany, 2019–2021. Genome assemblies from 15 isolates (labeled LB) compared with *Pandora* spp. genomes in the National Center for Biotechnology Information RefSeq database (<https://www.ncbi.nlm.nih.gov>) found the genome assembly GCF_902459615.1 of *P. commovens* strain LMG 31010 was the most similar. The tree was created by using neighbor joining the calculated pairwise phylogenetic distances between genome assemblies and available database sequences. Scale bar indicates nucleotide substitutions per site.

About the Author

Dr. Tassilo Kruis is an internist and medical microbiologist at Labor Berlin Charité Vivantes GmbH, Berlin, Germany. His research interests focus on clinical infectious diseases.

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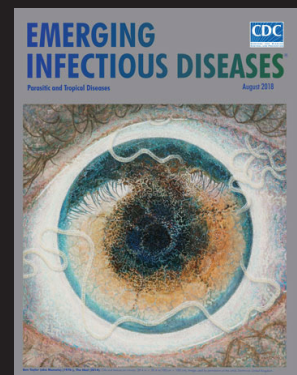
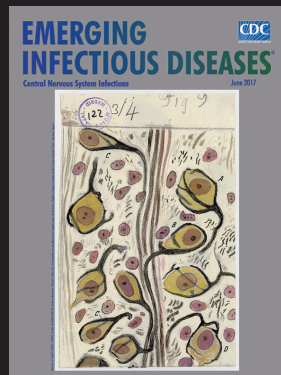
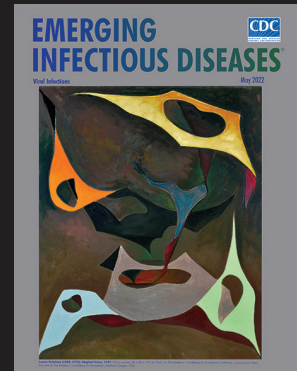
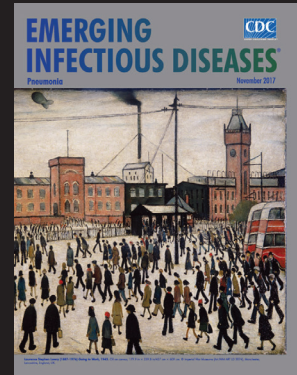
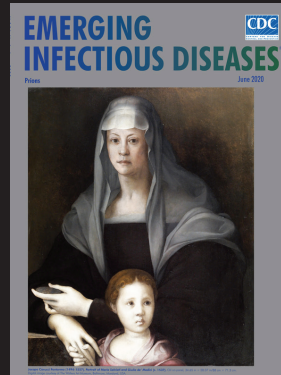
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Address for correspondence: Tassilo Kruijs, Charité Vivantes GmbH, Sylter Str. 2, Berlin 13353, Germany; email: tassilo.kruijs@laborberlin.com

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Outbreak of *Pandoraea commovens* among Non–Cystic Fibrosis Intensive Care Patients, Germany, 2019–2021e

Appendix

Case vignettes

Examples of Difficult Patient Classifications as Infection or Colonization

Patient 4 was an 85-year-old man with coronary heart disease, congestive heart failure, diabetes mellitus, chronic kidney disease, and liver cirrhosis. He was admitted with non–ST-elevation myocardial infarction and acute kidney injury requiring renal replacement therapy. He remained in intensive care for several weeks with several severe complications (e.g., *Candida* spp. blood stream infection, ventilator-associated pneumonia due to *Pseudomonas aeruginosa*, *Clostridioides difficile* infection). Numerous specimens were sent for microbiological investigation. Two respiratory samples 2 days apart grew *P. commovens*. At the time of identification, the patient was mechanically ventilated but did not receive antibiotics apart from caspofungin for *Candida* spp. blood stream infection. Radiology revealed pleural effusions and lung infiltrates, which were both in regression. Three days after the last detection of *P. commovens*, *P. aeruginosa* was cultured from tracheal secretions. The patient’s clinical status deteriorated and meropenem was started. This case was classified as colonization.

Patient 14 was a 60-year-old woman who had undergone hematopoietic stem cell transplantation for acute myeloid leukemia. She was admitted to intensive care with right heart failure due to pulmonary hypertension and acute kidney injury requiring renal replacement therapy. The course in the intensive care unit was complicated by reactivation of cytomegalovirus, pulmonary embolism, and several episodes of nosocomial pneumonia.

Numerous specimens were sent for microbiological investigation. *P. commovens* was cultured from tracheal secretions only once. At the time of identification, imaging of the lung revealed new infiltrates. Concomitantly, values of C-reactive protein rose to 136 mg/l. A diagnosis of nosocomial pneumonia was made and treatment with imipenem was initiated. Values of C-reactive protein declined thereafter, and the patient's clinical condition improved. This case was classified as infection.

Patients with Complicated Intraabdominal Infections

Patient 2 was admitted from an ICU of an external hospital with exudative pancreatitis due to hypercalcemia secondary to primary hyperparathyroidism. On admission, she was in septic shock necessitating fluid resuscitation, high-dose vasopressors, and antimicrobials. Oxygenation was severely impaired with a PaO₂/FIO₂ ratio of 80 mm Hg. Renal failure was addressed with renal replacement therapy. Hyperparathyroidism was treated with cinacalcet and intravenous bisphosphonates. Pancreatic fluid collections were drained. The patient's status stabilized, and she could be transferred to a normal ward. However, the course of the disease remained complicated. She had to be readmitted to the ICU with hypernatremia, intra-abdominal bleeding episodes, and superinfection of the pancreatic fluid collections. The latter required repeated endoscopic necrosectomies. Punctures from the abdomen and the ascites revealed *C. glabrata*, *E. faecium*, *Pandora* spp., *S. maltophilia*, and *S. epidermidis*. The patient received several courses of intravenous antimicrobials. *Pandora* was regarded as relevant as it was repeatedly cultured from normally sterile sites. A 4-week course of meropenem was administered, accompanied by vancomycin and caspofungin to address gram-positive bacteria and fungi, respectively. Thereafter, *Pandora* spp. could not be cultivated anymore from samples sent to the microbiology department. Surgery was eventually performed with resection of the pancreas tail, splenectomy, necrosectomy, and partial gastric resection. Furthermore, an adenoma of the parathyroid was removed. The patient's condition gradually improved following surgery. However, she had severe critical illness myopathy and peripheral neuropathy. After a total of almost 7 months, she could be transferred to rehabilitation.

Patient 7 was also admitted from the ICU of an external hospital. He had previously been healthy apart from a posttraumatic stress disorder and symptomatic gallstones. He developed exudative pancreatitis as a complication after endoscopic retrograde cholangiography (ERC) for the treatment of the gallstones. Initial treatment in the external hospital comprised intravenous

antibiotics, fluids, and analgesics. However, acute respiratory distress syndrome (ARDS) developed, and the patient was transferred to Charité - CVK for further treatment. The treatment in Charité - CVK was long and complicated. Open laparotomies had to be performed on several occasions for necrosectomies, adhesiolyses, abdominal lavage and reconstruction of the abdominal wall. Eventually, subtotal left-sided pancreatectomy, splenectomy, and subtotal colectomy had to be carried out with terminal ileostomy. *Pandoraea commovens* was first isolated from blood culture on day 74 after transfer with exact species identification possible only by whole-genome sequencing. In the following 18 days, *Pandoraea* spp. was also repeatedly isolated from intra-abdominal specimens (together with *C. albicans*, vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, *S. epidermidis*, and *E. cloacae*) and from tracheobronchial secretions (together with *E. cloacae* and *C. albicans*). Susceptibility testing revealed low MICs to imipenem and TMP-SMX. Thus, imipenem was administered for a total of 33 days accompanied by antimicrobials addressing gram-positive bacteria and fungi. TMP-SMX was added after 30 days of imipenem treatment at a dose of 800/160 mg q8h. Two days after stopping imipenem, *P. commovens* was again isolated within a polymicrobial culture from the abdominal cavity. Dosing of TMP-SMX was adjusted to 1600/320 mg q12 and TMP-SMX was given for a total of 30 days. Thereafter, *Pandoraea* spp. could no longer be detected from any specimen during the following 73 days on the ICU. The patient's status remained stable for roughly 2 months and then suddenly deteriorated. Imaging revealed gastric and duodenal perforation and leakage from the remainder of the rectosigmoid. ERC showed perforation of the bile duct. Surgery was deemed impossible. The patient eventually died from multiorgan failure.

Appendix Table. Antimicrobial resistance *Pandoraea commovens*

BRC ID	RefSeq locus tag	Gene	Product	Antimicrobial drugs
fig 2508289.5.peg.4200	NTU39_20675	<i>OXA-62</i>	Class D β -lactamase (EC 3.5.2.6) = >OXA-62 family, carbapenem-hydrolyzing	
fig 2508289.5.peg.5109	NTU39_25115	<i>rpsJ</i>	SSU ribosomal protein S10p (S20e)	
fig 2508289.5.peg.2427	NTU39_12160	<i>dxr</i>	1-deoxy-D-xylulose 5-phosphate reductoisomerase (EC 1.1.1.267)	Fosmidomycin
fig 2508289.5.peg.5396	NTU39_26555	<i>gidB</i>	16S rRNA (guanine(527)-N(7))-methyltransferase (EC 2.1.1.170)	Streptomycin
fig 2508289.5.peg.3124	NTU39_15500	<i>fabG</i>	3-hydroxyacyl-CoA dehydrogenase (EC 1.1.1.35), FabG4	Triclosan
fig 2508289.5.peg.4543	NTU39_22325	<i>kasA</i>	3-oxoacyl-[acyl-carrier-protein] synthase, KASII (EC 2.3.1.179)	Isoniazid, triclosan
fig 2508289.5.peg.2402	NTU39_12040	<i>alr</i>	Alanine racemase (EC 5.1.1.1)	D-cycloserine

BRC ID	RefSeq locus tag	Gene	Product	Antimicrobial drugs
fig 2508289.5.peg.4099	NTU39_20160	<i>AAC(6)-lc,f,g,h,j,k,l,r-z</i>	Aminoglycoside N(6')-acetyltransferase (EC 2.3.1.82) = >AAC(6')-lc,f,g,h,j,k,l,r-z	Tobramycin, kanamycin A, amikacin, dibekacin, sisomicin, gentamicin B, isepamicin, arbekacin, netilmicin, neomycin
fig 2508289.5.peg.4524	NTU39_22235	<i>pgsA</i>	CDP-diacylglycerol-glycerol-3-phosphate 3-phosphatidyltransferase (EC 2.7.8.5)	Daptomycin
fig 2508289.5.peg.68	NTU39_00730		Class C β -lactamase (EC 3.5.2.6)	
fig 2508289.5.peg.4200	NTU39_20675	<i>OXA-62 family</i>	Class D β -lactamase (EC 3.5.2.6) \geq OXA-62 family, carbapenem-hydrolyzing	Oxacillin
fig 2508289.5.peg.4869	NTU39_23905	<i>Ddl</i>	D-alanine-D-alanine ligase (EC 6.3.2.4)	D-cycloserine
fig 2508289.5.peg.1404	NTU39_07215	<i>gyrA</i>	DNA gyrase subunit A (EC 5.99.1.3)	Clofazimine, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, nalidixic acid, ofloxacin, sparfloxacin, trovafloxacin
fig 2508289.5.peg.3	NTU39_00420	<i>gyrB</i>	DNA gyrase subunit B (EC 5.99.1.3)	Clofazimine, gatifloxacin, ciprofloxacin, levofloxacin, moxifloxacin, nalidixic acid, ofloxacin, sparfloxacin, novobiocin, coumermycin A1, clorobiocin, coumermycin, trovafloxacin
fig 2508289.5.peg.2263	NTU39_11380	<i>H-NS</i>	DNA binding protein H-NS	Cloxacillin, oxacillin, ciprofloxacin, norfloxacin, erythromycin, tetracycline
fig 2508289.5.peg.5138	NTU39_25260	<i>rpoB</i>	DNA-directed RNA polymerase β subunit (EC 2.7.7.6)	Rifamycin, daptomycin, rifabutin, rifampin
fig 2508289.5.peg.5137	NTU39_25255	<i>rpoC</i>	DNA-directed RNA polymerase β' subunit (EC 2.7.7.6)	Daptomycin
fig 2508289.5.peg.1925	NTU39_09720	<i>folA, Dfr</i>	Dihydrofolate reductase (EC 1.5.1.3)	Trimethoprim, brodimoprim, tetroxoprim, iclaprim
fig 2508289.5.peg.3664	NTU39_18075	<i>folP</i>	Dihydropteroate synthase (EC 2.5.1.15)	Sulfadiazine, sulfadimidine, sulfadoxine, sulfamethoxazole, sulfisoxazole, sulfacetamide, mafenide, sulfasalazine, sulfamethizole, dapsone
fig 2508289.5.peg.3962	NTU39_19515	<i>fabV</i>	Enoyl-[acyl-carrier-protein] reductase [NADH] (EC 1.3.1.9), FabV \geq refractory to triclosan	Triclosan
fig 2508289.5.peg.1824	NTU39_09235	<i>GdpD</i>	Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46)	Daptomycin

BRC ID	RefSeq locus tag	Gene	Product	Antimicrobial drugs
fig 2508289.5.peg.4177	NTU39_20570	<i>GdpD</i>	Glycerophosphoryl diester phosphodiesterase (EC 3.1.4.46)	Daptomycin
fig 2508289.5.peg.986	NTU39_05160	<i>OxyR</i>	Hydrogen peroxide-inducible genes activator \geq OxyR	Isoniazid
fig 2508289.5.peg.4272	NTU39_21040	<i>Iso-tRNA</i>	Isoleucyl-tRNA synthetase (EC 6.1.1.5)	Mupirocin (pseudomonic acid)
fig 2508289.5.peg.4247	NTU39_20915	<i>MacB</i>	Macrolide export ATP binding/permease protein MacB	Erythromycin
fig 2508289.5.peg.1581	NTU39_08085	<i>MacB</i>	Macrolide export ATP binding/permease protein MacB	Erythromycin
fig 2508289.5.peg.1580	NTU39_08080	<i>MacA</i>	Macrolide-specific efflux protein MacA	Erythromycin
fig 2508289.5.peg.4246	NTU39_20910	<i>MacA</i>	Macrolide-specific efflux protein MacA	Erythromycin
fig 2508289.5.peg.2144	NTU39_10780	<i>MdfA/Cmr</i>	Multidrug efflux pump MdfA/Cmr (of MFS type), broad spectrum	Tetracycline, rhodamine, benzalkonium chloride
fig 2508289.5.peg.2326	NTU39_11700	<i>EmrAB-ToIC</i>	Multidrug efflux system EmrAB-OMF, inner-membrane proton/drug antiporter EmrB (MFS type)	Nalidixic acid
fig 2508289.5.peg.5450	NTU39_26805	<i>EmrAB-ToIC</i>	Multidrug efflux system EmrAB-OMF, inner-membrane proton/drug antiporter EmrB (MFS type)	Nalidixic acid
fig 2508289.5.peg.2327	NTU39_11705	<i>EmrAB-ToIC</i>	Multidrug efflux system EmrAB-OMF, membrane fusion component EmrA	Nalidixic acid
fig 2508289.5.peg.4211	NTU39_20735	<i>MdtABC-ToIC</i>	Multidrug efflux system MdtABC-ToIC, inner-membrane proton/drug antiporter MdtB (RND type)	Novobiocin
fig 2508289.5.peg.2601	NTU39_13000	<i>MdtABC-ToIC</i>	Multidrug efflux system MdtABC-ToIC, inner-membrane proton/drug antiporter MdtB (RND type)	Novobiocin
fig 2508289.5.peg.2600	NTU39_12995	<i>MdtABC-ToIC</i>	Multidrug efflux system MdtABC-ToIC, inner-membrane proton/drug antiporter MdtC (RND type)	Novobiocin
fig 2508289.5.peg.4210	NTU39_20730	<i>MdtABC-ToIC</i>	Multidrug efflux system MdtABC-ToIC, inner-membrane proton/drug antiporter MdtC (RND type)	Novobiocin
fig 2508289.5.peg.2602	NTU39_13005	<i>MdtABC-ToIC</i>	Multidrug efflux system MdtABC-ToIC, membrane fusion component MdtA	Novobiocin
fig 2508289.5.peg.4212	NTU39_20740	<i>MdtABC-ToIC</i>	Multidrug efflux system MdtABC-ToIC, membrane fusion component MdtA	Novobiocin
fig 2508289.5.peg.4135	NTU39_20370	<i>MexXY-OMP</i>	Multidrug efflux system, membrane fusion component \geq MexX of MexXY/AxyXY	Acriflavin, amikacin, arbekacin, chloramphenicol, cefepime, ciprofloxacin, erythromycin, gentamicin C, meropenem, norfloxacin, ofloxacin, tetracycline, tobramycin
fig 2508289.5.peg.4200	NTU39_20675	<i>blaOXA</i>	Class D β -lactamase (EC 3.5.2.6) \geq OXA-62 family, carbapenem-hydrolyzing	
fig 2508289.5.peg.2328	NTU39_11710	<i>EmrAB-OMF</i>	Outer membrane factor (OMF) lipoprotein associated with EmrAB-OMF efflux system	Nalidixic acid
fig 2508289.5.peg.4209	NTU39_20725	<i>MdtABC-OMF</i>	Outer membrane factor (OMF) lipoprotein associated with MdtABC efflux system	Novobiocin
fig 2508289.5.peg.5109	NTU39_25115	<i>S10p</i>	SSU ribosomal protein S10p (S20e)	Tetracycline, tigecycline
fig 2508289.5.peg.5113	NTU39_25135	<i>S12p</i>	SSU ribosomal protein S12p (S23e)	Streptomycin
fig 2508289.5.peg.2157	NTU39_10845	<i>rho</i>	Transcription termination factor Rho	Bicyclomycin
fig 2508289.5.peg.5111	NTU39_25125	<i>EF-G</i>	Translation elongation factor G	Fusidic acid
fig 2508289.5.peg.2255	NTU39_11325	<i>EF-G</i>	Translation elongation factor G	Fusidic acid

BRC ID	RefSeq locus tag	Gene	Product	Antimicrobial drugs
fig 2508289.5.peg.5146	NTU39_25300	<i>EF-Tu</i>	Translation elongation factor Tu	Kirromycin, enacyloxin IIa, pulvomycin
fig 2508289.5.peg.5110	NTU39_25120	<i>EF-Tu</i>	Translation elongation factor Tu	Kirromycin, enacyloxin IIa, pulvomycin
fig 2508289.5.peg.5033	NTU39_24745	<i>MurA</i>	UDP-N-acetylglucosamine 1-carboxyvinyltransferase (EC 2.5.1.7)	Fosfomycin
fig 2508289.5.peg.4598	NTU39_22600	<i>MurA</i>	UDP-N-acetylglucosamine 1-carboxyvinyltransferase (EC 2.5.1.7)	Fosfomycin
fig 2508289.5.peg.2651	NTU39_13235	<i>BcrC</i>	Undecaprenyl-diphosphatase BcrC (EC 3.6.1.27), conveys bacitracin resistance	Bacitracin

*Resistance determined by the Bacterial and Viral Bioinformatics Resource Center (BV-BRC) genome annotation pipeline (<https://www.bv-brc.org>). BRC, Bioinformatics Resource Center; ID, identification.