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ORIGINAL ARTICLE

Clinical and epidemiological features of *Chryseobacterium indologenes* infections: Analysis of 215 cases☆

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KEYWORDS
Chryseobacterium indologenes;
Colistin;
Tigecycline;
Trimethoprim-sulfamethoxazole

Purpose: This study investigates the clinical and epidemiological features of *Chryseobacterium indologenes* infections and antimicrobial susceptibilities of *C indologenes*.
Methods: With 215 *C indologenes* isolates between January 1, 2004 and September 30, 2011, at a medical center, we analyzed the relationship between the prevalence of *C indologenes* infections and total prescription of colistin and tigecycline, clinical manifestation, antibiotic susceptibility, and outcomes.
Results: Colistin and tigecycline were introduced into clinical use at this medical center since August 2006. The increasing numbers of patients with *C indologenes* pneumonia and bacteremia correlated to increased consumption of colistin ($p = 0.018$) or tigecycline ($p = 0.049$). Among patients with bacteremia and pneumonia, the in-hospital mortality rate was 63.6% and 35.2% ($p = 0.015$), respectively. Administration of appropriate antibiotics showed significant benefit in 14-day survival in patients with *C indologenes* bloodstream infection ($p = 0.040$). In bacteremic patients, old cardiovascular accident ($p = 0.036$) and cancer ($p = 0.014$) were the most common comorbidity. The most common co-infection pathogen in patients with *C indologenes* pneumonia was *Acinetobacter baumannii* (36/91, 39.6%), followed by *Pseudomonas aeruginosa* (23/91, 25.3%), carbapenem-resistant *A baumannii* (22/91, 24.2%), and *Klebseilla pneumoniae* (13/91, 14.3%). Antimicrobial susceptibility testing of the

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215 isolates showed that trimethoprim-sulfamethoxazole was the most active agent (susceptibility rate: 87.4%), followed by cefoperazone-sulbactam (48.0%).
Conclusion: The present study showed a trend of increasing prevalence of *C indologenes* infection after introduction of colistin and tigecycline usage. The bacteremia group had higher mortality rate than the pneumonia group. Increasing resistance to piperacillin-tazobactam, ceftazidime, cefepime, and newer fluoroquinolone were noticed in our analysis. Trimethoprim-sulfamethoxazole was a potential antimicrobial agent *in vitro* for *C indologenes*. To avoid collateral damage, we emphasize the importance of antibiotic stewardship program.

Introduction

Chryseobacterium indologenes, formerly known as *Flavobacterium indologenes*, or *Flavobacterium aureum*, belongs to CDC group IIb. It is non-motile, catalase-positive, oxidase-positive, indole-positive, non-glucose-fermenting Gram-negative bacilli. *C indologenes* is a rare pathogen in humans and is not normally present in the human microflora although it is widely distributed in nature.[1] *C indologenes* can cause various types infections, such as bacteremia, pneumonia, meningitis, and artificial shunt infection,[2–7] especially in those who are hospitalized with long-term indwelling devices and prolonged exposure to broad-spectrum antibiotics. With increasing clinical usage of colistin and tigecycline against emerging carbapenem-resistant pathogens, such as *Acinetobacter baumannii*, extended-spectrum β-lactamases-producing *Escherichia coli* and *Klebsiella pneumoniae*, *Chryseobacterium* species have caused significant problems in critical healthcare setting.[8,9] At present, even with the increasing incidence of healthcare-associated infections due to *Chryseobacterium* species other than *C meningosepticum*,[1] there is no "gold standard" or guideline for management of *C indologenes* infection. Vancomycin and aminoglycoside are not effective against *C indologenes*.[1,10] *C indologenes* is also intrinsically resistant to carbapenems and cephalosporins due to its production of molecular class A β-lactamase[11] and class B carbapenem-hydrolyzing β-lactamase (IND1–IND7).[12–15] Susceptibility data to tigecycline, a glycylcycline antibiotic, structurally similar to the minocycline, remain limited.

In this retrospective study, we investigated the trend in *C indologenes* infection after clinical usage of colistin and tigecycline. We also analyzed the clinical manifestations and microbiological characteristics of *C indologenes* infections.

Materials and methods

Clinical data collection

We isolated and identified *C indologenes* isolates from clinical samples, such as bloodstream, central venous catheter (CVC) tip, sputum, wound culture, urine culture, and other aseptic body fluid, between January 1, 2004 and September 30, 2011, at a 732-bed medical center in northern Taiwan. The sputum isolates obtained from a patient with new-onset pneumonia within 14 days and bacteremic isolates from a patient with new-onset bacteremia within 7 days were thought as the same strains and thus excluded.

We retrospectively reviewed the medical records of patients from whose samples *C indologenes* had been isolated. Data on underlying diseases, initial admission diagnosis, the use of indwelling catheters, ventilator, hemodialysis, administration of chemotherapy, infectious complication, and clinical outcome were recorded.

Microbiology

We examined all positive cultures following Gram staining and subcultured them on blood agar plates and eosin–methylene blue agar plates for further identification. The Becton Dickinson Phoenix™ Automated Microbiology System was used to identify the bacterial species according to the manufacturer's instructions. All isolates of *C indologenes*, *Flavobacterium indologenes*, or *Flavobacterium aureum* were included in the study. Only the blood isolates were stored at −70°C in a refrigerator and subcultured twice before further studies.

The minimal inhibitory concentration (MIC) values of cefotaxime, ceftazidime, cefepime, piperacillin-tazobactam, aztreonam, imipenem, meropenem, gentamicin, amikacin, ciprofloxacin, levofloxacin, chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMZ), and colistin were determined using the Becton Dickinson Phoenix™ Automated Microbiology System following the manufacturer's instructions. Susceptibility to cefoperazone-sulbactam and tigecycline was determined using the agar diffusion disk. An inhibition zone of more than 21 mm around a 75–35 μg cefoperazone-sulbactam disk or more than 19 mm by a 15 μg tigecycline disk (the criteria recommended by the U.S. Food and Drug Administration for Enterobacteriaceae) was regarded as susceptible. The MIC values of tigecycline for bacteremic isolates were determined using the E-test, and the susceptibility breakpoints of MICs followed those recommend by the Clinical and Laboratory Standards Institute for *Pseudomonas aeruginosa* and non-Enterobacteriaceae.[16]

Definitions

Significant bacteremia was defined as having the growth of *C indologenes* in one or more blood cultures as well as clinically manifesting signs of systemic inflammatory response syndrome. The manifestations of systemic inflammatory response syndrome include: (1) body

temperature lower than 36°C or greater than 38°C; (2) heart rate greater than 90 beats/min; (3) tachypnea with greater than 20 breaths/min or an arterial partial pressure of carbon dioxide less than 32 mmHg; and (4) white blood cell count of less than 4000 cells/mm^3 or greater than 12,000 cells/mm^3; or the presence of greater than 10% immature neutrophils (band forms). Sputum samples were collected from hospitalized patients with the clinical diagnosis of pneumonia, as evidenced by the presence of fever, productive cough, purulent sputum, or new infiltrations in chest X-ray when compared to previous films, which were reviewed by a chest physiologist. Gram staining was performed on all sputum samples, which all yielded Gram-negative rods with more than 25 polymorphonuclear cells and less than 10 epithelial cells in the low power field (100×) of light microscopy. No pathogens other than *C indologenes*, which showed significant growth in semi-quantitative cultures, were noted. Co-pathogens of *C indologenes* pneumonia were defined as the pathogens in sputum samples within 7 days before or after the isolation of *C indologenes*.

Immunosuppressive therapy was defined as the use of cytotoxic agents or corticosteroids (>30 mg prednisolone daily or equivalent for ≥1 week). Polymicrobial bacteremia was defined as the presence of bacteria or yeasts in addition to *C indologenes* in the blood culture. Prior exposure to antibiotics was defined as enteral or parenteral use of antibiotics for at least 3 days, within 1 week before the isolation of *C indologenes*. Appropriate antibiotic therapy was defined as the use of at least one intravenous antibiotic within 72 hours of the infection onset to which the microorganism was susceptible to the antibiotics. Clinical prescriptions of colistin, tigecycline, and daptomycin were expressed as the total daily doses in 3 months per 1000 patient-days (DDD/1000PD). Mortality due to *C indologenes* bacteremia was defined as death within 14 days of onset of bacteremia with no other identified cause of death.

Statistical analysis

We analyzed the correlation between the consumption colistin, tigecycline, or daptomycin, and the number of patients with *C indologenes* bacteremia and pneumonia by multiple linear regression method. We analyzed the differences between bacteremic and pneumonic patients, with or without appropriate antibiotics using the Pearson chi-square or Fisher's exact test for dichotomous variables, and *t*-test for continuous variables. A significant *p* value was defined as less than 0.05.

Results

After the exclusion of 70 sputum isolates and 10 bacteremic isolates, there were 215 *C indologenes* isolates—including 138 from sputum of 91 patients, 39 from bloodstream of 22 patients, and 38 from other samples of 38 patients—available for the study. The correlation between colistin, tigecycline, or daptomycin consumption and the prevalence of *C indologenes* infections is shown in Fig. 1. The incidence of *C indologenes* increased gradually after 2006 ($P < 0.0001$). The isolate numbers of *C indologenes* were correlated to increasing consumption of colistin ($p = 0.018$) or tigecycline ($p = 0.049$), but not daptomycin ($p = 0.051$). The pulse field-gel electrophoresis profiles of bacteremic *C indologenes* isolates, demonstrated in Fig. 2, showed no cluster among *C indologenes* bacteremic isolates.

As shown in Table 1, there was no apparent statistical difference among patients with bacteremia and pneumonia, in terms of age, length of hospital stay, prior exposure antibiotics, and disease severity [evaluated by Acute Physiology and Chronic Health Evaluation (APACHE) II score]. The only significant factor was male gender which was more common in those with pneumonia than bacteremia (64.8% vs. 40.9%, $p = 0.040$). Patients with *C indologenes* bacteremia had more prior stroke (45.5% vs. 23.1%, $p = 0.035$) and underlying malignancy (50.0% vs. 23.1%, $p = 0.012$) than those with *C indologenes* pneumonia. Other factors, such as ventilator-dependent status, prior corticosteroid exposure, chronic kidney disease, diabetes mellitus, and liver cirrhosis, were not different among the two groups.

Only two (9.1%) patients with *C indologenes* bacteremia and 19 (20.9%) patients with *C indologenes* pneumonia were younger than 65 years. In patients with *C indologenes* bacteremia, there was no documented infective

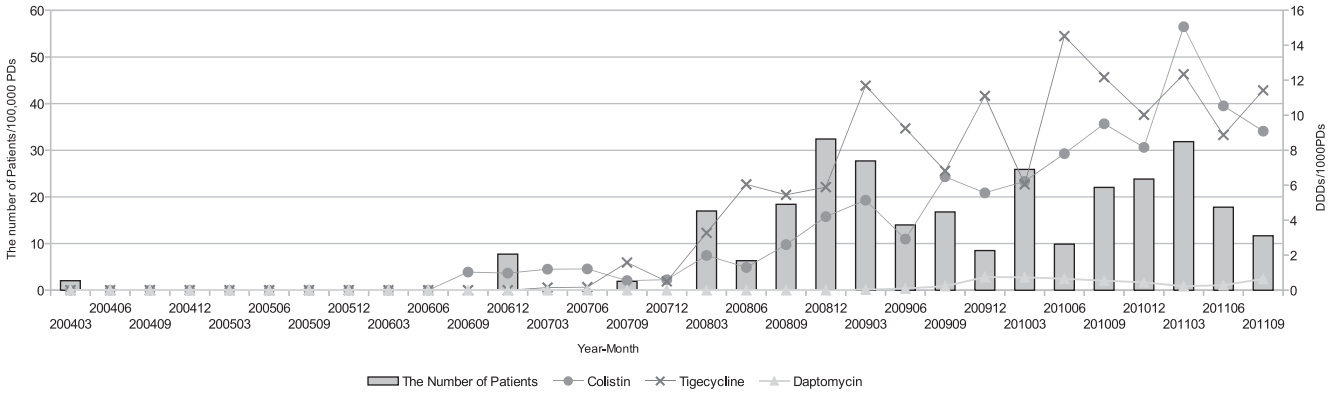

Figure 1. The correlation between colistin, tigecycline, and daptomycin consumption and prevalence of *Chryseobacterium indologenes* infections. Consumption of colistin, tigecycline, and daptomycin is shown, defined as daily dose (DDDs)/1000 patient-days (DDDs/1000 PDs, right *y*-axis). Prevalence rate is calculated as patients' number/100,000 patient-days (left, *y*-axis).

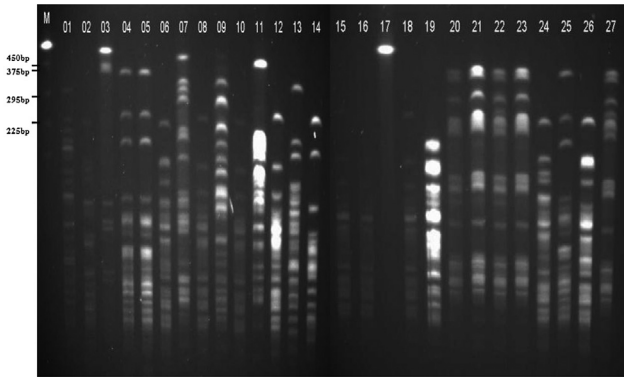

Figure 2. Pulse field-gel electrophoresis (PFGE) profile of bacteremic *Chryseobacterium indologenes* isolates.

endocarditis or neutropenia. Three (13.6%) patients with *C indologenes* bacteremia were thought to have community-acquired infection because the onset of bacteremia occurred less than 48 hours after admission and these patients had no recent hospitalization or visits to the emergency department in the past year. Eighteen (81.8%) of 22 patients with *C indologenes* bacteremia had indwelling CVC and six had CVC-related bloodstream infections, and one had concurrent bacteremia due to methicillin-resistant *Staphylococcus epidermidis*, which was also isolated from the CVC tip. In *C indologenes* bacteremic patients, one had concurrent candidemia, one had *Pseudomonas* bacteremia, and three had *Enterococcus faecalis* bacteremia. In patients with *C indologenes* pneumonia, there was no pleural empyema.

The common co-pathogens (Fig. 3) were *Acinetobacter baumannii* (36 patients; carbapenem-resistant: 22 [61.1%]) and *P aeruginosa* (23 patients; carbapenem-resistant: 10 [43.5%]). The results of *in vitro* susceptibility tests of 16 antimicrobial agents are shown in Tables 2 and 3. TMP-SMZ was the most active agent, followed by cefperazone-sulbactam. A total of six strains of *C indologenes* isolated from wound and cerebrospinal fluid were all susceptible (100%) to TMP-SMZ. However, only two wound isolates were susceptible to cefoperazone-sulbactam, and only one wound isolate was susceptible to ciprofloxacin and levofloxacin.

The mortality rates of patients with bacteremia or pneumonia, with or without appropriate antibiotics

Table 1 Demographic data and clinical manifestations of patients with *Chryseobacterium indologenes* bacteremia and pneumonia

Variables	Bacteremia, $n = 22$	Pneumonia, $n = 91$	p
Age (y)	78.8 ± 12.6	74.8 ± 16.4	0.214
Hospitalization duration (d)	54.6 ± 53.6	70.5 ± 110.5	0.332
APACHE II score	24.4 ± 11.5	21.2 ± 8.40	0.178
Male gender	9 (40.9)	59 (64.8)	0.040
Underlying diseases			
Chronic obstructive pulmonary disease	7 (31.8)	19 (20.9)	0.274
Hypertensive cardiovascular disease	16 (72.7)	54 (59.3)	0.246
Arrhythmia	5 (22.7)	14 (15.4)	0.295
Congestive heart failure	4 (18.2)	17 (18.7)	0.613
Old stroke	10 (45.5)	21 (23.1)	0.035
Chronic kidney disease[a]	10 (45.5)	27 (29.7)	0.157
Liver cirrhosis	2 (9.1)	2 (2.2)	0.170
Malignancy	11 (50.0)	21 (23.1)	0.012
Diabetes mellitus	4 (18.2)	33 (36.3)	0.105
Tracheostomy	6 (27.3)	35 (38.5)	0.327
Ventilator use	14 (63.6)	49 (53.8)	0.407
Corticosteroid	11 (50.0)	34 (37.4)	0.277
Previous antibiotic exposure within 7 d			
Quinolone	6 (27.3)	39 (42.9)	0.180
Broad-spectrum cephalosporin	9 (40.9)	35 (38.5)	0.833
Piperacillin/tazobactam	5 (22.7)	14 (15.4)	0.409
Carbapenem	6 (27.3)	45 (49.5)	0.061
Tigecycline	2 (9.1)	13 (14.3)	0.405
Colistin	1 (4.5)	9 (9.9)	0.381
Clinical outcome			
14-d mortality	8 (36.4)	19 (20.9)	0.126
30-d mortality	11 (50.0)	29 (31.9)	0.110
In-hospital mortality	14 (63.6)	32 (35.2)	0.015

Data are expressed as case numbers (%) or means ± standard deviations.
APACHE = acute physiology and chronic health evaluation.
[a] Include patients depending on renal replacement therapy.

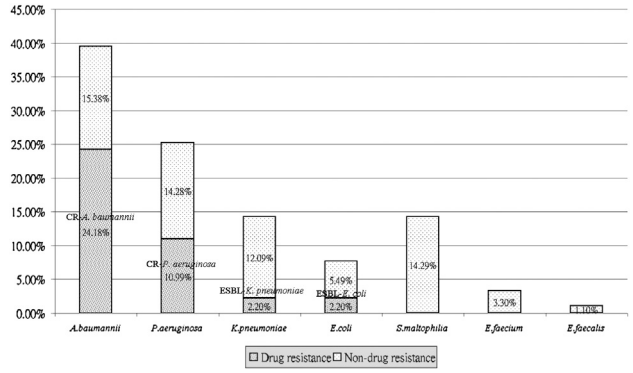

Figure 3. Concurrent pneumonic pathogens among patients with *Chryseobacterium indologenes* pneumonia. CR = carbapenem-resistant; ESBL = extended-spectrum β-lactamases.

treatment, are shown in Table 4. All pneumonic patients received appropriate antibiotics therapy according to the susceptibility for coexisting pathogens, such as *A baumannii*, *P aeruginosa*, *E coli*, *K pneumoniae* and methicillin-resistant *S aureus*. Those patients with *C indologenes* bacteremia had a higher in-hospital mortality rate than those with *C indologenes* pneumonia (63.6% vs. 35.2%, $p = 0.015$) or urinary tract infection (63.6% vs. 25.0%, $P = 0.012$). Even the APACHE II scores were similar in these three groups. Of 22 patients with *C indologenes* bacteremia, eight died within 14 days after onset of bacteremia.

Discussion

As stated previously, *C indologenes* is ubiquitous in nature and is found in soil, plants, food products, and water sources despite adequate chlorination. *C indologenes* is frequently recovered from wet surfaces and water sources in the hospital environment. In 1993, Bonten et al[3] first isolated a strain of *C indologenes* from a tracheal aspirate in a patient with ventilator-associated pneumonia. In 1996, Hsueh et al[1] found increasing incidence of healthcare-associated infection due to *Chryseobacterium* species other than *C meningosepticum* (*Elizabethkingia meningoseptica*). In our study, we introduced colistin and tigecycline into clinical use at this medical center in August 2006. There was only one patient with *C indologenes* bacteremia before August 1, 2006. Thereafter, the prevalence of *C indologenes* greatly increased. After 2006, the numbers of patients with isolated *C indologenes* infection correlated with the increased consumption of colistin and tigecycline. To our knowledge, this study is the first to describe a correlation between *C indologenes* infection and the consumption of colistin and tigecycline.

Chryseobacterium species are known to exhibit resistance to aminoglycosides, tetracyclines, chloramphenicol, erythromycin, clindamycin, and teicoplanin.[1,17,18] Most *Chryseobacterium* isolates are also resistant to colistin.[19] *C indologenes* can produce several kinds of β-lactamase.[11–15] It is possible that *C indologenes* may potentially survive well in the environment, if there is frequent exposure to broad-spectrum antibiotics, such as third- or fourth-generation cephalosporins and carbapenems. Increased use of broad-spectrum antibiotics, such as colistin and tigecycline, especially aerosol colistin therapy, may cause collateral damage and increase healthcare-associated *C indologenes* infections.[8,20]

Nosocomial pneumonia and catheter-related bacteremia accounted for most cases of *C indologenes* infections.[1,21,22] In this study, which included 22 cases of bacteremia, 91 of pneumonia, and 38 of other infections, all but three were healthcare-associated infections. Accordingly, 18 of 22

Table 2 *In vitro* susceptibility of 39 *Chryseobacterium indologenes* isolates from bloodstream

Drugs	MIC (μg/mL)			Susceptibility breakpoint (μg/mL)	Susceptible (%)
	Range	MIC_{50}	MIC_{90}		
Cefotaxime	≤1 to >32	>32	>32	≤8	2.6
Ceftazidime	≤1 to >16	>16	>16	≤8	7.7
Cefepime	≤2 to >16	>16	>16	≤8	7.7
Piperacillin-tazobactam	≤4/4 to >64/4	>64/4	>64/4	≤16/4	25.6
Aztreonam	>16	>16	>16	≤8	0.0
Imipenem	≤1 to >8	>8	>8	≤4	7.7
Meropenem	≤1 to >8	>8	>8	≤4	7.7
Gentamicin	≤2 to >8	>8	>8	≤4	0.0
Amikacin	≤8 to >32	>32	>32	≤16	0.0
Ciprofloxacin	≤0.5 to >2	>2	>2	≤1	41.0
Levofloxacin	≤1 to >8	8	>8	≤2	41.0
Chloramphenicol	≤4 to >16	>16	>16	≤8	5.1
TMP-SMZ	≤0.5/9.5 to >2/38	≤0.5/9.5	1/19	≤2/38	94.9
Colistin	>2	>2	>2	≤1	0.0
Tigecycline[a]	0.125 to 12	2	12	≤2[b]	51.9
Cefoperazone-sulbactam[b]					59.0

MIC = minimal inhibitory concentration; TMP-SMZ = trimethoprim-sulfamethoxazole.
[a] Susceptibility test by E-test; only 27 strains were available for analysis.
[b] Susceptibility test by diffusion disk.

Table 3 Susceptibility of 138 *Chryseobacterium indologenes* isolates from sputum in patients with pneumonia

Drugs	MIC (μg/mL)			Susceptibility breakpoint (μg/mL)	Susceptible (%)
	Range	MIC_{50}	MIC_{90}		
Cefotaxime	≤1 to >32	>32	>32	≤8	2.2
Ceftazidime	≤1 to >16	>16	>16	≤8	2.2
Cefepime	≤2 to >16	>16	>16	≤8	2.2
Piperacillin-tazobactam	≤4/4 to >64/4	>64/4	>64/4	≤16/4	30.5
Aztreonam	>16	>16	>16	≤8	0.7
Imipenem	≤1 to >8	>8	>8	≤4	2.9
Meropenem	≤1 to >8	>8	>8	≤4	8.7
Gentamicin	≤2 to >8	>8	>8	≤4	0.0
Amikacin	≤8 to >32	>32	>32	≤16	0.0
Ciprofloxacin	≤0.5 to >2	>2	>2	≤1	29.0
Levofloxacin	≤1 to >8	8	>8	≤2	32.6
Chloramphenicol	≤4 to >16	>16	>16	≤8	9.4
TMP-SMZ	≤0.5/9.5 to >2/38	≤0.5/9.5	1/19	≤2/38	85.5
Colistin	>2	>2	>2	≤1	0.0
Tigecycline[a]					39.1
Cefoperazone-sulbactam[a]					44.9

MIC = minimal inhibitory concentration; TMP-SMZ = trimethoprim-sulfamethoxazole.
[a] Susceptibility test by diffusion disk.

cases of *C indologenes* bacteremia had CVC (data not shown). Those findings are compatible with the published data,[1,21,22] suggesting that indwelling devices are frequent causes of *C indologenes* bloodstream infection.[7] The production of biofilm on indwelling devices and protease activity may play an important role in the virulence of invasive *C indologenes* infections.[23]

Effective empirical treatment for *C indologenes* infections remains uncertain due to limited data in the literature. In an earlier study conducted by Hsueh et al[1] in 1996, all *C indologenes* isolates from the bloodstream were uniformly susceptible to piperacillin, and 92% isolates were susceptible to cefoperazone, ceftazidime, and minocycline. Susceptibility to TMP-SMZ, ofloxacin, and ciprofloxacin was variable.[1] The isolates were consistently resistant to other β-lactam antibiotics, including aztreonam and imipenem, aminoglycosides, erythromycin, clindamycin, or teicoplanin.[1] In 2004, Kirby et al[10] found that TMP-SMZ, newer fluoroquinolones, ceftazidime, cefepime, and piperacillin-tazobactam showed reasonable activity against more than 80% of the study isolates. In 2010, Lin et al[7] suggested that only newer fluoroquinolones and TMP-SMZ could possibly represent the most appropriate antimicrobial agents. In this study, we found that piperacillin-tazobactam and newer fluoroquinolones are no longer reliable due to decreased susceptibility. On the other hand, TMP-SMZ and cefoperazone-sulbactam remained as reliable antimicrobial agents to *C indologenes*, especially for bloodstream infections. The usefulness of vancomycin against *Chryseobacterium* infections has recently been questioned,[1,10,18,24] and vancomycin has not been included in routine susceptibility testing. However, minocycline has been shown to be active *in vitro* against *C indologenes* isolates, with a susceptible rate of 92−100%.[1,25]

Table 4 Mortality rates in patients with *Chryseobacterium indologenes* bacteremia or pneumonia with or without appropriate antibiotics treatment

	Case no. (%)		*p*
	Appropriate antibiotics	Inappropriate antibiotics	
Bacteremia	9	13	
14-d mortality	1 (11.1)	7 (53.9)	0.040
30-d mortality	3 (33.3)	8 (61.5)	0.193
In-hospital mortality	4 (44.4)	10 (76.9)	0.119
Pneumonia	41	50	
14-d mortality	9 (22.0)	10 (20)	0.820
30-d mortality	13 (33.3)	16 (32)	0.976
In-hospital mortality	16 (39.0)	16 (32)	0.485

There are limited data on susceptibility to tigecycline of *C meningosepticum* isolates.[20] This is the first study to evaluate the susceptibility of *C indologenes* to tigecycline, and 52% of 27 bacteremic isolates were susceptible *in vitro* to tigecycline, as determined by MICs (E-test). However, tigecycline has not been recommended to treat bloodstream infections. Among sputum isolates, the susceptibility rate of tigecycline was higher (39.1%) than that of fluoroquinolones, including levofloxacin (32.6%) and ciprofloxacin (29.0%); thus tigecycline could not be recommended for critically ill patients with presumed *C indologenes* infections. Our study revealed, in comparison with published data, an increased resistance rate of *C indologenes* to previously potent antibiotics, including fluoroquinolones, and we hypothesized that a resistant pattern of *C indologenes* may evolve over time and vary according to different trends of antibiotic usage.[7]

Hsueh et al in 1996[21] suggested that removal of the indwelling device is not necessary for *C indologenes* bacteremia. Lin et al[7] in 2010 also found that *C indologenes* can be eradicated with appropriate antibiotics without removal of CVC. In this study, we found that there was a significant benefit from using appropriate antibiotics for

cases of *C indologenes* bacteremia with or without removal of CVC ($P = 0.04$), although most patients died later due to an underlying disease. However, no significant benefit of appropriate antibiotics was noted for *C indologenes* pneumonia. The reason may be the clinical problem in distinguishing true pathogens from respiratory tract colonization with the results of the growth of *C indologenes* in respiratory secretions. In addition, many patients with pneumonia may have concurrent pathogens other than *C indologenes*. Based on these observations, it is likely that co-infections or colonization by pathogens which secrete carbapenem-hydrolyzing β-lactamase, such as *C indologenes*, can cause higher treatment failure rate and higher mortality rate.[26]

The present study has several limitations. First, this is a retrospective study, and missing data may hide potential risk factors which were not documented in records. Second, the pathogenicity and virulence factors of *C indologenes* remain unclear. Our patients with *C indologenes* isolated from wound, cerebrospinal fluid, or ascites, were not compared due to the limited number of cases. Third, the introduction of an aggressive method for infection control, such as care bundles for catheter-related bloodstream infection or ventilator-associated pneumonia, in the intensive care units since 2009 and the general wards since 2012, may influence the prevalence of *C indologenes* infections. Lastly, the results of susceptibility testing varied because of different testing methods. Disk diffusion methods are especially unreliable, and broth microdilution should be used, if possible.[24] Although the E-test has been suggested as a possible alternative for testing the susceptibility of certain antibiotics,[27] only strains from bloodstream in this study were available and examined. A well-designed prospective study to address these four limitations may be necessary in the future to observe the change of *C indologenes* infections after restricting the use of tigecycline and colistin.

In conclusion, the present study demonstrated the increasing prevalence of *C indologenes* infection since colistin and tigecycline were introduced into clinical use. *C indologenes* bacteremia resulted in a higher mortality rate than pneumonia did, and the therapeutic benefit from appropriate antibiotics was more evident in the former infection entity. According to *in vitro* susceptibility study, TMP-SMZ and cefoperazone-sulbactam may be potential antimicrobial agents for *C indologenes* infections.

Conflicts of interest

All contributing authors declare that they have no conflicts of interest relevant to this article.

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