Original Article

Clinical and molecular characteristics of *Chryseobacterium indologenes* isolates at a teaching hospital in Shanghai, China

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Background: *Chryseobacterium indologenes* (*C. indologenes*) has recently emerged as a cause of life-threatening nosocomial infections in humans. This study aims to investigate the clinical characteristics, homology, and antimicrobial patterns of *C. indologenes* clinical isolates at a teaching hospital in Shanghai, China.

Methods: A total of 135 consecutive non-replicate clinical *C. indologenes* isolates from January 2010 to December 2018 were collected at a tertiary care university hospital in Shanghai, China. Genetic relatedness of the isolates was performed by pulsed-field gel electrophoresis (PFGE). The antimicrobial susceptibility of these isolates was measured by the microdilution broth method. The prevalence of β-lactamase genes was investigated by polymerase chain reaction (PCR), while the quinolone resistance-determining regions (QRDRs) were sequenced.

Results: All 135 *C. indologenes* isolates were collected from hospitalized patients with an average age of 55 years. Most of these clinical isolates were derived from ascites (59.3%) or urine (23.7%) specimens. Eighty (80/135) of the strains were classified as clone D by PFGE. *In vitro* drug susceptibility tests showed that minocycline and trimethoprim-sulfamethoxazole had sound antibacterial effects. However, more than 86% of the tested strains were resistant to cephalosporins (ceftazidime, cefotaxime), β-lactamase/β-lactamase inhibitors (cefoperazone-sulbactam), and carbapenems (meropenem, imipenem). Metallo-β-lactamase bla_{IND} and type A broad-spectrum β-lactamase genes bla_{CIA} were present in 135 and 103 isolates, respectively. The clinical strains in our hospital mainly carried bla_{IND-2} (89.6%, 121/135). Compared with previous studies, these strains had a high rate of resistance to quinolones. The resistance rates to levofloxacin, ciprofloxacin, norfloxacin, gatifloxacin, and nemonoxacin were as high as 83.7–94.8%. The mutations at Ser83Val, Ser83Tyr, and Asp87Gly in the QRDRs of GyrA were significantly related to the resistance of *C. indologenes* to levofloxacin. All but one quinolone-resistant strain contained at least one significant mutation.

Conclusions: This study showed a clonal dissemination of *C. indologenes* isolates in infections at a tertiary care university hospital in Shanghai, China. Minocycline and trimethoprim-sulfamethoxazole had favorable in vitro antibacterial effects. However, the high resistance rate to β-lactams and quinolones was due to carrying β-lactamase (bla_{IND}, bla_{CIA}), and mutations in the QRDRs of GyrA.

Keywords: *Chryseobacterium indologenes* (*C. indologenes*); nosocomial infection; drug resistance; quinolone-resistance determining region

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Introduction

Chryseobacterium indologenes (*C. indologenes*), is a non-lactose fermenting gram-negative bacillus formally classified under the *Flavobacterium* CDC group IIb (1). Since its first identification in 1993 from the tracheal aspirate of a patient with ventilator-associated pneumonia (VAP) as an opportunistic pathogen (2), *C. indologenes* has been notorious for causing nosocomial infections due to its presence in fluid-associated devices which serve as a potential reservoir of infection (3). *C. indologenes* causes many kinds of infections such as catheter-related bacteremia, urinary tract infection, biliary tract infection, peritonitis, surgical wound infection, and hospital-associated pneumonia (HAP), especially in immunocompromised patients (4-7). Nosocomial infections attributable to *C. indologenes* have been increasingly reported in numerous countries and have caused significant morbidity and mortality. A study conducted in Taiwan found that 98% (212/215) of *C. indologenes* infections were nosocomial, and the mortality rates of patients with bacteremia or pneumonia was 35.4% (40/113) (8). More recently, Cantero *et al.* reported an outbreak of *C. indologenes* infections in an intensive care unit of a Spanish hospital where mortality reached 25% (3).

C. indologenes exhibits resistance to the majority of antimicrobial agents such as carbapenems, cephalosporins, aminoglycosides, and chloramphenicol which are used to empirically treat infections caused by other gram-negative bacteria (1,9). Therefore, the infection caused by *C. indologenes* is challenging to manage and often results in unfavorable outcomes (10). In addition, according to the SENTRY Antimicrobial Surveillance Program, clinical *C. indologenes* isolates from Asia generally have higher resistance rates to cephalosporins and carbapenems than other continents (11). The resistance rate of the *Chryseobacterium* species to ceftazidime and imipenem from 1997–2001 in Latin America and North America was 40–42.9% and 73.3–85.7%. In contrast, the resistance rates to ceftazidime and imipenem in Asia manifested as 87.5% and 100% (11). It has been speculated that *C. indologenes* is intrinsically resistant to cephalosporins and carbapenems due to its production of molecular class A β-lactamase bla_{CIA} and class B carbapenem-hydrolyzing β-lactamase bla_{IND} (12,13).

Minocycline, trimethoprim-sulfamethoxazole, and quinolones have demonstrated favorable *in vitro* susceptibility test results. Among them, quinolones were the most active anti-infective agents with susceptibility rates of >95% in the SENTRY program (11). Together with their broad antibacterial spectrum and high tissue concentration, quinolones were recommended for the treatment of *C. indologenes* infections (14). However, the emergence of a quinolones-resistant *C. indologenes* strain has raised concern. It has been recently reported that the susceptibility rates to quinolones of *C. indologenes* isolates obtained in Taiwan during 2005–2017 have dropped to 16.7–19% (15). The quinolone resistance in *C. indologenes* has been attributed to alterations in DNA gyrase.

However, clinical reports and the molecular characterization of *C. indologenes* collected in mainland China are limited, resulting in relatively insufficient clinical evidence for the treatment of infectious diseases caused by the bacteria. This study aimed to explore the clinical characteristics, homology, and antimicrobial patterns of *C. indologenes* clinical isolates from January 2010 to December 2018 at a teaching hospital in Shanghai, China. Moreover, the distribution of bla_{CIA}, $bla_{IND,}$ and the mutation of quinolone resistance-determining regions (QRDRs) were also investigated. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-933).

Methods

Bacterial isolates

A total of 135 consecutive non-replicate clinical *C. indologenes* isolates from January 2010 to December 2018 were collected at a tertiary care university hospital in Shanghai, China. A 16s-rRNA sequence analysis was performed for bacterial identification (type strain, DSM 16777T158; GenBank accession no. LN681561). All the clinical isolates were stored at –80 ℃ prior to use. These isolates were collected from different specimens including ascites, sputum, and urine. Medical records were anonymously collected to review clinical information, including age, sex, hospitalization department, and type of infection acquisition. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Huashan Hospital, Fudan University, China (approval number: KY2017-274). Individual consent for this retrospective analysis was waived. Nosocomial infection was defined as previously reported (16).

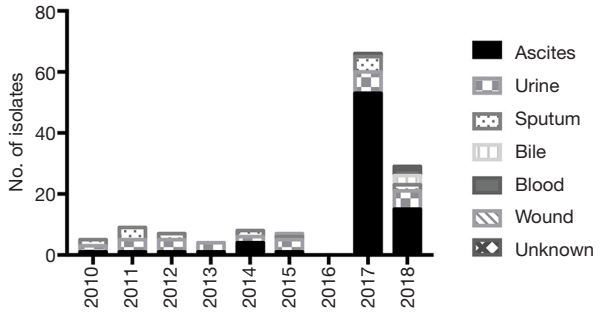

Figure 1 The distribution of 135 *C. indologenes* isolates according to the year and site of isolation. Unknown: missing information.

Homology analysis

The homology analysis of clinical isolates was performed by pulsed-field gel electrophoresis (PFGE). Chromosomal DNA was prepared in agarose blocks and digested with *Xbo*I. DNA fragments were separated by PFGE on a CHEF Mapper XA (Bio-Rad, Hercules, CA, USA) for 19 h at 14 ℃, at 6 V/cm, a pulse angle of 120, and pulse times ranging from 0.5 to 13.6 s. We constructed dendrograms using the Dice coefficient and unweighted pair–group method using average linkage clustering. Isolates were regarded as a joint pulsed-field group if the Dice similarity coefficient >85% in this study. The result was analyzed by BioNumerisc software version 7.6 (Applied-Maths, Belgium)

Antimicrobial susceptibility testing

The minimum inhibitory concentrations (MICs) of 16 antimicrobial agents were measured by the microdilution broth method according to the Clinical and Laboratory Standards Institute 29th edition (CLSI 29th ed.), including cefotaxime, ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem, meropenem, norfloxacin, levofloxacin, gatifloxacin, ciprofloxacin, moxifloxacin, nemonoxacin, amikacin, minocycline, trimethoprim-sulfamethoxazole (TMP-SMZ), and rifampicin (17). *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC27853, and *Enterococcus faecalis* ATCC29212 were used as quality control reference strains. The results were interpreted according to the criteria of "other non-*Enterobacteriaceae*" in CLSI 29th ed., except that the MICs of rifampin were interpreted according to the *Enterococcus* susceptibility breakpoints.

Detection and sequencing of β-lactamase genes and QRDRs

The presence of crucial β-lactamase [bla_{CIA}, bla_{TEM}, bla_{SHV}, $bla_{CTX\text{-}M\ (group1,\ group2,group9)}$, bla_{KPC}, $bla_{OXA48,}$ bla_{IMP}, bla_{VIM}, bla_{NDM}] (12,18,19) and QRDRs (GyrA, GyrB, ParC, and ParE) (15) were amplified and sequenced by polymerase chain reaction (PCR) with primers and PCR conditions as previously described. The primers and PCR conditions for the amplification of bla_{IND} are listed in Table S1.

Statistical analysis

Statistical analysis was conducted by a two-tailed Student's *t*-test or chi-square test with SPSS Statistics 25 software (IBM, https://www.ibm.com), and a P value less than 0.05 was considered statistically significant.

Results

Bacterial isolates and site of isolation

Among 135 clinical *C. indologenes* isolates, 39 strains were isolated from 2010 to 2016, accounting for 28.9%. Since then, there has been a continual growth in the number of isolates. In 2017 and 2018, 66 strains and 30 strains were collected, accounting for 48.9% and 22.2%, respectively (*Figure 1*). The isolates were mainly collected from ascites (77/135, 57.0%) and urine (32/135, 23.7%). Other sites of isolation included sputum (18/135, 13.3%), bile (3/135, 2.2%), blood (2/135, 1.5%), wound secretions (1/135, 0.7%), and two isolates were missing information.

Demographic data and clinical characteristics

The demographic data and clinical characteristics of the 135 *C. indologenes* infections are summarized in *Table 1*. Male patients predominated (97/135, 71.9%), and the mean age was 55 years (range, 5–98 years), with 36 patients over 65 years. Most of these patients came from the general surgery department (79/135, 58.5%), followed by the intensive care unit (ICU) (8/135, 5.9%), the neurosurgery department (8/135, 5.9%), and the gerontology department (7/135, 5.2%). Remaining patients came from other departments including the infectious disease, nephrology, hematology, neurology and pneumology departments. Nosocomial infection accounted for the vast majority (84.4%, 114/135), three infections were identified as

Table 1 Demographic data and clinical characteristics of patients with *Chryseobacterium indologenes* infection

Variables	Total (n=135)
Sex, n (%)	
Male	97 (71.9)
Female	38 (28.1)
Age	
Range, years	5–98
Median, years	55
Age ≥65, n (%)	36 (26.7)
Department, n (%)	
General surgery	79 (58.5)
Intensive care unit	8 (5.9)
Neurosurgery	8 (5.9)
Gerontology	7 (5.2)
Infectious disease	5 (3.7)
Nephrology	4 (3.0)
Hematology	3 (2.2)
Neurology	2 (1.5)
Pneumology	1 (0.7)
Others*	18 (13.3)
Type of infection acquisition, n (%)	
Community-acquired	3 (2.2)
Healthcare-associated	114 (84.4)
Unclear*	18 (13.3)

*, information was hard to ascertain due to missing data.

community-acquired, while others remained difficult to ascertain due to lack of information.

Homology analysis

The homology analysis of 135 *C. indologenes* isolates was determined by PFGE. With a similarity coefficient of 85% as a cutoff value, eight significant clusters were found (*Figure 2*). Among them, the D type was the most prevalent, accounting for 59.3% (80/135), followed by the H and E types which accounted for 23.0% (31/135) and 8.9% (12/135), respectively.

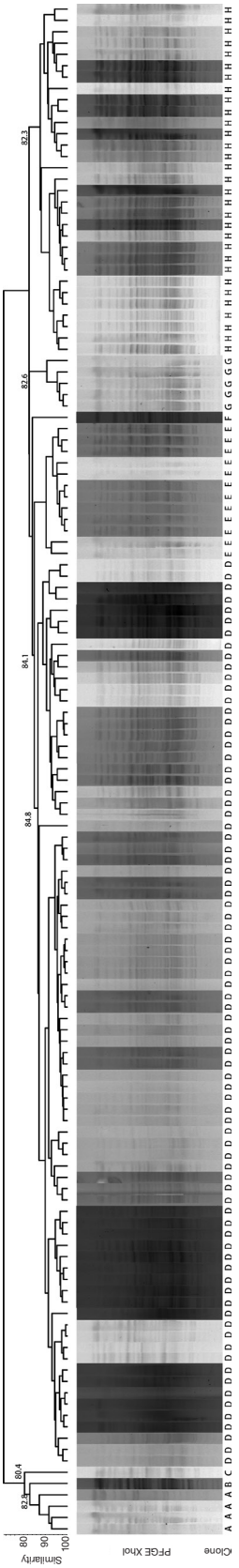

Figure 2 Dendrogram generated from the analysis of 135 C. indologenes isolates.

Table 2 Antimicrobial susceptibility of 135 *Chryseobacterium indologenes* isolates (μg/mL)

Antimicrobial agent	S (%)	I (%)	R (%)	MIC_{50}	MIC_{90}	Susceptibility breakpoint	MIC range
Cefotaxime	0.0	5.9	94.1	>128	>128	≤8	1–128
Ceftazidime	6.7	5.9	87.4	>128	>128	≤8	1–128
Piperacillin-tazobactam	37.0	9.6	53.3	>128/4	>128/4	≤16/4	1/4–128/4
Cefoperazone-sulbactam	10.4	3.0	86.7	>128/64	>128/64	≤8/4	1/0.5–128/64
Imipenem	0.7	1.5	97.8	>64	>64	≤4	0.5–64
Meropenem	0.0	2.2	97.8	>64	>64	≤4	0.5–64
Norfloxacin	13.3	3.0	83.7	>32	>32	≤2	0.25–32
Levofloxacin	14.8	0.7	84.4	32	>32	≤2	0.25–32
Gatifloxacin	14.1	1.5	84.4	>32	>32	≤2	0.25–32
Ciprofloxacin	12.6	0.7	86.7	>32	>32	≤1	0.25–32
Moxifloxacin	23.7	20.0	56.3	8	>32	≤2	0.25–32
Nemonoxacin	5.2	0.0	94.8	>32	>32	≤2	0.25–32
Amikacin	0.7	1.5	97.8	>128	>128	≤16	1–128
Minocycline	98.5	0.7	0.7	2	4	≤4	0.5–64
TMP-SMZ	97.8	0.0	2.2	0.5/9.5	1/19	≤2/38	0.125/2.375–16/304
Rifampicin	72.6	3.7	23.7	0.5	16	≤1	0.25–32

S, susceptible; I, intermediate; R, resistant; MIC, minimal inhibitory concentration; MIC_{50}, minimal inhibitory concentration for 50% isolates; MIC_{90}, minimal inhibitory concentration for 50% isolates; TMP-SMZ, trimethoprim-sulfamethoxazole.

Antimicrobial susceptibility testing

The MICs results of 16 antimicrobial agents are shown in *Table 2*. Minocycline and trimethoprim/sulfamethoxazole appeared to be the most potent antimicrobial agents against *C. indologenes*, with a low resistance rate of 0.7% (1/135) and 2.2% (3/135), respectively. Rifampicin also showed a good antibacterial effect (resistance rate 23.7%). More than 86% of the tested strains were resistant to cephalosporins (cefotaxime and ceftazidime), β-lactamase/β-lactamase inhibitors (cefoperazone-sulbactam), carbapenems (meropenem and imipenem), and aminoglycosides (amikacin). Furthermore, most *C. indologenes* clinical isolates were resistant to quinolones, and the resistance rates to norfloxacin, levofloxacin, gatifloxacin, and ciprofloxacin were all over 83%, followed by moxifloxacin (resistance rate 56.3%). We also tested the new fluorine-free quinolone nemonoxacin. However, the result was unsatisfactory with a drug resistance rate of 94.8%. At the same time when the high level of resistance to quinolones was detected, the MIC_{50} values of norfloxacin, levofloxacin, gatifloxacin, ciprofloxacin, and nemonoxacin were >32 μg/mL.

Detection of β-lactamase genes

All *C. indologenes* isolates carried the metallo-β-lactamase bla_{IND}, and the type A broad-spectrum β-lactamase bla_{CIA} was present in 103 isolates. According to the sequence results, bla_{IND-2} was found in 121 (89.6%) isolates, which accounted for the majority, followed by bla_{IND-7} (n=4), bla_{IND-3} (n=3), bla_{IND-14} (n=3), bla_{IND-5} (n=2), bla_{IND-8} (n=1), and bla_{IND-11} (n=1). None of these isolates had a combination of more than two types of bla_{IND}. No bla_{TEM}, bla_{SHV}, bla_{CTX-M} (group 1, group 2, group 9), bla_{KPC}, bla_{OXA48}, bla_{IMP}, bla_{VIM}, bla_{NDM} were detected.

Table 3 Amino acid alterations in the quinolone resistance-determining regions of *Chryseobacterium indologenes* isolates

Amino acid	Susceptibility of levofloxacin, n (%)		P value
	Susceptible (n=20)	Non-susceptible (n=115)	
Position 83 of GyrA			
Serine	20 (100.0)	2 (1.7)	<0.001
Valine	0 (0.0)	50 (43.5)	<0.001
Tyrosine	0 (0.0)	60 (52.2)	<0.001
Phenylalanine	0 (0.0)	3 (2.6)	>0.999
Position 87 of GyrA			
Aspartic acid	19 (95.0)	53 (46.1)	<0.001
Glycine	1 (5.0)	62 (53.9)	
Position 425 of GyrB			
Leucine	2 (10.0)	2 (1.7)	0.1044
Isoleucine	18 (90.0)	113 (98.3)	
Position 473 of GyrB			
Lysine	2 (10.0)	2 (1.7)	0.1044
Arginine	18 (90.0)	113 (98.3)	
Position 539 of ParE			
Valine	20 (100.0)	105 (91.3)	0.3575
Isoleucine	0 (0.0)	10 (8.7)	

Mutations in the QRDRs

The mutations of amino acids in the QRDRs of *C. indologenes* are shown in *Table 3*. QRDR mutations of GyrA, GyrB, and ParE were detected. In the QRDR of GyrA, among the 115 levofloxacin non-susceptible isolates, 60 isolates carried mutations at Ser83Tyr, 50 isolates carried mutations at Ser83Val, 3 isolates carried mutations at Ser83Phe, and 62 isolates carried the mutation at Asp87Gly in GyrA. Compared with susceptible isolates, mutations at Ser83Tyr, Ser83Val, and Asp87Gly were significantly correlated with levofloxacin non-susceptibility (P<0.001). Amino acid mutations were detected in GyrB at codons 425 and 473, and in ParE at codon 539 but these mutations were not significantly related to the susceptibility of levofloxacin (P=0.081, P=0.081, P=0.362). No amino acid mutation was found in ParC. It is noteworthy that all but one resistant strain contained at least one significant mutation.

Analysis of quinolones-resistant level

The connection between the level of quinolones resistance and significant amino acid mutations at codons 83 and 87 of GyrA were analyzed. As shown in *Table 4*, the strain with a single amino acid substitution in GyrA at Ser83Val (n=50) and Ser83Tyr (n=1) was moderately resistant to levofloxacin (MIC_{50} =8 μg/mL). The isolates had two mutations in GyrA at Ser83Tyr and Asp87Gly (n=59) and showed a high level of levofloxacin resistance (MIC_{50} >32 μg/mL). We also found three strains carrying substitutions in GyrA at Phe83Ser and Asp87Gly. Although Phe83Ser was not related to levofloxacin resistance, the strains containing these two mutations also showed high levels of resistance (MIC_{50} >32 μg/mL). Strains carrying the GyrA subunit double-site mutations showed a 4–32 times higher MIC value for quinolones than the single-point mutation strains. The same trend was observed in gatifloxacin, ciprofloxacin, and moxifloxacin.

Table 4 The correlation between amino acid mutations at different sites of GyrA and MIC_{50} (μg/mL) of quinolones

No. amino acid mutation	No. isolates (n)	Amino acid of GyrA		MIC range (MIC_{50})			
		83	87	Levofloxacin	Ciprofloxacin	Gatifloxacin	Moxifloxacin
Wild	21	–	–	≤0.25–32 (0.5)	≤0.25–>32 (0.5)	≤0.25–16 [1]	≤0.25–8 (≤0.25)
1	1	–	Asp87Gly	1	1	1	0.5
1	50	Ser83Val	–	8–16 [8]	16–>32 [32]	4->32 [8]	2–32 [4]
1	1	Ser83Tyr	-	8	32	32	4
2	3	Ser83Phe	Asp87Gly	32–>32 (>32)	>32	16–>32 (>32)	8–>32 (>32)
2	59	Ser83Tyr	Asp87Gly	8–>32 (>32)	>32	8–>32 [32]	4–>32 [16]

MIC_{50}, minimal inhibitory concentration for 50% isolates.

Discussion

C. indologenes is widely distributed in plants, soil and water, and in the past was rarely considered a human pathogen (9). Based on a PUBMED literature search using the keywords '*Chryseobacterium indologenes* infections', we identified 44 studies published in the period 2010–2019 which are summarized in Table S2. Analysis of the scientific literature suggests that the highest frequency of *C. indologenes* infections occurs in Asia, several clinical cases were occurred in North America, South America, and Europe. *C. indologenes* infections were mainly sporadic, sometimes outbreaks could also be a threat in hospital. Susceptible populations are mainly infants (especially premature babies), the elderly, long-term hospitalized patients, patients with serious underlying diseases or immunocompromised. *C. indologene* can cause multiple types of infection, the most frequently reported infections were pneumonia and bacteraemia. The long-term indwelling devices especially tracheal tubes and intravascular catheters increased the risk of infection. It is worth noting that *C. indologenes* infections have also been gradually appearing in patients with normal immunity and no catheter implantation. In this study, we conducted a 9-year retrospective study and described a clonal dissemination of hospital-acquired infection caused by *C. indologenes*. Our findings are in accord with previous literature indicating that most cases of *C. indologenes* are due to nosocomial infection. It should be stressed that *C. indologenes* can be colonized and spread in the hospital environment through contaminated and humid medical equipment (20). Furthermore, with the development of medical technology and the increased use of various invasive procedures and broad-spectrum antibacterial drugs, there has been a phenomenal growth of nosocomial infection caused by *C. indologenes* (9). The clonal dissemination of multidrug-resistant bacteria in hospitals has become a public health problem that jeopardizes patients and increases medical burden. This is the first report to describe a clonal dissemination of *C. indologenes* in mainland China. According to our results, this clonal dissemination was related to an intra-abdominal infection after liver transplantation in the general surgery department, which highlights the need for active surveillance and implementation of infection control measures.

The susceptibilities of *C. indologenes* vary dramatically from one region to another, making it difficult to choose an effective drug for empirical treatment (11). Previous studies have demonstrated that *Chryseobacterium* sepsis is nearly uniformly resistant to extended-spectrum penicillin, aztreonam, cephalosporins, imipenem, meropenem, chloramphenicol, and aminoglycosides. Quinolones, minocycline, rifampicin, and trimethoprim-sulfamethoxazole are, however, usually effective (7,8,10,21). Quinolones used to be considered an appropriate antimicrobial agent to treat *C. indologenes* infections (22). However, according to a recent study, the resistance rate to quinolones is rising, especially for those strains isolated in Asia. In our study, *in vitro* drug susceptibility tests showed that minocycline and trimethoprim-sulfamethoxazole had sound antibacterial effects on *C. indologenes*, with resistance rates of 0.7% and 2.2%, respectively. Cephalosporins, β-lactam/β-lactamase inhibitors, carbapenems, and aminoglycosides showed insufficient activity against these pathogens, and our study showed a much higher resistance rate to these antimicrobial agents than previous reports. Moreover, the high resistance rate to quinolones suggested that they were no longer an appropriate choice. It is noteworthy that our study showed the lowest susceptibility

to ciprofloxacin compared with other Asian studies (12.6% *vs.* 14.7–68%) (10,15,22,23).

Our study revealed that *C. indologenes* displayed an increased rate of resistance to previously potent antibiotics. Hence, we investigated the resistant mechanism of β-lactams and fluoroquinolones. Usually, *C. indologenes* shows intrinsic resistance to carbapenems and cephalosporins as a result of molecular class A β-lactamase bla_{CIA} and class B carbapenem-hydrolyzing β-lactamase bla_{IND}. These two β-lactamases are peculiar to the *Chryseobacterium* species. Lin *et al.* detected bla_{IND1-4} in clinical isolates of *C. indologenes* during 2004 to 2006 in Hefei, China, and reported that bla_{IND1} (32.1%, 9/28) and bla_{IND2} (35.7%, 10 /28) were the most prevalent (23). To date, twelve new bla_{IND} alleles have been registered in GenBank, but as yet no investigation of the prevalence of all 16 bla_{IND} alleles and bla_{CIA} in clinical isolates has been conducted. In our study, we found that all isolates carried $bla_{IND,}$ and 76.2% (103/135) of isolates carried bla_{CIA}. The dominant genotype was bla_{IND-2}, accounting for 89.6% (121/135).

The mechanism of resistance to quinolones is mainly caused by mutations in QRDRs (GyrA, GyrB, ParC, and ParE subunits), efflux pumps (QepA and OqxAB), DNA topoisomerase protection protein Qnr, and quinolone acetyltransferase Aac (6')-Ib-cr (24-27). The gene mutations in QRDRs resulting in changes of the enzyme's affinity for quinolone is the primary resistant mechanism of quinolones (28). Quinolone resistance in *C. indologenes* was previously identified to be associated with the alterations in DNA gyrase. A study reported that mutations of Ser83Tyr and Asp87Tyr in the GyrA subunit lead to the non-susceptibility of *C. indologenes* ($P<0.001$, $P=0.018$) (15). In this study, we found that both the mutations at codons 83 and 87 of the GyrA were associated with quinolones resistance ($P<0.001$), and the mutation types were Ser83Val, Ser83Tyr, and Asp87Gly. When the hydroxyl-containing serine at position 83 of the GyrA mutates into valine or tyrosine, it will affect the formation of hydrogen bonds and the replacement of aliphatic chains. After replacing aspartic acid at position 87 with glycine, the negatively charged amino acids are replaced by uncharged amino acids, and the charge of the peptide chain changes accordingly. These changes in amino acids verify that the formation of hydrogen bonds and the presence of negatively charged amino acids play a vital role in the interaction of quinolones with gyrase-DNA complexes (26). This is the first study to report that Ser83Val and Asp87Gly are associated with quinolones resistance of *C. indologenes*. Among the *Enterobacteriaceae*, the most frequently identified mutations in GyrA were at codons 83 and 87 (29). Notably, double mutations in GyrA are related to high levels of resistance to fluoroquinolones in *Escherichia coli* isolates (30). We detected a similar phenomenon in *C. indologenes* insofar as double amino acid alterations in the QRDRs of GyrA were significantly associated with high levels of quinolones resistance.

The present results were limited by small sample size and retrospective single-center study design. A prospective multi-center study should be conducted to monitor antimicrobial agent resistance pattern and mechanisms of *C. indologenes*. In conclusion, this study reveals the clinical characteristics and antimicrobial susceptibility patterns of *C. indologenes*. A clonal dissemination of *C. indologenes* in Huashan Hospital has been observed. Minocycline and TMP-SMZ were the most suitable antimicrobial agents to treat infections caused by this pathogen. An increased resistance rate to β-lactams and quinolones was exhibited compared with previous studies. The resistance mechanism of β-lactams in *C. indologenes* is mediated by bla_{CIA} and bla_{IND}. The resistance mechanism of quinolones is related to amino acid mutations in the quinolone resistance-determining region of the GyrA subunit.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-933

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appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Huashan Hospital, Fudan University, China (approval number: KY2017-274). Individual consent for this retrospective analysis was waived.

References

1. Fraser SL, Jorgensen JH. Reappraisal of the antimicrobial susceptibilities of Chryseobacterium and Flavobacterium species and methods for reliable susceptibility testing. Antimicrob Agents Chemother 1997;41:2738-41.
2. Bonten MJ, van Tiel FH, van der Geest S, et al. Topical antimicrobial prophylaxis of nosocomial pneumonia in mechanically ventilated patients. Microbiological observations. Infection 1993;21:137-9.
3. Cantero M, Parra LM, Munez E, et al. A cluster of Chryseobacterium indologenes cases related to drainage water in intensive care units. Infect Control Hosp Epidemiol 2018;39:997-9.
4. Lambiase A, Del Pezzo M, Raia V, et al. Chryseobacterium respiratory tract infections in patients with cystic fibrosis. J Infect 2007;55:518-23.
5. Antonello VS, Daht P, Polli J, et al. Ventilator-associated pneumonia in neonatal intensive care unit due to Chryseobacterium indologenes. Pediatr Infect Dis J 2017;36:e353-e355.
6. González-Castro A, Alsasua A, Peñasco Y, et al. Tracheo-bronchitis and pneumonia associated with mechanical ventilation by Chryseobacterium indologenes. Rev Esp Anestesiol Reanim 2017;64:294-8.
7. Esposito S, Russo E, De Simone G, et al. Transient bacteraemia due to Chryseobacterium indologenes in an immunocompetent patient: a case report and literature review. J Chemother 2015;27:324-9.
8. Chen FL, Wang GC, Teng SO, et al. Clinical and epidemiological features of Chryseobacterium indologenes infections: analysis of 215 cases. J Microbiol Immunol Infect 2013;46:425-32.
9. Hsueh PR, Teng LJ, Yang PC, et al. Increasing incidence of nosocomial Chryseobacterium indologenes infections in Taiwan. Eur J Clin Microbiol Infect Dis 1997;16:568-74.
10. Chang YC, Lo HH, Hsieh HY, et al. Identification, epidemiological relatedness, and biofilm formation of clinical Chryseobacterium indologenes isolates from central Taiwan. J Microbiol Immunol Infect 2015;48:559-64.
11. Kirby JT, Sader HS, Walsh TR, et al. Antimicrobial susceptibility and epidemiology of a worldwide collection of Chryseobacterium spp: report from the SENTRY Antimicrobial Surveillance Program (1997-2001). J Clin Microbiol 2004;42:445-8.
12. Matsumoto T, Nagata M, Ishimine N, et al. Characterization of CIA-1, an Ambler class A extended-spectrum beta-lactamase from Chryseobacterium indologenes. Antimicrob Agents Chemother 2012;56:588-90.
13. Bellais S, Léotard S, Poirel L, et al. Molecular characterization of a carbapenem-hydrolyzing beta-lactamase from Chryseobacterium (Flavobacterium) indologenes. FEMS Microbiol Lett 1999;171:127-32.
14. Lin YT, Jeng YY, Lin ML, et al. Clinical and microbiological characteristics of Chryseobacterium indologenes bacteremia. J Microbiol Immunol Infect 2010;43:498-505.
15. Lin JN, Lai CH, Yang CH, et al. Differences in clinical manifestations, antimicrobial susceptibility patterns, and mutations of fluoroquinolone target genes between Chryseobacterium gleum and Chryseobacterium indologenes. Antimicrob Agents Chemother 2019;63:e02256-18.
16. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309-32.
17. Wayne P; Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-ninth Informational Supplement M100-S29. CLSI, 2019, USA.
18. Poirel L, Walsh TR, Cuvillier V, et al. Multiplex PCR for detection of acquired carbapenemase genes. Diagn Microbiol Infect Dis 2011;70:119-23.
19. Dallenne C, Da Costa A, Decre D, et al. Development of a set of multiplex PCR assays for the detection of genes

encoding important beta-lactamases in Enterobacteriaceae. J Antimicrob Chemother 2010;65:490-5.
20. Beattie RE, Skwor T, Hristova KR. Survivor microbial populations in post-chlorinated wastewater are strongly associated with untreated hospital sewage and include ceftazidime and meropenem resistant populations. Sci Total Environ 2020;740:140186.
21. Mirza HC, Tuncer O, Olmez S, et al. Clinical strains of Chryseobacterium and Elizabethkingia spp. isolated from pediatric patients in a university hospital: performance of MALDI-TOF MS-based identification, antimicrobial susceptibilities, and baseline patient characteristics. Microb Drug Resist 2018;24:816-21.
22. Liang CY, Yang CH, Lai CH, et al. Genomic features, comparative genomic analysis, and antimicrobial susceptibility patterns of Chryseobacterium arthrosphaerae strain ED882-96 isolated in Taiwan. Genes 2019;10:309.
23. Lin XH, Xu YH, Cheng J, et al. Heterogeneity of bla(IND) metallo-beta-lactamase-producing Chryseobacterium indologenes isolates detected in Hefei, China. Int J Antimicrob Agents 2008;32:398-400.
24. Yamane K, Wachino J, Suzuki S, et al. New plasmid-mediated fluoroquinolone efflux pump, QepA, found in an Escherichia coli clinical isolate. Antimicrob Agents Chemother 2007;51:3354-60.
25. Kim HB, Wang M, Park CH, et al. oqxAB encoding a multidrug efflux pump in human clinical isolates of Enterobacteriaceae. Antimicrob Agents Chemother 2009;53:3582-4.
26. Hooper DC, Jacoby GA. Topoisomerase inhibitors: fluoroquinolone mechanisms of action and resistance. Cold Spring Harb Perspect Med 2016;6:a025320.
27. Nordmann P, Poirel L. Emergence of plasmid-mediated resistance to quinolones in Enterobacteriaceae. J Antimicrob Chemother 2005;56:463-9.
28. Hooper DC. Mechanisms of action of antimicrobials: focus on fluoroquinolones. Clin Infect Dis 2001;32 Suppl 1:S9-S15.
29. Ostrer L, Khodursky RF, Johnson JR, et al. Analysis of mutational patterns in quinolone resistance-determining regions of GyrA and ParC of clinical isolates. Int J Antimicrob Agents 2019;53:318-24.
30. Vila J, Ruiz J, Marco F, et al. Association between double mutation in gyrA gene of ciprofloxacin-resistant clinical isolates of Escherichia coli and MICs. Antimicrob Agents Chemother 1994;38:2477-9.

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Supplementary

Table S1 The primers and PCR conditions for the amplification of *bla*$_{IND}$

Gene	Primer	Sequence(5'-3')	Amplicon size	Reference
bla_{IND-1}, bla_{IND-7}	IND-1/7F	TGTTGAGCCCTTTTGCAAGT	460 bp	This study
	IND-1/7R	ATCATGGGAGTGTGTGGCAA		
bla_{IND-2}, $bla_{IND-11to13}$, bla_{IND-15}	IND-2F	ATGAAAAAAAAGTATTCAGCTTTTG	732 bp	(1)
	IND-2R	TTATTCCGGCTTTTTATTCTTATC		
bla_{IND-3}, bla_{IND-5}, bla_{IND-14}	IND-3F	ATGAAAAAAAAGAATTCAGTTC	720 bp	(1)
	IND-3R	TTATTTTTTGTTAAGAAGTTC		
bla_{IND-4}	IND-4F	CCTTCGGAGTTTTTGACGGC	367 bp	This study
	IND-4R	CCTTCGGAGTTTTTGACGGC		
bla_{IND-5}	IND-5F	AACAGGAAAGCCTTACCGCA	277 bp	This study
	IND-5R	CTCAACATGTCCTCCGCCTT		
bla_{IND-6}	IND-6F	CGATGACTATAGAAATTGAGGGCA	202 bp	This study
	IND-6R	ATCCAGCAGCTCCAAAGTATG		
bla_{IND-8}, bla_{IND-10}, bla_{IND-16}	IND-8F	TTGAGCCCTTTTGCCAATGC	279 bp	This study
	IND-8R	GCTTAAGTCTCCTGCACGGT		
bla_{IND-9}	IND-9F	AGTCCGTTTGCTAATGCTCAG	390 bp	This study
	IND-9R	TATGTTCTACATGTCCGCCGC		

The conditions were as follows: an initial extended denaturation step of 94 ℃ for 5 min, followed by 30 cycles of 30 s at 94 ℃, 30 s at 54 ℃, 1 min at 72 ℃, and a final 5 min at 72 ℃.

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Table S2 Clinical studies published in the period 2010–2019 concerning *Chryseobacterium indologenes*

Author, year (reference)	Country	No. of cases	Gender (No. of patients)	Age (or average age)	Type of infection (No. of patients)	Underlying disease (No. of patients)	Catheter (No. of patients)	Sensitive antimicrobial agents (sensitive rate)	Treatment (No. of patients)	Outcome (No. of patients)
Douvoyiannis *et al.*, 2010 (2)	USA	1	Female	33 days	Bloodstream infection	None	None	TMP-SMZ, piperacillin-tazobactam, cefepime, ciprofloxacin	Cefepime	Recovered
Lin *et al.*,2010 (3)	Taiwan, China	16	Male [12]; Female [4]	66	Bloodstream infection [12]; CVC related bloodstream infection [2]; Peritonitis [1]; Urinary tract infection [1]	Diabetes mellitus [8]; hypertension [8]; Lymphoma [2]; Chronic heart insufficiency [5]; Chronic kidney disease [6]; Chronic obstructive pulmonary disease [2]; Breast cancer [1]; Prostate cancer [1]; kidney cancer [1]	CVC [8]; urinary catheter [7]; Mechanical ventilation [3]	TMP-SMZ (75%), piperacillin-tazobactam (50%), cefepime (12.5%), levofloxacin (62.5%), ciprofloxacin (43.8%)	Appropriate antimicrobial therapy [2]	Recovered [13]; Died [3]
Calderón *et al.*, 2011(4)	Spain	1	Male	Neonate	VAP	Congenital heart disease	Ventilator	TMP-SMZ, piperacillin-tazobactam, cefepime, quinolones	Piperacillin-tazobactam	Recovered
Wang *et al.*,2011(5)	Taiwan, China	1	Female	68	Catheter-related peritonitis	Breast cancer	Intraabdominal catheter	TMP-SMZ	TMP-SMZ	Recovered
Sudharani *et al.*,2011(6)	India	1	…*	3 6 weeks	Bloodstream infection	Low birth weight premature infant	Mechanical ventilation	Cefoperazone-sulbactam, piperacillin-tazobactam	Cefoperazone-sulbactam	Recovered
Ceylan *et al.*, 2011(7)	Turkey	1	Male	2 months	Bloodstream infection and central nervous system infection	Congenital hydrocephalus	Cerebrospinal fluid external drainage tube	TMP-SMZ, ciprofloxacin, levofloxacin	Ampicillin-sulbactam, and levofloxacin	Died
Chou *et al.*, 2011(8)	Taiwan, China	10	Male [5]; Female [5]	71.1	Bloodstream infection [10]	Diabetes mellitus [3]; History of stroke [2]; Liver cirrhosis [2]; Colon tumor [2]; Stomach tumor [1]; Hepatocellular carcinoma [1]; Traumatic brain injury [1]	Mechanical ventilation [10]; CVC [8]	TMP-SMZ (100%), minocycline(100%), ciprofloxacin (30%), levofloxacin (30%), piperacillin-tazobactam (20%), imipenem (10%)	Appropriate antimicrobial therapy [4]	Recovered [6]; Died [4]
Bhuyar *et al.*, 2012(9)	India	1	Female	19	Urinary tract infection	Renal calculus	Malecot catheter	Piperacillin-tazobactam	Ciprofloxacin, and piperacillin-tazobactam	Recovered
Shah *et al.*, 2012(10)	USA	1	Female	26	Subcutaneous port-related bloodstream infection	Liver transplant; Cystic fibrosis; Hypothyroidism; Immunosuppression	Subcutaneous port	TMP-SMZ, levofloxacin	Levofloxacin, and TMP-SMZ	Recovered
Chen *et al.*, 2013(11)	Taiwan, China	113	Male [68]; Female [45]	75.6	Pneumonia [91]; Bloodstream infection [22]; Others [38]	Congestive heart failure [21]; Chronic obstructive pulmonary disease [26]; Malignancy [32]; Chronic kidney disease [37]; History of stroke [31]; Diabetes mellitus [37]; Hypertensive cardiovascular disease [70]; Liver cirrhosis [4]	Tracheostomy [41]; Mechanical ventilation [63]; Indwelling CVC [18]	TMP-SMZ (94.9%), cefoperazone-sulbactam (59%), tigecycline (51.9%), ciprofloxacin (41%), levofloxacin (41%), piperacillin-tazobactam (25.6%), imipenem (7.7%), meropenem (7.7%)	Appropriate antimicrobial therapy [50]	Recovered [67]; Died [46]
Ozcan *et al.*, 2013(12)	Turkey	1	Male	6 months	Central nervous system infection	Congenital hydrocephalus	Ventriculo-peritoneal shunt	TMP-SMZ, cefoperazone, ciprofloxacin, levofloxacin	TMP-SMZ, and cefoperazone-sulbactam	Recovered
Yasmin *et al.*, 2013(13)	USA	1	Female	32	VAP	Metastatic breast cancer; Respiratory failure	Prolonged mechanical ventilation; Tracheostomy	TMP-SMZ, ciprofloxacin, levofloxacin	Levofloxacin	Died
Monteen *et al.*, 2013(14)	USA	1	Male	66	VAP	Trauma; Diabetes mellitus; Hypertension; Small-bowel resection	Mechanical ventilation	Piperacillin/tazobactam, cefepime, imipenem, ciprofloxacin, gentamicin, amikacin	Ampicillin-sulbactam, and moxifloxacin	Recovered
Afshar *et al.*, 2013(15)	USA	1	Male	51	Peritoneal dialysis-related peritonitis	End-stage renal disease; HIV; Hypertension	Peritoneal dialysis catheter	TMP-SMZ, piperacillin/tazobactam, cefepime, ceftazidime, ciprofloxacin,	Ceftazidime	Recovered
Hendaus *et al.*, 2013(16)	Qatar	1	Female	Neonate	Meningitis	None	None	TMP-SMZ, cefepime	Cefepime	Recovered
Gauna *et al.*, 2013(17)	Brazil	5	…	…	Bacteremia [5]	End-stage renal disease [5]; Hemodialysis [5]	CVC [5]	…	…	…
Olbrich *et al.*, 2013(18)	Spain	1	Male	11 months	Central nervous system infection	Holoprosencephaly; Obstructive; Hydrocephalus	Post-natal ventriculoperitoneal shunt	TMP-SMZ, ceftazidime, cefepime, ciprofloxacin	TMP-SMZ, and ceftazidime	Recovered
Eshwara *et al.*, 2014(19)	India	1	Female	Neonate	Neonatal meningitis and sepsis	Small for gestational age	None	TMP-SMZ, ciprofloxacin	Ciprofloxacin	Recovered
Wang *et al.*, 2014(20)	China	1	Male	73	Central nervous system infection	Subarachnoid hemorrhage Ruptured middle cerebral artery aneurysm Hypertension	Lumbar external drainage	TMP-SMZ	TMP/SMZ, SMZ, and teicoplanin	Recovered
Deng *et al.*, 2015(21)	China	23	Male [14]; Female [9]	48.2	Urinary tract infection [9]; Pneumonia [7]; Bacteremia [6]; Central nervous system infection [1]	Organ cancer [5]; Leukemia [4]; AlloHSCT [2]; Chemotherapy [2]; Post-renal transplantation [1]	CVC [1]; Ventilator [2]; Tracheotomy [1]	TMP-SMZ (73.9%), piperacillin/tazobactam (26.1%), minocycline (21.7%)	Appropriate antimicrobial therapy [5]	Recovered [19]; Died [4]
Nemli *et al.*, 2015(22)	Turkey	1	Male	82	VAP	Respiratory failure; Trauma	Tracheostomy	Levofloxacin	Ertapenem, and levofloxacin	Recovered
Esposito *et al.*, 2015(23)	Italy	1	Female	51	Bacteremia	Chronic obstructive; Pulmonary disease; Hypertension; Bradycardia; Ischemic heart disease; Bilateral carotid atheroma	None	TMP-SMZ, ciprofloxacin	None	Recovered
Srinivasan *et al.*, 2016(24)	India	1	Female	11	Soft tissue infection	None	None	Ceftazidime, imipenem, levofloxacin, ciprofloxacin, cotrimoxazole, minocycline	Ceftazidime, and metronidazole	Recovered
Baruah *et al.*, 2016(25)	India	1	Female	22	Bacteremia	None	None	Piperacillin, piperacillin-tazobactam, ofloxacin, ciprofloxacin	Ciprofloxacin	Recovered
Atıcı *et al.*, 2016(26)	Turkey	1	Female	3 months	VAP	Meningomyelocele Congenital Diaphragmatic hernia	Ventriculo-peritoneal shunt Mechanical Ventilation	Piperacillin–tazobactam, cefepime, ciprofloxacin, levofloxacin,	Ciprofloxacin	Recovered
Aykac *et al.*, 2016(27)	Turkey	6	Male (3); Female (3)	22.9 months	Bloodstream infection [2]; CVC related bloodstream infection [2]; Pneumonia [1]; Central nervous system infection [1]	Congenital heart disease [1]; Congenital metabolic disease [1]; Congenital hydrocephalus [1]; Nephrotic syndrome with cystic fibrosis [1]; Intestinal obstruction [1]; Congenital thrombocytopenic purpura [1]	Mechanical ventilation [1]; CVC [3]; Ventriculo-peritoneal shunt [1]; None [2]	Ciprofloxacin (83.3%), piperacillin/tazobactam (66.6%), cefepime (66.6%), ceftazidime (50%), amikacin (50%)	Ciprofloxacin, imipenem and linezolid [1] Ciprofloxacin, and TMP-SMZ [1] Ceftriaxone [2] Meropenem, and amikacin [1] Ciprofloxacin, meropenem, and vancomycin [1]	Recovered [5]; Died [1]
Osamu *et al.*,2017(28)	Japan	1	Female	64	VAP	T-cell leukemia/lymphoma; Human herpes virus (type 6); Meningoencephalitis	Tracheostomy	Ceftazidime, piperacillin-tazobactam, cefoperazone-sulbactam, minocycline, amikacin	Piperacillin/tazobactam, and meropenem	Died
Antonello *et al.* ,2017(29)	Brazil	1	Male	10 days	VAP	Meconium in the amniotic fluid; HIV exposure	Mechanical ventilation	Piperacillin-tazobactam, cefepime, ceftazidime	Cefepime	Recovered
Das *et al.*, 2017(30)	India	1	Female	10 weeks	VAP	Atrioventricular canal defect; Hyperkinetic pulmonary arterial hypertension	Mechanical ventilation	TMP/SMZ, cefepime, ciprofloxacin	Cefepime	Recovered
Corbella *et al.*, 2017(31)	Italy	1	Male	11	Catheter-related bloodstream infection	Ewing's sarcoma; Chemotherapy	CVC	TMP/SMZ, ciprofloxacin, levofloxacin	Ciprofloxacin	Recovered
Soydan *et al.*, 2017(32)	Turkey	1	Male	69	pneumonia	Chronic obstructive pulmonary disease	None	None	Levofloxacin	Recovered
Kaur *et al.*, 2017(33)	India	9	Male [6]; Female [3]	48.2	Urinary tract infection (9)	Renal stone disease [5]; Carcinoma urinary bladder [3]; Transitional cell carcinoma [1]; Chronic obstructive pulmonary disease [2]; Diabetes mellitus [2]; Hypertension [1]	Urinary catheter or nephrostomy [9]	…	Amikcacin, and ceftriaxone [4]; TMP/SMZ [3]; Levoflocacin, and TMP/SMZ [1]; Nitroflurantion, and amoxycillin [1]	Recovered [9]
Mehta *et al.*,2018(34)	India	1	Male	Neonate	Bloodstream infection	Low birth weight premature infants; Acute respiratory distress syndrome; Neonatal jaundice	Mechanical ventilation	Cefoperazone-sulbactam, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin	Ciprofloxacin	Recovered
Lin *et al.*, 2018)(35)	Taiwan, China	5	…	…	Bloodstream infection [5]	Burn [5]	CVC [3]	…	…	…
Carvalho *et al.*, 2018(36)	Portugal	1	Male	76	Peritonitis	End-stage renal disease Peritoneal dialysis Atrial fibrillation Arterial hypertension Pulmonary emphysema Smoker	Peritoneal dialysis catheter	…	Ceftazidime, and ciprofloxacin	Recovered
Mirza *et al.*, 2018(37)	Turkey	16	Male [2]; Female [14]	3.4	Pneumonia [15]; Bacteremia [1]	Cystic fibrosis [15]; Operated on for craniopharyngioma [1]	CVC [1]; Ventilator [1]	Ciprofloxacin (100%), levofloxacin (100%), TMP/SMZ (100%), piperacillin-tazobactam (100%), ceftazidime (100%), cefepime (100%), imipenem (81.2%), meropenem (81.2%), amikacin (25%), gentamicin (18.8%)	…	…
Cantero *et al.*, 2018(38)	Spain	4	…		Pneumonia [4]	…	…	…	…	Recovered [1]; Died [3]
Jain *et al.*, 2018(39)	India	11	…	54.2	Bacteremia [6]; Ventilation-associated pneumonia [2]; Urinary tract infection [4]	Diabetes mellitus [7]; Hypertension [9]; History of stroke [4]; Coronary artery disease [5]; End-stage renal disease [3]	Tracheostomy [4]; Central line catheter [8]; Recent surgery [9]; Urinary catheter [12]	TMP/SMZ (91.67%), levofloxacin (75%), ciprofloxacin (41.67%), piperacillin-tazobactam (16.67%).	…	Recovered [7]; Died [4]
Agarwal *et al.*, 2018(40)		2	Male [1]; Female [1]	64.5	CVC related bacteremia [1]; VAP [1]	Breast cancer [1]; Multiple connective tissue disorder [1]; Interstitial lung disease [1]; Hypertension [1]	CVC [1] Ventilator [1]	None	None	Died [2]
Mirza *et al.*, 2019(41)	Pakistan	1	Male	Neonate	Bacteremia	Low birth weight premature infant	Ventilator	TMP-SMZ, piperacillin-tazobactam, cefoperazone-sulbactam, ciprofloxacin, levofloxacin,	Cefotaxime, and amikacin	Died
Lin *et al.*, 2019(42)	Taiwan, China	84	Male [59]; Female [25]	59.1	…	Diabetes mellitus [35]; Cardiovascular disease [42]; End-stage renal disease [4]; Malignancy [21]; Liver cirrhosis [7]; Chronic obstructive pulmonary disease [8]	…	Minocycline (73%), TMP-SMZ (47.6%), levofloxacin (32.5%), tigecycline (34.1%), piperacillin-tazobactam (19.8%), piperacillin (19%), ciprofloxacin (18.3%), cefepime (17.5%), ceftazidime (13.5%)	Appropriate antimicrobial therapy [10]	Recovered [63]; Died [21]
Bhagawati *et al.*, 2019(43)	India	1	Male	59	Bacteremia	Squamous cell carcinoma	CVC	Minocycline	Levofloxacin, and minocycline	Died
Arif *et al.*, 2019(44)	India	1	Male	42	Pleural effusion	None	None	TMP-SMZ, minocycline, tigecycline	Tigecycline, and cotrimoxazole	Recovered
Cooper *et al.*, 2019(45)	Israeli	9	Male [6]; Female [3]	5.6	…	Hematological malignances [6]; Hunter disease [1]; Cardiomyopathy [1]; Prematurity [1]; Congenital military tuberculosis [1]	Tracheostomy [1]; CVC [2]; Mechanical ventilation [1]	…	…	Recovered [7]; Died [2]

Note: appropriate antimicrobial therapy was defined if the isolates were susceptible to the prescribed antibiotics. AlloHSCT: allogeneic hematopoietic stem cell transplantation; CVC: central venous catheter; VAP: Ventilator-associated pneumonia; TMP-SMZ: Trimethoprim-sulfamethoxazole; *Information not available

References

1. Lin XH, Xu YH, Cheng J, et al. Heterogeneity of bla(IND) metallo-beta-lactamase-producing Chryseobacterium indologenes isolates detected in Hefei, China. Int J Antimicrob Agents 2008;32:398-400.
2. Douvoyiannis M, Kalyoussef S, Philip G, et al. Chryseobacterium indologenes bacteremia in an infant. Int J Infect Dis 2010;14:e531-2.
3. Lin YT, Jeng YY, Lin ML, et al. Clinical and microbiological characteristics of Chryseobacterium indologenes bacteremia. J Microbiol Immunol Infect 2010;43:498-505.
4. Calderón G, García E, Rojas P, et al. Chryseobacterium indologenes infection in a newborn: a case report. J Med Case Rep 2011;5:10.
5. Wang YC, Yeh KM, Chiu SK, et al. Chryseobacterium indologenes peritonitis in a patient with malignant ascites. Int Med Case Rep J 2011;4:13-5.
6. Sudharani V; Asiya, Saxena NK. Chryseobacterium indologenes bacteraemia in a preterm baby. Indian J Med Microbiol 2011;29:196-8.
7. Ceylan A, Güdücüoğlu H, Akbayram S, et al. Sepsis caused by Chryseobacterium indologenes in a patient with hydrocephalus. Mikrobiyol Bul 2011;45:735-40.
8. Chou DW, Wu SL, Lee CT, et al. Clinical characteristics, antimicrobial susceptibilities, and outcomes of patients with Chryseobacterium indologenes bacteremia in an intensive care unit. Jpn J Infect Dis 2011;64(6):520-4.
9. Bhuyar G, Jain S, Shah H, et al. Urinary tract infection by Chryseobacterium indologenes. Indian J Med Microbiol 2012;30:370-2.
10. Shah S, Sarwar U, King EA, et al. Chryseobacterium indologenes subcutaneous port-related bacteremia in a liver transplant patient. Transpl Infect Dis 2012;14:398-402.
11. Chen FL, Wang GC, Teng SO, et al. Clinical and epidemiological features of Chryseobacterium indologenes infections: analysis of 215 cases. J Microbiol Immunol Infect 2013;46:425-32.
12. Ozcan N, Dal T, Tekin A, et al. Is Chryseobacterium indologenes a shunt-lover bacterium? A case report and review of the literature. Infez Med 2013;21:312-6.
13. Yasmin S, Garcia G, Sylvester T, et al. Chryseobacterium indologenes in a woman with metastatic breast cancer in the United States of America: a case report. J Med Case Rep 2013;7:190.
14. Monteen M, Ponnapula S, Wood G, et al. Treatment of Chryseobacterium indologenes ventilator-associated pneumonia in a critically ill trauma patient. Ann Pharmacother 2013;47(12):1736-9.
15. Afshar M, Nobakht E, Lew SQ. Chryseobacterium indologenes peritonitis in peritoneal dialysis. BMJ Case Rep 2013;2013:bcr2013009410.
16. Hendaus MA, Zahraldin K. Chryseobacterium indologenes meningitis in a healthy newborn: a case report. Oman Med J 2013;28(2):133-4.
17. Gauna TT, Oshiro E, Luzio YC, et al. Bloodstream infection in patients with end-stage renal disease in a teaching hospital in central-western Brazil. Rev Soc Bras Med Trop 2013;46(4):426-32.
18. Olbrich P, Rivero-Garvía M, Falcón-Neyra MD, et al. Chryseobacterium indologenes central nervous system infection in infancy: an emergent pathogen? Infection 2014;42(1):179-83.
19. Eshwara V, Sasi A, Munim F, et al. Neonatal meningitis and sepsis by Chryseobacterium indologenes: a rare and resistant bacterium. Indian J Pediatr 2014;81(6):611-3.
20. Wang X, Hu Z, Fan Y, et al. Chryseobacterium indologenes catheter-related meningitis in an elderly patient after intracranial aneurysm clipping surgery. Neurol Sci 2014, 35(1): 113-5.
21. Deng L, Li MF, Li YH, et al. Chryseobacterium indologenes in four patients with leukemia. Transpl Infect Dis 2015;17(4):583-7.
22. Nemli SA, Demirdal T, Ural S. A case of healthcare associated pneumonia caused by Chryseobacterium indologenes in an immunocompetent patient. Case Rep Infect Dis 2015;2015:483923.
23. Esposito S, Russo E, De Simone G, et al. Transient bacteraemia due to Chryseobacterium indologenes in an immunocompetent patient: a case report and literature review. J Chemother 2015;27:324-9.
24. Srinivasan G, Muthusamy S, Raveendran V, et al. Unforeseeable presentation of Chryseobacterium indologenes infection in a paediatric patient. BMC Res Notes 2016;9:212.
25. Baruah M, Lyngdoh C, Lyngdoh WV, et al. Noncatheter-related bacteraemia due to Chryseobacterium indologenes in an immunocompetent patient. Indian J Med Microbiol 2016;34(3):380-1.
26. Atıcı S, Ünkar ZA, Erdem K, et al. Ventilator-associated pneumonia caused by Chryseobacterium indologenes: a rare infant case and review of the literature. SpringerPlus 2016;5(1):1741.
27. Aykac K, Ozsurekci Y, Tuncer O, et al. Six cases during 2012-2015 and literature review of Chryseobacterium

http://dx.doi.org/10.21037/atm-21-933

indologenes infections in pediatric patients. Can J Microbiol 2016;62(10):812-9.
28. Imataki O, Uemura M. Chryseobacterium indologenes, a possible emergent organism resistant to carbapenem antimicrobials after stem cell transplantation. Clin Case Rep 2017;5(1):22-5.
29. Antonello VS, Daht P, Polli J, et al. Ventilator-associated pneumonia in neonatal intensive care unit due to Chryseobacterium indologenes. Pediatr Infect Dis J 2017;36:e353-e355.
30. Das P, Karade S, Kaur K, et al. Chryseobacterium indologenes pneumonitis in an infant: a case report. J Clin Diagn Res 2017;11(6):Dd07-dd8.
31. Corbella M, Brandolini M, Cambieri P, et al. A catheter-related bloodstream infection caused by Chryseobacterium indologenes successfully treated with antibiotic-lock rescue therapy. New Microbiol 2017;40(3):223-5.
32. Soydan S, Ignak S, Unay Demirel O, et al. Chryseobacterium indolegenes infection in a patient with chronic obstructive pulmonary disease. Drug Discov Ther 2017;11(3):165-7.
33. Kaur H, Mohan B, Hallur V, et al. Increased recognition of Chryseobacterium species as an emerging cause of nosocomial urinary tract infection following introduction of matrix-assisted laser desorption/ionisation-time of flight for bacterial identification. Indian J Med Microbiol 2017;35(4):610-6.
34. Mehta R, Pathak A. Emerging Chryseobacterium indologenes infection in Indian neonatal intensive care units: a case report. Antibiotics 2018;7(4):109.
35. Lin TC, Wu RX, Chiu CC, et al. The clinical and microbiological characteristics of infections in burn patients from the Formosa fun coast dust explosion. J Microbiol Immunol Infect 2018;51(2):267-77.
36. Carvalho T, Branco P, Martins A, et al. Chryseobacterium indologenes peritonitis in a peritoneal dialysis patient. BMJ Case Rep 2018;11(1): e227713.
37. Mirza HC, Tuncer O, Olmez S, et al. Clinical strains of Chryseobacterium and Elizabethkingia spp. isolated from pediatric patients in a university hospital: performance of MALDI-TOF MS-based identification, antimicrobial susceptibilities, and baseline patient characteristics. Microb Drug Resist 2018;24:816-21.
38. Cantero M, Parra LM, Munez E, et al. A cluster of Chryseobacterium indologenes cases related to drainage water in intensive care units. Infect Control Hosp Epidemiol 2018;39:997-9.
39. Jain V, Sahu C, Afzal Hussain N, et al. The era of device colonizers: Chryseobacterium indologenes infections from a tertiary care center in north India. Indian J Crit Care Med 2018; 22(7):537-40.
40. Agarwal S, Kakati B, Khanduri S. Severe sepsis due to Chryseobacterium indologenes, a possible emergent multidrug-resistant organism in intensive care unit-acquired infections. Indian J Crit Care Med 2018; 22(11):817-9.
41. Mirza IA, Khalid A, Hameed F, et al. Chryseobacterium indologenes as a novel cause of bacteremia in a neonate. J Coll Physicians Surg Pak 2019;29(4):375-8.
42. Lin JN, Lai CH, Yang CH, et al. Differences in clinical manifestations, antimicrobial susceptibility patterns, and mutations of fluoroquinolone target genes between Chryseobacterium gleum and Chryseobacterium indologenes. Antimicrob Agents Chemother 2019;63:e02256-18.
43. Bhagawati G, Bhardwaj A, Sajikumar R, et al. Bacteremia by Chryseobacterium indologenes in a patient with lung cancer: a clinical and microbiological investigation. Indian J Crit Care Med 2019;23(3):157-9.
44. Arif N, Khullar S, Kumar R, et al. Pleural effusion due to Chryseobacterium indologenes: case report and review of literature. J Lab Physicians 2019;11(3):284-6.
45. Cooper S, Levy I, Ben-Zvi H, et al. Flavobacteriaceae Bacteremia in Children: A Multicenter Study. Pediatr Infect Dis J 2019;38(11):1096-9.

http://dx.doi.org/10.21037/atm-21-933