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Increasing Incidence of Nosocomial *Chryseobacterium indologenes* Infections in Taiwan

P. R. Hsueh[1,2], L. J. Teng[1,3], P. C. Yang[2], S. W. Ho[1,3], W. C. Hsieh[2], K. T. Luh[1,2*]

To understand the clinical features, antimicrobial therapy, and epidemiology of *Chryseobacterium indologenes* infections, the medical records of 36 patients with nosocomial *Chryseobacterium indologenes* infections seen over a three-year period at National Taiwan University Hospital were reviewed. The 36 isolates recovered from these patients were studied by molecular typing and determination of antimicrobial susceptibility patterns. Nine patients had underlying neoplastic diseases, seven had diabetes mellitus, five had burn wounds, and four had uremia. The clinical syndrome included ten patients with intraabdominal infections, nine with wound sepsis, six with intravascular catheter-related bacteremia, and four with ventilator-associated pneumonia. Thirteen patients had monomicrobial bacteremia, and four had polymicrobial bacteremia. Nineteen patients (53%) developed infections associated with various indwelling devices. The deaths of five patients (14%) were directly attributable to infection with *Chryseobacterium indologenes*. All isolates recovered showed a wide range of resistance to commonly used antimicrobial agents. The random amplified polymorphic DNA (RAPD) patterns of the isolates differed from each other, indicating the absence of epidemiological relatedness among these isolates. Nosocomial infection caused by multiresistant *Chryseobacterium indologenes* appears to be an emerging problem in Taiwan and should be studied further.

The genus *Chryseobacterium*, defined by Vandamme et al. (1), comprises six species that were previously designated as species of *Flavobacterium* (2). These organisms are gram-negative, nonmotile, oxidase-positive, glucose-nonfermenting, aerobic bacilli. *Chryseobacterium* spp. are ubiquitous in nature, being found in soil, plants, foodstuffs, and water sources (1,2). In the hospital, indwelling devices, vials, sink traps, feeding tubes, and other fluid-associated apparatuses are thought to be reservoirs for flavobacteria (1–3). Among the members of the genus *Chryseobacterium*, strains of *Chryseobacterium meningoseptcum* are known to be associated with severe infections in humans (2–8). Though strains of *Flavobacterium* spp. CDC group IIb, including *Chryseobacterium indologenes* and *Chryseobacterium gleum*, are the most common flavobacteria isolated from clinical specimens, few cases of definite infections such as meningitis, bacteremia, and those related to intravascular devices have been reported as being caused by these organisms (1, 2, 9–11).

In 1993 Bonten et al. (12) first isolated a strain of *Chryseobacterium indologenes* from a tracheal aspirate in a patient with ventilator-associated pneumonia; the pathogenic role of the isolate in their patient, however, was unclear. Recently, we documented the invasive nature of this organism in humans and highlighted its significance as a true pathogen, implicated in a wide spectrum of clinical infections in Taiwan (13–15).

In the present study we reviewed the clinical features and antimicrobial therapy of 36 patients with nosocomial *Chryseobacterium indologenes* infections seen over a three-year period at National Taiwan University Hospital. We determined the antimicrobial susceptibilities of the 36 isolates recov-

[1]Department of Laboratory Medicine, and [2]Department of Internal Medicine, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei 100, Taiwan.

[3]School of Medical Technology, National Taiwan University, Taipei, Taiwan.

Table 1: In vitro antimicrobiological susceptibilities of the 36 strains of *Chryseobacterium indologenes* isolated from patients with nosocomial infections.

Antimicrobial agent	MIC (μg/ml)			Susceptibility breakpoint[a] (μg/ml)	No. (%) of isolates susceptible
	MIC50	MIC90	Range		
Piperacillin	4	>128	1 – >128	≤ 16	23 (64)
Cephalothin	>128	>128	32 – >128	≤ 8	0 (0)
Cefotaxime	64	64	16 – >128	≤ 8	0 (0)
Ceftriaxone	32	64	16 – >128	≤ 8	0 (0)
Ceftazidime	16	64	4 – >128	≤ 8	15 (42)
Cefoperazone	16	>128	4 – >128	≤ 16	17 (38)
Moxalactam	128	>128	32 – >128	≤ 8	0 (0)
Aztreonam	>128	>128	>128	≤ 8	0 (0)
Imipenem	64	64	32 – >128	≤ 4	0 (0)
Ofloxacin	8	32	2 – 64	≤ 2	6 (16)
Ciprofloxacin	4	32	0.25 – 128	≤ 1	6 (18)
Erythromycin	>128	>128	64 – >128	≤ 0.5	0 (0)
Minocycline	4	16	2 – 16	≤ 4	27 (74)
Gentamicin	64	>128	8 – >128	≤ 4	0 (0)
Netilmicin	>128	>128	64 – >128	≤ 8	0 (0)
Amikacin	128	>128	32 – >128	≤ 16	0 (0)
Trimethoprim	4	16	0.5 – 16	≤ 2	11 (30)
Clindamycin	4	16	4 – 16	≤ 0.5	0 (0)
Rifampin	32	64	0.03 – 64	≤ 1	5 (14)
Vancomycin	16	64	4 – 128	≤ 4	5 (14)
Teicoplanin	32	64	16 – 128	≤ 8	0 (0)

[a] The susceptibility breakpoint of each antimicrobial agent for *Chryseobacterium indologenes* was adapted from that of *Pseudomonas aeruginosa*.

ered from these patients and used molecular typing to study possible epidemiological relatedness.

Patients and Methods

Study Patients and Sources of Data. Cultures of clinical specimens submitted to the bacteriology laboratory at the National Taiwan University Hospital, a 2000-bed medical center in northern Taiwan, from 1 July 1992 through 30 June 1995 were reviewed, and those positive for *Chryseobacterium indologenes* were identified. During the study period, 36 patients were diagnosed as having nosocomial *Chryseobacterium indologenes* infections, and their relevant medical information was obtained retrospectively. Along with outcome, the following criteria were examined: underlying diseases, associated conditions (use of indwelling devices, invasive procedures, chemotherapy, antimicrobial regimens before isolation of *Chryseobacterium indologenes*), clinical syndromes, isolation site(s), other bacteria isolated simultaneously from the *Chryseobacterium indologenes* isolation site(s), and antimicrobial therapy after positive culture results for *Chryseobacterium indologenes*.

Bacterial Isolates. Thirty-six isolates of *Chryseobacterium indologenes* from 36 corresponding patients with nosocomial infections were identified by conventional methods as described previously (2) as well as by the API 20 NE system (bio Merieux, France), the ATB 32 GN system (bioMerieux) and the Vitek GNI system (bioMerieux Vitek, USA) (2, 16). We also performed the following tests described by Yabuuchi et al. (11) to differentiate between *Chryseobacterium indologenes* and *Chryseobacterium gleum* grown at 41°C: esculin hydrolysis within 4 h and after 24 h, acid production from D-xylose and L-arabinose, and the presence of urease (10, 11, 13, 15).

Antimicrobial Susceptibility Testing. Antimicrobial susceptibility of all the isolates was determined using the agar dilution method described by the National Committee for Clinical Laboratory Standards (NCCLS) (20). The 21 antimicrobial agents tested (Table 1) and their respective concentrations incorporated into Mueller-Hinton agar (BBL, Becton Dickinson, USA) were in accord with those described previously (13, 15). *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were used as control strains in each set of tests. The MIC of each antibiotic was defined as the lowest concentration that inhibited visible growth of the organism. The percentage of isolates susceptible to these antimicrobial agents was determined presumptively by applying the NCCLS susceptibility criteria used for *Pseudomonas aeruginosa* (13, 17).

Random Amplified Polymorphic DNA Assay. Preparation of the DNA of the isolate for the RAPD assay followed the technique described previously (13). The RAPD typing, generated by arbitrarily primed polymerase chain reaction (APPCR), was performed with the following two arbitrary oligonucleotide primers: OPB-18 (5'-CCACAGCAGT-3') and OPB-12 (5'-CCTTGACGCA-3') (Operon Technologies, USA). The reaction mixture for the polymerase chain reaction (PCR) contained 10 mM Tris-HCl (pH 8.3); 50 mM KCl; 2 mM $MgCl_2$; 100 μM each of dATP, dCTP, dGTP, and dTTP; 5 pM of primer, 0.5 U of *Taq* DNA polymerase (Perkin-Elmer Cetus, USA); and 1 μl of bacterial DNA extract. The PCR assay consisted of 40 cycles each for 1 min at 94°C, 1 min at 35°C, 2 min at 72°C, and a final extension of 5 min at 72°C. The samples were overlaid with 10 μl of mineral oil and amplified in a PTC-100 thermocycler (MJ Research, USA). Amplification fragments were separated by electrophoresis in 1.4% agarose gel. Both faint and intense bands were included for interpreting RAPD patterns, and the patterns differing by more than one band were considered as different. Otherwise, patterns were considered identical.

Definitions. Nosocomial *Chryseobacterium indologenes* infection was defined as an infection caused by this organism that

developed at least 48 h after hospitalization that contributed to clinical sepsis isolated from an infected focus. Patients with an intravascular device-related infection due to *Chryseobacterium indologenes* were defined as those with a body temperature of > 38.3°C and tachypnea or chills without an identified source of infection other than the exit site or tunnel infection. Furthermore, at least two blood cultures, or one blood culture and one culture of the catheter tip or exit site, had to be positive for *Chryseobacterium indologenes* (18). Ventilator associated pneumonia was defined according to the criteria of Salata et al. (19). Wound infection (traumatic or burn wound) caused by *Chryseobacterium indologenes* was defined as isolation of this organism from infected wounds on at least two occasions, with or without associated bacteremia. Infections associated with surgical drains were defined as isolation of *Chryseobacterium indologenes* from purulent drainage fluids and infection of the drainage site with or without bacteremia. Septic complications, including shock, acute renal failure, hepatic dysfunction, adult respiratory distress syndrome, and disseminated intravascular coagulation, were defined according to the criteria described by Bone et al. (20).

Antimicrobial therapy was presumed to be appropriate (i) if the MIC of at least one of the drugs chosen proved to be below the corresponding breakpoint for the isolate, or (ii) if MIC data were not available, on the basis of the results of disk diffusion testing. Antibiograms of the isolates were considered identical if the MICs of the antimicrobial agents tested were the same or within a one-dilution discrepancy. Isolates were defined as the same strain or derived from a single clone if they had identical antibiograms as well as identical RAPD patterns.

Results

Clinical Features. From 1993 to 1995, an average of 120 isolates of *Chryseobacterium* spp. other than *Chryseobacterium meningosepticum* were recovered per year from various clinical specimens. This number accounted for about 0.5% of the total clinical isolates and approximately 2% of isolates of glucose-nonfermentative, gram-negative bacilli. Among these isolates, four-fifths were recovered from hospitalized patients, and about one-third were linked to nosocomial infections. This incidence approximated 1.8% (ranked 12th) of the total nosocomial pathogens found at our hospital annually.

During the study period, 36 patients with nosocomial *Chryseobacterium indologenes* infections were identified (Table 2). Their mean age was 50.5 years (range, 1–85 years). Fifty-three percent of these patients developed *Chryseobacterium indologenes* infections associated with the use of indwelling devices, including surgical drains (n = 8), intravascular catheters (n = 6), endotracheal tubes (n = 4), and a Foley catheter (n = 1). In three patients with ventilator-associated pneumonia, materials from protected-sheath brushing, in addition to sputum specimens, were positive for this organism. Three patients with intraabdominal infections associated with surgical drains developed bacteremia. Among the five patients with a *Chryseobacterium indologenes* burn infection, three had *Chryseobacterium indologenes* bacteremia; in two nonbacteremic patients, *Chryseobacterium indologenes* was the only species isolated from obviously infected burn wounds.

Table 2: Characteristics of 36 patients with nosocomial *Chryseobacterium indologenes* infections.

Variable	No. of patients
Sex	
Male	25
Female	11
Underlying diseases	
Neoplastic diseases[a]	9
Diabetes mellitus[b]	8
Burn wound	5
Uremia	4
Biliary tract stones	3
Miscellaneous[c]	6
None	3
Infections	
Intraabdominal infection	10
Biliary tract infection	7
Peritonitis	2
Pancreatic abscess	1
Wound sepsis	9
Intravascular catheter-related bacteremia	6
Ventilator-associated pneumonia	4
Primary bacteremia	3
Pyelonephritis	2
Bacteremic pneumonia	1
Anal abscess	1
Associated conditions	
Indwelling devices	19
Neutropenia	2
Presence of other bacteria	14
Septic complications	10
Received appropriate therapy	11
Deaths	5

[a] Includes hepatocellular carcinoma (n = 3 patients), leukemia (n = 2), multiple myeloma (n = 1), lung carcinoma (n = 1), esophageal carcinoma (n = 1), and prostate carcinoma (n = 1).
[b] Includes one patient each with concomitant uremia and prostate carcinoma.
[c] Includes congenital heart disease (n = 3 patients), idiopathic thrombocytopenic purpura (n = 1), myocardial infarction (n = 1), and chronic pancreatitis (n = 1).

A total of 17 patients (47%) had bacteremia, and polymicrobial bacteremia was found in four. In 17 patients (47%) *Chryseobacterium indologenes* was isolated simultaneously from more than one body site. The bacteria recovered from the same body site as *Chryseobacterium indologenes* consisted most often of glucose-nonfermenting gram-negative bacilli (*Pseudomonas* spp., 6 instances; *Acinetobacter baumanii*, 5; and *Stenotrophomonas maltophilia*, 2), staphylococci (8 instances), *Klebsiella pneumoniae* (2 instances), and enterococci (2 instances).

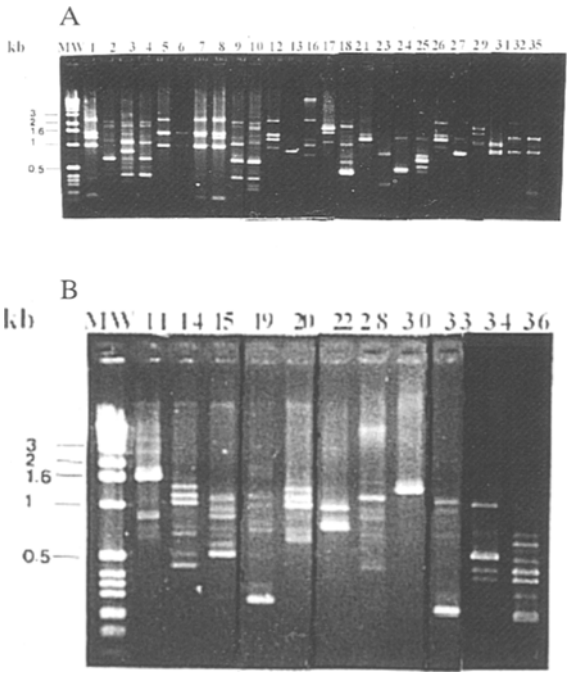

Figure 1: Random amplified polymorphic DNA (RAPD) patterns generated by arbitrarily primed PCR using the two primers OPB-18 (A) and OPB-12 (B) for 36 *Chryseobacterium indologenes* isolates. Lane MW, molecular weight marker (1 kb ladder, Gibco, USA); lanes 1 to 36, *Chryseobacterium indologenes* isolates from patients 1 to 36, respectively, as indicated in Table 2. Molecular sizes are indicated in kilobase (kb) pairs.

The majority (78%) of patients received a wide variety of antimicrobial agents before culture for *Chryseobacterium indologenes*; the drugs administered were later considered to be appropriate treatment for only five patients (18%). Of the five patients (14%) with septic complications who died as a result of *Chryseobacterium indologenes* infection, two had peritonitis, two had biliary tract infections, and one had bacteremic pneumonia. Three of these five harbored other well known pathogens and received effective antibiotics against these isolates. Only one of these five received appropriate antimicrobial therapy against *Chryseobacterium indologenes*. However, the other five patients with septic complications recovered, and four of them received antimicrobial agents with low MICs against the flavobacteria isolated. Among the 31 patients who recovered from *Chryseobacterium indologenes* infections, 16 died of other infections, and another six had prolonged hospital stays due to diseases unrelated to the infections.

Bacterial Isolates. All 36 isolates were oxidase positive, gram-negative bacilli. On sheep blood agar they grew as smooth, circular, yellow-pigmented colonies, 1 to 2 mm in diameter, within 24 h of incubation. Biochemical profiles produced by the API 20NE, the ATB 32 GN system, and the Vitek GNI card showed a probability of > 99% that each organism isolated was *Chryseobacterium indologenes*. All of the isolates failed to grow at 41°C, failed to produce acid from D-xylose and L-arabinose, and failed to hydrolyze esculin within 4 h of incubation, but positive reactions were found after 24 h of incubation, indicating that the characteristics of these isolates were typical of *Chryseobacterium indologenes* strains (11). Isolates of *Chryseobacterium indologenes* recovered concurrently from different sites in the same patient all had the same biochemical profiles according to the three commercial identification systems and identical antimicrobial susceptibility patterns as determined by the disk diffusion method.

Antimicrobial Susceptibilities. The MICs of antimicrobial agents for the 36 isolates of *Chryseobacterium indologenes* are shown in Table 1. All of the isolates tested were resistant to cephalothin, cefotaxime, ceftriaxone, moxalactam, aztreonam, imipenem, erythromycin, aminoglycosides, clindamycin, and teicoplanin. More than 80% of the isolates were resistant to ofloxacin, ciprofloxacin, rifampin, and vancomycin. Susceptibilities of ceftazidime, cefoperazone, and trimethoprim were also limited. Piperacillin and minocycline could inhibit more than 60% of the isolates tested, with MIC50s of 4 and 4 μg/ml, respectively.

Genotyping. As shown in Figure 1, the RAPD patterns of the 36 *Chryseobacterium indologenes* isolates could be differentiated easily from each other by using two primers, OPB12 and OPB18, simultaneously.

Discussion

In the present study, *Chryseobacterium indologenes* was implicated in 36 patients with nosocomial infections over a three-year period at our hospital. However, the annual incidence of this organism as the cause of nosocomial infections is difficult to determine, partly because the majority of *Chryseobacterium* spp. other than *Chryseobacterium meningosepticum* (i.e., those not recovered from normally sterile body fluids) were not identified to the species level because of their questionable role in human disease (3, 5, 21). As compared with the rare isolation of these organ-

isms at our hospital before 1993, the increasing incidence of nosocomial infection due to *Chryseobacterium* spp. other than *Chryseobacterium meningosepticum* is impressive.

Although a rather large number of nosocomial infections caused by an unusual organism at the same hospital might suggest a common source, even though the infections occurred over a three-year period, the variation in antimicrobial susceptibilities and the highly heterogeneous RAPD patterns among these isolates of *Chryseobacterium indologenes* indicate that these infections were epidemiologically unrelated. The results further showed that the RAPD technique provides excellent discriminating power for epidemiological typing of *Chryseobacterium indologenes* isolates.

Clearly, the majority of *Chryseobacterium indologenes* infections were linked to the use of indwelling devices during hospital stay (13, 15). In this study nearly half of the patients with infections related to indwelling devices had simultaneous bacteremia, suggesting that indwelling devices may serve as a foothold for this organism to invade the bloodstream. Interestingly, four of the six patients with monomicrobial intravascular catheter-related bacteremia caused by *Chryseobacterium indologenes* improved clinically while the catheters remained in place, but only received an appropriate antimicrobial agent. This finding supports our previous observations and suggests that, like that due to *Flavimonas oryzihabitans* (13, 22), intravascular catheter-related bacteremia caused by *Chryseobacterium indologenes* may be a clinically benign process that does not usually require removal of the catheter.

Of the three patients with primary *Chryseobacterium indologenes* bacteremia unrelated to the use of indwelling devices, two received no antimicrobial therapy and one received an inappropriate regimen; in all three patients, however, fever resolved in less than 24 h without apparent infectious complications. Strains of *Chryseobacterium* spp. have been reported to be widely distributed in hospital environments and have been demonstrated in such places as the ice for cooling syringes used to obtain arterial specimens for blood gas determination (2, 3, 8). Strains of *Chryseobacterium meningosepticum* have also been documented as contaminants in disinfectants (chlorhexide solution) (23). The possibility exists that these are cases of pseudobacteremia due to contamination of *Chryseobacterium indologenes* during the management of blood cultures. However, this possibility is difficult to verify, especially in patients with severely debilitating diseases.

Wound sepsis caused by *Chryseobacterium meningosepticum* has been reported (6); however, *Chryseobacterium indologenes* has never been described as a true pathogen causing bacteremia associated with wound infection. Four of the five patients with burn infections developed *Chryseobacterium indologenes* septicemia, and one of them also suffered septic shock, but all of these patients recovered. Virulence-associated factors that play a significant role in the pathogenic process of *Pseudomonas aeruginosa* burn wound sepsis have been described (24, 25). Whether a similar scenario regarding the pathogenesis of *Chryseobacterium indologenes* burn infections exists is unknown and needs further investigation.

The optimal choice of antimicrobial agents for the management of nosocomial *Chryseobacterium indologenes* infections is hard to determine, and clinical efficacy of antimicrobial therapies is also difficult to evaluate for four reasons. First, the appropriate MIC breakpoints for defining susceptibility and resistance of *Chryseobacterium indologenes* isolates to antimicrobial agents have not been approved by the NCCLS (17). Second, nearly all extended-spectrum penicillins, first- and second-generation cephalosporins, and aminoglycosides show poor in vitro activity against *Chryseobacterium* spp. (including *Chryseobacterium indologenes*). Moreover, the susceptibilities of these organisms, as shown in this study and others (13–15, 26–30), to third-generation cephalosporins, imipenem, aztreonam, and quinolones are highly unpredictable. This situation makes the choice of an effective drug for empirical treatment of *Chryseobacterium indologenes* infections impossible. Third, discrepancies have been reported between the standard agar dilution test and the routinely used disk diffusion method for susceptibility testing of *Chryseobacterium* spp. to several frequently prescribed antimicrobial agents (26). In the present study, though the majority of our patients received antimicrobial agents on the basis of the results of the disk diffusion test, only one third received appropriate antimicrobial therapy according to MIC testing. Fourth, the majority of our patients had severe underlying disease, had undergone invasive surgical procedures or implantation of various indwelling devices, and, to a lesser extent, had polymicrobial infections. Such scenarios might complicate an evaluation of the ef-

fectiveness of antimicrobial therapy. Among the antimicrobial agents tested, piperacillin and minocycline were the most active against isolates of *Chryseobacterium indologenes*. Piperacillin, rather than minocycline, may appear to be promising for the treatment of severe infections due to this organism.

The collective results of this study serve as the basis for the first large-scale analysis of clinical and microbiological data on nosocomial *Chryseobacterium indologenes* infections and emphasize that nosocomial infections due to these multiresistant organisms are appearing as an emerging problem in Taiwan. However, the pathogenicity of *Chryseobacterium indologenes* in various clinical infections is multifactorial in nature and remains unclear. The factors regulating invasion from either indwelling devices or wounds have not yet been identified. The lack of approved MIC breakpoints to antimicrobial agents for these organisms and the unreliable results of routinely used disk diffusion tests result in therapeutic dilemmas regarding the treatment of *Chryseobacterium indologenes* infections. Further studies aimed at epidemiological surveillance of this organism in various hospital environments are necessary to elucidate probable linkage to nosocomial infections.

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