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(中、英文) *Klebsiella pneumoniae* Bacteremia with Liver Abscess : Clinical Characteristics, Antimicrobial Susceptibility and Molecular Epidemiology

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Antimicrobial Susceptibility and Pulsed-field Gel Electrophoresis Profile of *Klebsiella pneumoniae* Isolates Causing Liver Abscess in Taiwan

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<Abstract>

Klebsiella pneumoniae has been the leading cause of pyogenic liver abscess in Taiwan during the period from 1985 to 1999, which is different from other countries. The present study investigated the in vitro antimicrobial susceptibilities of 51 *K. pneumoniae* isolates collected from blood cultures of patients with liver abscess in Taiwan during the period from 1993-1997, and typed by pulsed-field gel electrophoresis (PFGE). All 51 isolates were resistant to ampicillin, but susceptible to other antimicrobial agents. The minimum inhibitory concentrations (MICs) were less than 1 μg/ml for the third- and fourth-generation cephalosporins, monobactam, carbapenems, and ciprofloxacin. In comparison, 62 isolates of *K. pneumoniae* from community-acquired bacteremic patients without liver abscess had similar antimicrobial susceptibilities, while 142 isolates from patients with hospital-acquired bacteremia without liver abscess were much less susceptible to all of the tested antimicrobial agents. PFGE molecular epidemiologic analysis found 20 out of 51 isolates belonged to eight clusters of genetically related strains, with two or three isolates in each clusters. The other 31 isolates were genetically distinct strains. This study demonstrated that *K. pneumoniae* isolates which cause liver abscess in Taiwan remained susceptible to a wide range of antimicrobial agents and that they were not genetically related.

<Introduction>

Pyogenic liver abscess is a life-threatening disease [1]. In Western countries, it is usually secondary to intra-abdominal or biliary tract infections, although hematogenous spread can be found in some cases [1-3]. The etiology is often polymicrobial due to the ascending route of infection from the gastrointestinal tract [1-3]. However, over the past 15 years, *K. pneumoniae* has been the leading reported pathogen causing pyogenic liver abscess in Taiwan, and most of the reported cases did not have intra-abdominal or biliary tract infections [4-7]. More than 50% of the previously reported cases of liver abscess cases in Taiwan were caused by *K. pneumoniae* and almost all reported cases of the *K. pneumoniae* liver abscess were monomicrobial infections [4-8]. Although *K. pneumoniae* liver abscess has been reported to have a low mortality rate in Taiwan, metastatic foci of infection in other sites, such as endophthalmitis and meningitis, can develop rapidly if appropriate antimicrobial therapy is not started early and adequate drainage performed [6, 9-11].

Compared to cases in Western countries, the etiology of liver abscess in Taiwan is very different. There has been no answer until now, to explain why there is such a distinct difference. It is not known whether this is due to a single virulent strain, which has hepatic tropism and thus causes a high prevalence of *K. pneumoniae* liver abscess, or if there is a common virulent factor in different strains, which results in a special invasiveness for liver.

Increasing resistance of *K. pneumoniae* to many antimicrobial agents, especially in strains producing extended-spectrum beta-lactamases (ESBLs) has been noted in many parts of the world [12-14]. *K. pneumoniae* isolates from patients in Taiwan have also been increasingly shown to produce ESBLs in recent years [15, 16]. In previous reports, most of the *K. pneumoniae* isolates causing liver abscess in Taiwan in early years were susceptible to cephalosporins and aminoglycosides [17]. However, it is not known whether isolates which cause liver abscess in Taiwan in recent years also demonstrate a similar increasing resistance to antimicrobial agents as those which have been reported for other kinds of infections, such as urinary tract infections and bacteremia.

In order to understand the trend of susceptibility of *K. pneumoniae* isolates and the relationship among various isolates from different patients, we examined the susceptibility of 51 bacteremic isolates of *K. pneumoniae* from patients with liver abscess during the period 1993 to 1997. The results were compared with those of isolates from bacteremia patients without liver abscess. The genotypes of all isolates were studied using pulsed-field gel electrophoresis (PFGE).

<Materials and Methods>

Bacterial Isolates

A total of 63 strains of *K. pneumoniae* were isolated from patients with bacteremic *K. pneumoniae* liver abscess, which was diagnosed at National Taiwan University Hospital (NTUH) during the period from 1993 to 1997. All of the organisms were isolated from blood and 51 viable strains were included in this study. All of the patients acquired the infection outside the hospital and belonged to community-acquired infection. The diagnosis of pyogenic liver abscess was confirmed by percutaneous aspiration of pus from the liver abscess or surgical drainage in 43 patients. In the remaining 8 patients, no aspiration or surgical drainage had been performed, and the diagnosis of liver abscess was made on the basis of signs, symptoms and imaging findings (abdominal sonography and computerized tomography scan) which resolved after antibiotic therapy.

For comparison, 204 strains isolated from the blood of patients with *K. pneumoniae* bacteremia without liver abscess during the same period, which were randomly selected from stock isolates, were also included in this study. The specimens had been collected daily either from patients with hospital-acquired bacteremia(142 isolates), defined as bacteremia which developed more than 48 hours after hospitalization, no matter it was due to primary bacteremia or secondary to any

infectious focus, or from patients with community-acquired bacteremia(62 isolates), defined as bacteremia which developed before admission to the hospital. None of the patients had been previously hospitalized for bacteremia. Only one isolate was used from each patient. The bacteria were preserved at -70℃ until experiments. The identification of *K. pneumoniae* was based on standard clinical microbiology methods [18].

Antimicrobial Agents

All antimicrobial agents used in this study were provided by individual pharmaceutical companies as standard reference powders for laboratory use. These included ampicillin, cefepime, aztreonam, and amikacin from Bristol-Myers Squibb (Syracuse, New York, USA); amoxicillin and clavulanic acid from Smith Klime & Beecham (Worthing, England); piperacillin from Lederle (New York, U.S.A.); cefazolin from Fujisawa (Osaka, Japan); cefuroxime from Glaxo Wellcome (Greenford, UK); cefmetazole from Sankyo (Tokyo, Japan); cefotaxime and cefpirome from Hoechst (Frankfurt, Germany); imipenem from Merck Sharp & Dohme (Rahway, New Jersey, U.S.A.); meropenem from Sumitomo Pharmaceuticals (Osaka, Japan); ciprofloxacin from Bayer GmbH (Leverkusen, Germany); gentamicin from Schering-Plough (Kenilworth, New Jersey, U.S.A.);and tobramycin from Eli Lilly (Indianapolis, Indiana, U.S.A.).

Susceptibility Testing

The minimum inhibitory concentrations (MICs) of 16 antimicrobial agents were determined by the agar dilution method as described by the NCCLS [19]. The Steers' replicator was used to apply 10^4 colony-forming units (CFU) onto Mueller-Hinton agar containing a 2-fold serial dilution (from 128 to 0.03 μg/ml) of each antimicrobial agent. The agar plates were incubated at 35°C for 18 hours before reading. The MIC was read as the lowest concentration of the antimicrobial agent that completely inhibited the growth of bacteria. *Escherichia coli* from the American Type Culture Collection (ATCC) 25922 was used as the internal control.

PFGE

Genomic DNA was prepared in agarose plugs using the method described by Mlynarczyk et al [20], with some modifications. Briefly, bacterial suspensions were prepared by scraping of several bacterial colonies directly from overnight-incubated cultures on sheep blood agar. After washing in 1 mL PIV buffer (1 M NaCl, 10 mM Tris-Cl, pH 8.0), the bacteria were suspended in 0.5 mL PIV buffer and the suspension was adjusted on OD_{620} of 3.0. The bacterial suspensions were then mixed with an equal volume of 1.6% low-melting agarose (Boehringer GmbH, Mannheim, Germany) in PIV buffer and allowed to solidify in plug molds. The cells were lysed by incubation of the agarose plugs at 37°C for 4 hours with lysostaphin (50 μg/mL) (Sigma, St Louis, MO, USA) and RNase (50 μg/mL) (Boehringer GmbH) in 1 mL EC buffer (6 mM Tris pH

8.0, 1 M NaCl, 0.1 M EDTA pH 8.0, 0.2% sodium deoxycholate, 0.5% Sarkosyl). Following this step, the lysis buffer was replaced with 1 mL ESP buffer (0.5 mM EDTA pH 9.0, 1% Sarkosyl, 1mg/mL proteinase K) and incubated overnight at 50℃. The agarose plugs were then washed three times with 10 mL TE buffer (10 mM Tris-HCL, 0.1 mM EDTA, pH 8.0) for 30 minutes at room temperature, and transferred to a tube containing ET buffer and placed in a refrigerator at 4℃ until use. For restriction endonuclease digestion, approximately 1-1.5 mm of a plug was cut and incubated overnight with 250 mL restriction buffer containing 20 V of Sba (Biolab Laboratories, Beverly, MA, USA) at 25℃. After DNA digestion, the agarose plug was incubated with 1 mL TE buffer at 37℃ for 1 hour. The plugs were then inserted into 1% agarose (Bio-Rad Laboratories, Hercules, CA, USA) gels in 0.5X TBE buffer. The resistriction fragments were separated using a contour-clamped homogeneous electric field system (CHEF-DRII; Bio-Rad Laboratories). Electrophoresis was performed at 200 V for 24 hours with pulse times of 1 to 35 seconds at 4℃ and the gels were stained with ethidium bromide and photographed under ultraviolet light. *S. aureus* NCTC 8325 [21] was used as the molecular weight marker. The PFGE results were analysed with the computer software Gelcompar for Windows Version 3.1 (Applied Maths, Kortrijk, Belgium). The PFGE patterns were compared by an algorithmic clustering method, called the unweighted-pair group method, using the arithmetic average (UPGMA) as described in previous reports [16].

<Results>

Antimicrobial Susceptibility

The susceptibilities of 51 isolates of *K. pneumoniae* from patients with liver abscess are shown in Table 1. Almost all isolates were resistant to ampicillin, with an MIC_{90} of 32 μg/ml, and all isolates were susceptible to other antimicrobial agents tested. They were very susceptible to the third-generation and fourth-generation cephalosporins, monobactam, carbapenems, and ciprofloxacin, with an MIC of less than 1 μg/ml in all strains. Similarly, isolates from community-acquired bacteremic patients without liver abscess were also resistant to ampicillin, but were susceptible to most antimicrobial agents tested except for some isolates which were not susceptible to cefazolin and cefuroxime. The MICs of all 62 isolates for the third-generation and fourth-generation cephalosporins, monobactam, carbapenem, and ciprofloxacin were also less than 1 μg/ml (Table 2).

In contrast, isolates from hospital-acquired bacteremic patients without liver abscess were much less susceptible to all antimicrobial agents tested (Table 3). The MIC_{90}s for other agents were all much higher than for imipenem and meropenem. The susceptible percentages to aminoglycosides ranged from 52.8 to 83.8%, while the susceptible percentage to cefotaxime was 87.5%, to aztreonam was 51.7%, to cefmetazole was 95.1%, and to imipenem and meropenem were 100% (Table 3).

PFGE Molecular Typing

The 51 isolates from bacteremic patients with liver abscess demonstrated different PFGE patterns. The patterns of some of the strains are illustrated in Figure 1 and the dendrogram of all 51 isolates is shown in Figure 2. Eight clusters of either two or three isolates demonstrated more than 80% similarity in their PFGE patterns, i.e., isolates No. 2, 7, and 8; No. 1 and 4; No. 18 and 20; No. 48 and 51; No. 17, 22, and 23; No. 9, 12, and 15; No. 30, 35 and 40; and No. 6 and 26. However, the cases infected by isolates with similar PFGE patterns did not have any relationship with each other in time and place of occurrence. The other 31 isolates had different PFGE patterns with more than 20% differences, compared with each other and with those isolates in clusters.

<Discussion>

In the present study, *K. pneumoniae* isolates causing liver abscess were very susceptible to various antimicrobial agents except ampicillin. Similarly, other *K. pneumoniae* isolates causing bacteremia without liver abscess in community-acquired cases were also very susceptible to antimicrobial agents. In contrast, those isolates causing nosocomial bacteremia had a higher prevalence of antibiotic resistance compared to community-acquired cases, and none of the hospital-acquired resistant strains resulted in liver abscess.

Although *K. pneumoniae* infection is known to be a major cause of liver abscess in Taiwan, the pathogenesis of this condition remains unclear since most reported cases of *K. pneumonae* liver abscess in Taiwan did not have intraabdominal illness or biliary tract problems [4-6, 8]. All of the previously reported cases were thought to be resulted from systemic bacteremia, with the bacteria in the blood stream seeding to the liver with subsequent bacterial proliferation and development of liver abscess. Similar to other reports from Taiwan [4-6], patients with *K. pneumoniae* liver abscess in the present study did not have intraabdominal illness or biliary tract problems. They all belonged to primary liver abscess cases and all acquired the infection outside the hospital. Because *K. pneumoniae* liver abscess is a rather unique character of *K. pneumoniae* bacteremia in Taiwan, almost all patients with *K. pneumoniae* bacteremia would be arranged to receive abdominal sonography and/or CT scan for the detection of possible existence of

liver abscess. However, even under such an active surveillance for detection of possible existence of liver abscess, we did not find any cases of liver abscess among those patients with nosocomial *K. pneumoniae* bacteremia.

Antibiotic usage is not strictly controlled in Taiwan, and antibiotics can be easily obtained without prescription. This has resulted in an increased prevalence of antibiotic resistance in various species of bacteria [22], including many bacteria causing community-acquired infections, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [23-25]. Among 584 strains of *S. pneumoniae* isolated from nasopharynx surveillance cultures of children in Southern Taiwan, 71% were non-susceptible to penicillin and 92% were resistant to macrolides [24] However, *K. pneumoniae* isolates causing community-acquired bacteremia with or without liver abscess remained very susceptible to almost all antimicrobial agents with anti-Gram-negative activity. The exact reasons why the community strains of *K. pneumoniae* remained susceptible to almost all antimicrobial agents under a high selection pressure of overuse of antibiotics in Taiwan are currently unknown. However, this highly susceptible nature of *K. pneumoniae* isolates probably is an important factor resulting in the low mortality of patients with primary *K. pneumoniae* liver abscess [4].

Resistance of *K. pneumoniae* is increasing in many parts of the world, and a similar trend has been shown in Taiwan. A previous report from NTUH demonstrated that 3.4% of all isolates from various clinical specimens were ESBL phenotypic strains. This prevalence increased rapidly to 10.3% in 1997 [15]. From current study, we

understand that all strains with ESBL phenotype resistance and almost all other resistant strains appeared in the isolates causing nosocomial infections. Besides, these resistant strains did not cause liver abscess; only the susceptible strains acquired from the community would cause liver abscess. Before this study was conducted, it was speculated that there might be only a single or a few susceptible strains circulating in the community that cause the endemic nature of liver abscess. However, from our results of PFGE analysis, there existed many different strains that could cause liver abscess. We believed that *K. pneumoniae* liver abscess is not caused by a single or a few epidemic strains, but by many genetically distinct strains instead. Moreover, whether the high percentage of antibiotic-resistance among nosocomial pathogens found in the present study were caused by the spread of several epidemic resistant strains within the hospital is an issue of interest. Our preliminary study of the PFGE patterns of nosocomial resistant strains did not indicate the presence of only a single or a few epidemic strains spreading but exhibited many different PFGE patterns as well (data not shown).

In summary, the results of the present study suggest that in Taiwan *K. pneumoniae* isolates which cause liver abscess remain very susceptible to various antimicrobial agents, although there is a high prevalence of antibiotic resistance in *K. pneumoniae* isolates causing nosocomial bacteremia. PFGE analysis demonstrated the presence of a variety of genetically different strains that cause liver abscess. Further studies are mandatory to elucidate the mechanisms causing the unique feature of liver

predilection of the susceptible strains of *K. pneumoniae*.

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Table 1. The antibiotic susceptibilities of 51 blood isolates of *K. pneumoniae* from patients with liver abscess

	MICs (μg/ml)			%
Drug	Range	MIC_{50}	MIC_{90}	Susceptibility
Ampicillin	8-64	16	32	3.9
Amoxicillin/ Clavulanate	1-8	2	4	100
Piperacillin	2-8	4	4	100
Cefazolin	0.5-2	1	2	100
Cefuroxime	0.5-8	2	4	100
Cefmetazole	0.25-4	0.5	1	100
Cefotaxime	≤0.03-0.25	≤0.03	0.06	100
Cefepime	≤0.03-0.06	≤0.03	0.06	100
Cefpirome	≤0.03-0.125	≤0.03	0.06	100
Aztreonam	≤0.03-0.125	≤0.03	0.06	100
Imipenem	0.06-0.5	0.125	0.5	100
Meropenem	≤0.03	≤0.03	≤0.03	100
Ciprofloxacin	≤0.03-0.25	≤0.03	≤0.03	100
Gentamicin	0.125-1	0.25	0.5	100
Tobramycin	0.125-2	0.25	1	100
Amikacin	0.25-2	0.5	1	100

Table 2. The antibiotic susceptibilities of 62 blood isolates of *K. pneumoniae* from patients with community-acquired bacteremia

	MICs (μg/ml)			%
Drug	Range	MIC_{50}	MIC_{90}	Susceptibility
Ampicillin	8-128	16	32	4.9
Amoxicillin/ Clavulanate	1-8	2	4	100
Piperacillin	2-16	4	4	100
Cefazolin	0.5-16	1	2	98.4
Cefuroxime	0.5-16	2	4	98.4
Cefmetazole	0.125-4	0.5	1	100
Cefotaxime	≤0.03-0.25	≤0.03	0.06	100
Cefepime	≤0.03-0.06	≤0.03	0.06	100
Cefpirome	≤0.03-0.125	≤0.03	0.06	100
Aztreonam	≤0.03-0.25	≤0.03	0.06	100
Imipenem	0.06-0.5	0.125	0.25	100
Meropenem	≤0.03-0.06	≤0.03	≤0.03	100
Ciprofloxacin	≤0.03-0.125	≤0.03	0.06	100
Gentamicin	0.125-1	0.25	0.5	100
Tobramycin	0.125-2	0.25	2	100
Amikacin	0.25-2	0.5	1	100

Table 3. The antibiotic susceptibilities of 142 isolates of *K. pneumoniae* from patients with nosocomial bacteremia

	MICs (μg/ml)			%
Drug	Range	MIC_{50}	MIC_{90}	Susceptibility
Ampicillin	8-≥256	128	≥256	5.6
Amoxicillin/ Clavulanate	1-64	8	32	64.1
Piperacillin	1-≥256	32	≥256	48.6
Cefazolin	1-≥256	2	≥256	52.1
Cefuroxime	1-≥256	4	≥256	59.2
Cefmetazole	0.25-≥256	1	8	95.1
Cefotaxime	≤0.03-≥256	0.06	16	88.7
Cefepime	≤0.03-128	0.06	32	85.9
Cefpirome	≤0.03-≥256	0.125	8	94.4
Aztreonam	≤0.03-≥256	0.125	128	62.0
Imipenem	0.06-1	0.125	0.25	100
Meropenem	≤0.03-0.25	≤0.03	≤0.03	100
Ciprofloxacin	≤0.03-32	≤0.03	1	93.7
Gentamicin	0.125-≥256	0.5	32	66.9
Tobramycin	0.25-≥256	1	64	52.8
Amikacin	0.25-≥256	1	32	83.8

Legends of figures:

Fig. 1. PFGE of *Xba*I-digested genomic DNA of 10 isolates of *K. pneumoniae* causing liver abscess. Lane M: molecular weight marker (*S. aureus* NCTC 8325).

Fig. 2. Dendrogram of PFGE results from 51 isolates of *K. pneumoniae* causing liver abscess.. Strains were clustered by the unweighted-pair group method using arithmetic averages (UPGMA). The scales indicate the percentage of genetic similarity.

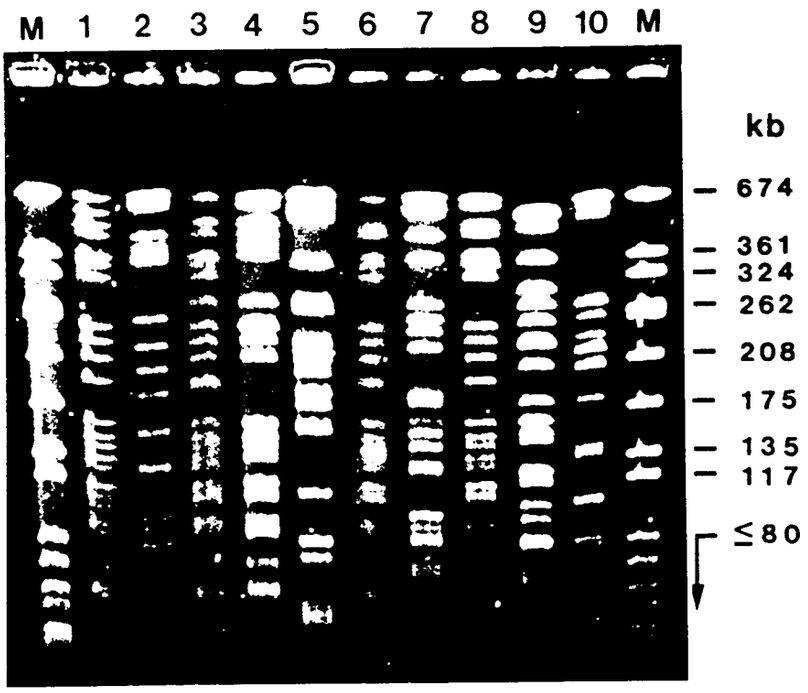

Fig. 1.

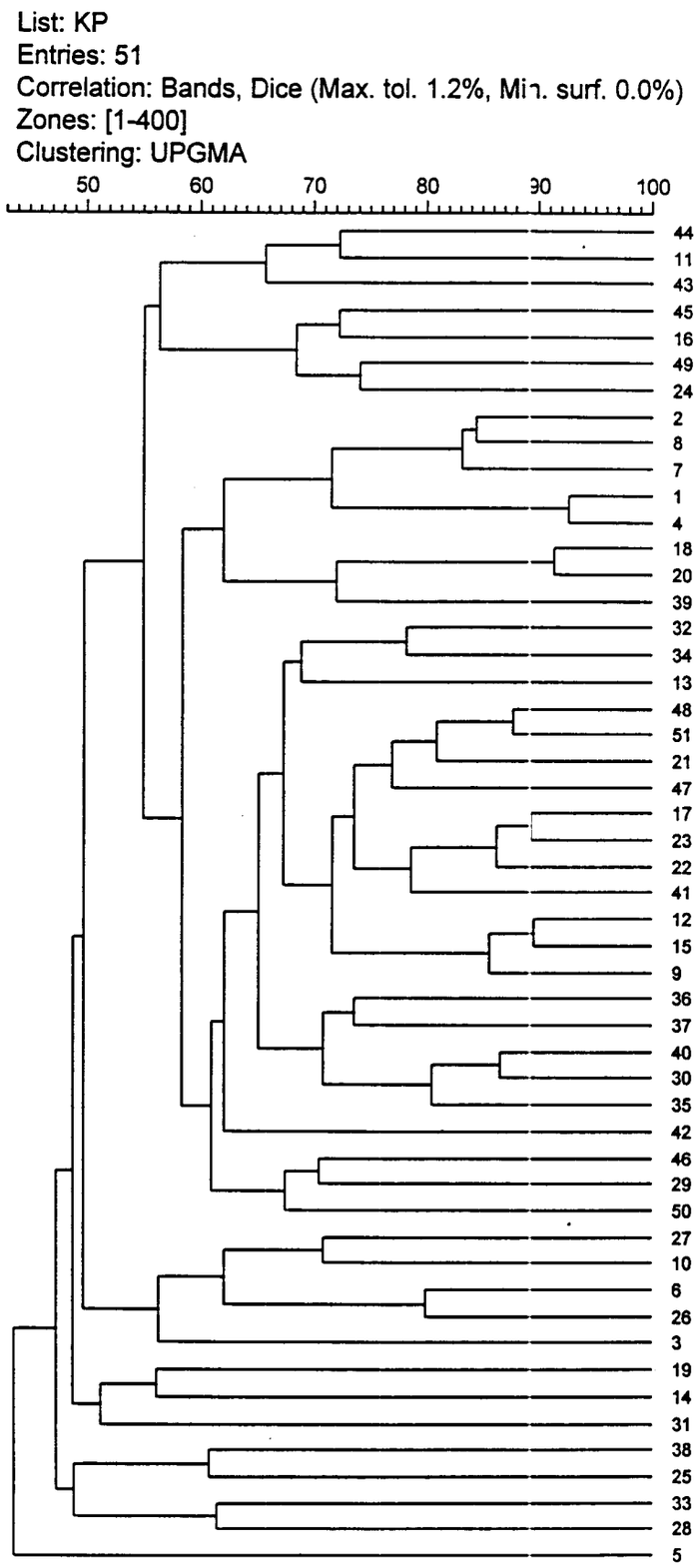
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Fig. 2.