

## Clinical Implications of *Mycobacterium kansasii* Species Heterogeneity: Swiss National Survey

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Several subtypes of *Mycobacterium kansasii* have been described, but their respective pathogenic roles are not clear. This study investigated the distribution of subtypes and the pathogenicity of *M. kansasii* strains ( $n = 191$ ) isolated in Switzerland between 1991 and 1997. Demographic, clinical, and microbiological information was recorded from clinical files. Patients were classified as having an infection according to the criteria of the American Thoracic Society. Subtypes were defined by PCR-restriction enzyme analysis of the *hsp65* gene. Subtype 1 comprised 67% of the isolates ( $n = 128$ ), while subtypes 2 and 3 comprised 21% ( $n = 40$ ) and 8% ( $n = 15$ ), respectively. Other subtypes (subtypes 4 and 6 and a new subtype, 7) were recovered from only 4% of patients ( $n = 8$ ). *M. kansasii* subtype 1 was considered pathogenic in 81% of patients, while *M. kansasii* subtype 2 was considered pathogenic in 67% of patients and other subtypes were considered pathogenic in 6% of patients. The majority of patients with *M. kansasii* subtype 2 were immunocompromised due to the use of corticosteroids (21% of patients) or coinfection with HIV (62.5% of patients). Subtyping *M. kansasii* may improve clinical management by distinguishing pathogenic from nonpathogenic subtypes.

*Mycobacterium kansasii* is, after *Mycobacterium avium*, the mycobacterial species most frequently responsible for disease due to nontuberculous mycobacteria (7). However, little is known about its pathogenicity, mode of transmission, and natural reservoir. *M. kansasii* is often recovered from tap water and occasionally from river or lake water (12, 16, 17, 24). The isolation of this bacterium from other environmental sources, such as soil and animals, is very rare (1, 2, 18). *M. kansasii* causes pulmonary disease similar to tuberculosis in immunocompetent patients and pulmonary, extrapulmonary, or disseminated disease in patients with various immunodeficiencies, in particular human immunodeficiency virus (HIV) infection (6, 15, 19). Blood culture isolates, especially those from HIV-infected patients, should always be considered pathogenic (14). However, the isolation of *M. kansasii* from sputum is not proof of disease, as it may represent a colonization of the respiratory tract (1). The American Thoracic Society has recently proposed diagnostic criteria based on radiographic, clinical, and microbiological data (2).

Phylogenetic and molecular analyses have demonstrated that *M. kansasii* is a heterogeneous species with several distinct subtypes (1, 18, 21, 22). *M. kansasii* subtype 1, as defined by polymorphism analysis of the *hsp65* gene, is the subtype by far the most frequently isolated from humans; however, it is only rarely isolated from the environment. In contrast, HIV-in-

ected patients seem to be particularly susceptible to infection with *M. kansasii* subtype 2, which may act as an opportunistic agent (1, 27). Little is known about the pathogenic roles of other subtypes (subtypes 3 to 7), which are generally isolated from environmental sources (1). The aim of the present study was to analyze *M. kansasii* subtypes isolated from clinical specimens in Switzerland in order to determine the pathogenicity of each subtype.

### MATERIALS AND METHODS

***M. kansasii* isolates.** *M. kansasii* strains isolated between 1991 and 1997 at six major Swiss laboratories (in Lausanne, Zurich, Bern, Basel, Geneva, and Lugano) were included in a national survey. *M. kansasii* isolates were identified both biochemically and genetically by using AccuProbe (GenProbe Inc., San Diego, Calif.) for *M. kansasii* or PCR-restriction enzyme pattern analysis (26). One isolate from each patient was included. *M. kansasii* isolates that were identified at other Swiss laboratories ( $n = 23$ ) could not be included in this national survey.

**PCR-restriction enzyme pattern analysis of *hsp65*.** For the purpose of the study, all the strains were retyped at one center (Lausanne) by using PCR and restriction enzyme analysis of the *hsp65* gene (20, 26; www.hospvd.ch/prasite). Analysis of the *hsp65* gene by PCR-restriction analysis has been widely used for the diagnosis of mycobacterial infections and the characterization of newly described isolates (5, 9, 11, 23). Strains were classified into subtypes according to the restriction fragment length polymorphism patterns observed (1, 21).

**Clinical data.** Demographic, clinical, microbiological, and follow-up information was recorded from clinical files by using a standardized anonymous form. Patients were classified as having an infection according to the criteria of the American Thoracic Society (2). *M. kansasii* isolates collected from a normally sterile tissue (biopsy specimen, blood, or bone marrow) were considered pathogenic. Disseminated infection was defined by the presence of *M. kansasii* in blood, bone marrow, or simultaneously from three different anatomic sites. Isolates from patients with clinical presentations that could not be classified according to the American Thoracic Society criteria were assessed by an infec-

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TABLE 1. Distribution of *M. kansasii* isolates in Switzerland according to subtype<sup>a</sup>

Area	No. of isolates	No. (%) classified as subtype:					
		1	2	3	4	6	7
Zurich	88	66 (75)	15 (17)	4 (5)	0 (0)	0 (0)	3 (4)
Lausanne	36	21 (58)	7 (19)	7 (19)	0 (0)	1 (3)	0 (0)
Bern	31	21 (68)	10 (32)	0 (0)	0 (0)	0 (0)	0 (0)
Geneva	20	7 (35)	6 (30)	4 (20)	1 (5)	2 (10)	0 (0)
Basel	13	11 (85)	1 (8)	0 (0)	0 (0)	1 (8)	0 (0)
Lugano	3	2 (67)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)
Total	191	128 (67)	40 (21)	15 (8)	1 (0.5)	4 (2)	3 (2)

<sup>a</sup> No subtype 5 strains were isolated.

tious disease specialist (A.T.) and a medical microbiologist (G.P.) as being pathogenic or not according to clinical and follow-up data, without knowledge of the *M. kansasii* subtype.

**Statistical analysis.** Statistical analysis was performed with SPSS software (SPSS version 10.0; SPSS, Chicago, Ill.). Fisher's exact test was used to compare the characteristics of patients with the same subtype of *M. kansasii*, and the Mann-Whitney test was performed for comparison of median ages and duration of symptoms. Logistic regression was performed to compare the pathogenic roles of the subtypes. The variables included in the multivariate model were as follows: subtype of *M. kansasii*, HIV status, presence or absence of chronic obstructive pulmonary disease (COPD), smoking habits, and use of corticosteroids.

## RESULTS

**Distribution of subtypes.** Of the *M. kansasii* isolates collected in Switzerland between 1991 and 1997, 89% (191 isolates; one per patient) were included in this study. Subtype 1 was the subtype most frequently isolated ( $n = 128$ ; 67% of all isolates in the study), followed by subtype 2 ( $n = 40$ ; 21%), subtype 3 ( $n = 15$ ; 8%), subtype 6 ( $n = 4$ ; 2%), and subtype 4 ( $n = 1$ ; 0.5%) (Table 1). Subtypes 1 and 2 were isolated at sites nationwide, whereas subtype 3 was most frequently isolated in the two contiguous areas, Lausanne and Geneva, where it accounted for 19 and 20% of the isolates, respectively. *M. kansasii* subtype 5 was never detected in our study. However, a novel subtype with a unique restriction pattern, subtype 7, was identified in three patients (2%). *BstEII* digestion of the PCR products of this subtype resulted in a pattern identical to that for subtypes 2, 3, and 6, while *HaeIII* digestion gave a unique pattern (Table 2). Subtype 7 was confirmed to belong to the *M. kansasii* species by sequencing the 16S rRNA gene and the 16S to 23S rRNA spacer region.

The mean number of positive cultures per patient was 1.84 (range, 1 to 12). Of the isolates producing positive cultures,

TABLE 2. Patterns of *hsp65* PCR product after restriction enzyme digestion with *BstEII* and *HaeIII*

<i>M. kansasii</i> subtype	<i>BstEII</i> fragment lengths (bp)	<i>HaeIII</i> fragment lengths (bp)
1	240, 210	140, 105, 80
2	240, 135, 85	140, 105
3	240, 135, 85	140, 95, 70
4	240, 125, 85	140, 115, 70
5	325, 125	140, 100, 80
6	240, 135, 85	140, 105, 70
7	240, 135, 85	140, 95, 80

73% were collected from the respiratory tract. Mycobacteremia was detected in 32.5% of HIV-infected patients, in 2.5% of non-HIV-infected patients, and in 4.5% of patients with unknown HIV serostatus.

**Characteristics of patients.** Clinical data were available for 114 of the 191 patients (Table 3). The distribution of *M. kansasii* subtypes 1 and 2 among the 77 patients for whom no clinical data were available was comparable to that found among the 114 patients for whom data were available. Data for the four patients with *M. kansasii* subtype 6 were not available.

Patients infected or colonized with *M. kansasii* subtype 1 were mostly middle-aged men living in an urban environment, 31% of whom were HIV infected. They presented symptoms with a median duration of 2 months. *M. kansasii* subtype 1 was most frequently isolated from the respiratory tract (in 90.5% of patients), and smear examinations were positive for 24 (52%) of the 46 patients for whom the test was available. A disseminated infection was observed in 23% of the patients. While interstitial infiltrates were the predominant radiographic finding (in 54% of patients), cavitory lesions were observed in 23% of patients. The mortality rate was 47%, and half of the deaths were attributed to *M. kansasii* infection: 11 (65%) of the 17 patients who died from *M. kansasii* infections were HIV coinfecting, with severe immunosuppression (number of CD4-positive cells,  $<20/\text{mm}^3$ ), and 7 (64%) of the 11 had disseminated *M. kansasii* infections. The remaining six patients, not known to be HIV coinfecting, were older (mean age, 69) and presented comorbidities, such as pulmonary neoplasia (1 of 6), chronic pulmonary disease (2 of 6), or corticosteroid treatment (2 of 6). One patient with unknown HIV serostatus had a disseminated *M. kansasii* infection.

Patients infected or colonized with *M. kansasii* subtype 2 were on average 40 years old and immunocompromised due to either coinfection with HIV (62.5%) or the use of corticosteroids (21%). *M. kansasii* subtype 2 was most frequently isolated from the respiratory tract (in 79% of patients), and smear examinations were positive for 4 (27%) of the 15 patients for whom the test was available. The association between HIV infection and *M. kansasii* subtype 2 was statistically significant ( $P, <0.009$ ) (Table 3).

Compared to those with subtypes 1 and 2, patients infected or colonized with subtypes 3, 4, and 7 were older ( $P, <0.001$ ). These patients, the majority of whom were male, had underlying pulmonary disease (100%), but few were infected with HIV ( $P = 0.001$ ). Among these patients, there were no signs of disseminated disease ( $P, <0.03$ ) or instances of death attributed to *M. kansasii* infection. While all presented abnormal chest X-ray findings (triggering the request for culture), none of the abnormalities could be attributed to a *M. kansasii* infection. None of these patients had positive specimens as determined by smear examination.

**Pathogenicity according to subtypes.** Among the 114 patients, 77 were considered to be infected rather than colonized with *M. kansasii*. Overall, 60 (81%) of 74 patients with isolates of *M. kansasii* subtype 1 and 16 (67%) of 24 with isolates of subtype 2 but only 1 (6%) with subtypes 3, 4, and 7 was considered infected according to the criteria of the American Thoracic Society or based on blind evaluation by two independent investigators. In a multivariate analysis, adjusted to take into account HIV infection, COPD, smoking habits, and the

TABLE 3. Characteristics of 114 patients from whom *M. kansasii* was isolated<sup>a</sup>

Characteristic(s)	Value for <i>M. kansasii</i> subtype:		
	1 (n = 74) <sup>b</sup>	2 (n = 24)	3, 4, and 7 (n = 16)
<b>Demography</b>			
Mean age ± SD (yr)	45 ± 19.5 <sup>c</sup>	40.5 ± 16.7 <sup>c</sup>	76.0 ± 22.3
Male	46 (62.0)	15 (62.5)	11 (68.7)
Urban residents	42 (56.7)	15 (62.5)	11 (68.7)
Swiss	54 (73.0)	20 (83.3)	11 (68.7)
<b>Risk factors</b>			
HIV infection	23 (31.1) <sup>c</sup>	15 (62.5) <sup>c</sup>	1 (6.2)
Corticoid use	5 (6.7)	5 (20.8)	3 (18.7)
Tobacco use	43 (58.1)	18 (75.0)	8 (50.0)
COPD	15 (20.3)	6 (25.0)	9 (56.2)
Other pulmonary diseases	45 (60.8)	16 (66.7)	9 (56.2)
<b>Source of isolate<sup>d</sup></b>			
Pulmonary	67 (90.5)	19 (79.2)	9 (56.2)
Nonpulmonary	20 (27.0)	8 (33.3)	4 (25.0)
Disseminated	17 (23.0) <sup>c</sup>	7 (29.2) <sup>c</sup>	0 (0.0)
<b>Clinical presentation</b>			
Asymptomatic	4 (5.4)	2 (8.3)	3 (18.7)
Systemic symptoms	55 (74.3) <sup>c</sup>	18 (75.0) <sup>c</sup>	6 (37.5)
Respiratory symptoms	60 (81.1)	20 (83.3)	13 (81.2)
Median duration of symptoms (wk)	8 <sup>c</sup>	6 <sup>c</sup>	2
<b>Results of chest radiography</b>			
Normal	9 (12.1)	1 (4.2)	0 (0.0)
Abnormal <sup>e</sup>	64 (86.5)	22 (91.7)	16 (100.0)
Interstitial infiltrate	40 (54.1)	8 (33.3)	6 (37.5)
Cavitation	17 (23.0) <sup>c</sup>	2 (8.3)	0 (0.0)
Alveolar infiltrate	7 (9.5) <sup>c</sup>	5 (20.8)	5 (31.3)
Nodular infiltrate	4 (5.4)	3 (12.5)	0 (0.0)
Mediastinal enlargement	4 (5.4)	4 (16.7)	1 (6.3)
Pleural effusion	3 (4.1)	0 (0.0)	1 (6.3)
Other	3 (4.1)	1 (4.2)	3 (18.8)
Not available	1 (1.4)	1 (4.2)	0 (0.0)
<b>Results of smear examination</b>			
Positive	24 (32.4) <sup>c</sup>	4 (16.7)	0 (0.0)
Negative	22 (29.7)	11 (45.8)	10 (62.5)
Not available	28 (37.8)	9 (37.5)	6 (37.5)
<b>Antimycobacterial therapy</b>			
	53 (71.6) <sup>c,f</sup>	10 (41.7) <sup>c</sup>	4 (35.0)
<b>Outcome</b>			
Cured	32 (43.2)	7 (29.2)	7 (43.7)
Treatment failure	8 (15.1)	2 (20.0)	0 (0.0)
Death	35 (47.3) <sup>c</sup>	11 (45.8) <sup>c</sup>	2 (12.5)
Attributed to <i>M. kansasii</i>	17 (22.9) <sup>c</sup>	6 (25.0)	0 (0.0)

<sup>a</sup> Numbers in parentheses are percentages.

<sup>b</sup> n, total number of patients.

<sup>c</sup> P is <0.05 compared to values for subtypes 3, 4, and 7.

<sup>d</sup> Patients may have *M. kansasii* strains isolated from multiple body sites.

<sup>e</sup> Patients may have more than one type of radiologic lesion.

<sup>f</sup> P is <0.05 compared to values for subtype 2.

use of corticosteroids, *M. kansasii* subtype 1 was shown to be independently associated with pathogenicity (odds ratio, 14.4; 95% confidence intervals, 2.9 to 71.2 [Fig. 1]). *M. kansasii* subtype 2 was considered pathogenic in 14 (93%) of the 15 HIV-infected patients and in 2 (22%) of the 9 patients that were not seropositive for HIV (*P*, <0.001). *M. kansasii* subtypes 3 and 4 were never considered pathogenic, while one patient with subtype 7 was classified as infected.

## DISCUSSION

This national survey documents for the first time, with a large collection of *M. kansasii* strains, the distribution and pathogenicity of the various *M. kansasii* subtypes. *M. kansasii* subtype 1 was the most commonly isolated, followed by subtype 2. While both subtypes were found in all regions of the country, other subtypes had a more diverse geographical dis-

		Odds ratio	95% CI
<i>M. kansasii</i>	subtype I	14.4	2.9 – 71.2
HIV infection		15.3	2.6 – 91.6
COPD		0.19	0.04 – 0.9
Tobacco use		3.02	0.64 – 14.4
Corticosteroid use		2.66	0.34 – 21.1

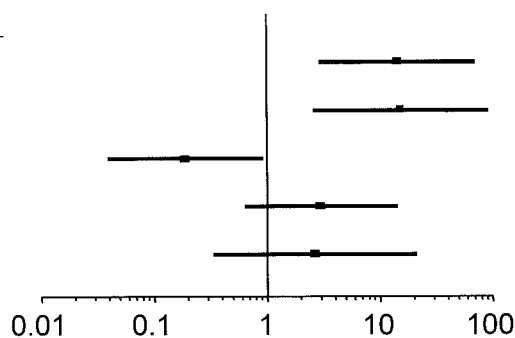


FIG. 1. Adjusted odds ratios of having a pathogenic strain of *M. kansasii* subtype I. Horizontal lines are 95% confidence intervals (95% CI).

tribution. In addition to the six subtypes previously described (21, 26), a novel subtype, subtype 7, was identified in three patients. Differences in local isolation rates for the different subtypes may reflect the existence of different ecosystems or, to a lesser extent, differences in the pretreatment of specimens in clinical laboratories. For example, nalidixic acid added to BACTEC media to control overgrowth of contaminants may compromise the recovery of *M. kansasii* from some specimens (8).

This study allowed the assignment of the degree of pathogenicity to the various subtypes. It confirms the morbidity and mortality associated with subtype 1 (10) and the role of subtype 2 as an opportunistic pathogen infecting immunosuppressed individuals (27). In HIV-infected patients, *M. kansasii* is generally identified at the stage of advanced immunodeficiency (mean CD4-positive cell count, <100 cells/mm<sup>3</sup>) (3, 4, 6, 28). In contrast, clinical infection with other subtypes appears to be exceptional, and the isolation of these subtypes from patients with underlying pulmonary disease suggests that they act as colonizing agents or environmental contaminants. This notion will have to be reassessed by larger epidemiological studies. Further investigation is necessary to elucidate the virulence factors of the *M. kansasii* subtypes 1 and 2, such as hemolytic activity and the production of phospholipase C or other similar enzymes, possibly related to pathogenicity (13).

Retaining the heterogeneous group of isolates within the *M. kansasii* taxon might be questioned. Given the differences in genetic structures, pathogenic roles, clinical significances, and environmental distributions and possibly in the routes of transmission (1), it may be speculated that some of the subtypes represent a distinct species of mycobacterium (25). Independent of these considerations, however, the present study underscores that the identification of *M. kansasii* to the subtype level may be not only an interesting epidemiological tool but also a process relevant to clinical management, as it allows the differentiation of pathogenic from the nonpathogenic subtypes.

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