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MINIREVIEW

Clinical, Bacteriological, and Serological Aspects of *Klebsiella* Infections and Their Spondylarthropathic Sequelae

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INTRODUCTION

Since Friedländer in 1883 first demonstrated capsulated rod-shaped bacteria in the lungs of patients dying of pneumonia, *Klebsiella* has been known to physicians primarily as the pathogen causing "Friedländer's pneumonia." The production of enormous amounts of capsular polysaccharides in vivo as well as on agar medium is characteristic of bacteria of this genus and is unique among the members of the family *Enterobacteriaceae*, to which *Klebsiella* belongs. Despite the discovery of other virulence factors such as fimbriae, siderophores, and O antigens (104), the efforts to clarify the pathogenic mechanisms of *Klebsiella* mainly focus on their capsular antigens, which are considered to be the ultimate determinants of their pathogenicity. Thus, *Klebsiella* is regarded as a paradigm for systemic infections caused by capsulated bacteria. In contrast to other capsulated pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, however, *Klebsiella* spp. are not closely adapted and restricted to the host habitat but are rather widespread in nature and can be found in water and soil as well as on plants.

CLINICAL SIGNIFICANCE OF *KLEBSIELLA*

Conventionally, a number of different infections are caused mainly by *Klebsiella pneumoniae*, medically the most important species of this genus. To a much lesser degree, *Klebsiella oxytoca* is also found in human clinical specimens.

Community-acquired pneumonia. *K. pneumoniae* is the most common gram-negative pathogen causing community-acquired bacterial pneumonia (18). Alcoholics constitute the main patient population at risk, comprising up to 66% of those suffering from this disease. Community-acquired pneumonia is a very severe illness with a rapid onset, and despite the availability of an adequate antibiotic regimen, the outcome is often fatal. The observed mortality rates are about 50% (37). In alcoholic patients with bacteremic *K. pneumoniae* pneumonia, mortality approaches 100% (55).

Rhinoscleroma and ozena. The only two pathogen-specific *Klebsiella* infections, rhinoscleroma and ozena, are very rare diseases today. Both infections have specific pathologic-anatomic changes in common. Rhinoscleroma, whose association with capsulated rod bacteria (*K. pneumoniae* subsp. *rhinoscleromatis*) was first described in 1882 by von Frisch is characterized by a chronic inflammatory process of the nasopharynx. This infection is distributed around the world but today is encountered in certain areas in eastern Europe, Latin America, central Africa, and southern Asia, where the infection is endemic. Ozena, a chronic atrophic rhinitis characterized by necrosis of the mucosa and mucopurulent nasal discharge, has also become rare (43). Although often present in pathologically changed nasal mucosa, *K. pneumoniae* subsp. *ozaenae* is no longer regarded as the causative agent but, rather, as the indicator organism of the disease.

Nosocomial infections. Nowadays, *Klebsiella* infections are particularly associated with hospitalization. As an opportunistic pathogen, *Klebsiella* primarily attacks immunocompromised individuals who are hospitalized and who have severe underlying diseases. It is estimated that *Klebsiella* species cause 8% of all hospital-acquired infections. In the United States they comprise 3 to 7% of all nosocomial bacterial infections, placing them among the eight most important pathogens in hospitals and second only to *Escherichia coli* as the most common cause of gram-negative sepsis. *Klebsiella* infections are observed in almost any body site, although infections of the urinary and respiratory tracts predominate. Depending on the type of infection and study, its prevalence ranges from 3 to 17% of all such infections. Table 1 lists the most frequent nosocomial infections caused by *Klebsiella*.

The principal pathogenic reservoirs for transmission of *Klebsiella* are the gastrointestinal tract of patients and the hands of personnel (69). The ability of this genus to spread rapidly (58) often leads to nosocomial outbreaks. Of the 145 epidemic nosocomial infections reported in the English language literature between 1983 and 1991, 13 were caused by *Klebsiella* (29). The Centers for Disease Control and Prevention in Atlanta, Ga., puts the proportion of endemic hospital infections caused by *Klebsiella* at 8% and indicates that, among epidemic outbreaks caused by all pathogens, *Klebsiella* strains cause 3% of epidemic outbreaks (92).

NEW TRENDS

Emergence of multiresistant strains. Especially feared are epidemic hospital infections caused by multiresistant *Klebsiella* strains. In the 1970s these were mainly aminoglycoside-resistant *Klebsiella* strains (20, 72). Since 1982 strains whose production of so-called extended-spectrum β-lactamases renders them resistant to extended-spectrum cephalosporins have emerged (7, 54, 67). Their β-lactamases are plasmid mediated and are mostly of the SHV-5 type in Europe, whereas TEM-10 and TEM-12 types are more prevalent in the United States. Apart from being resistant to a variety of antibiotics, these strains are characterized by their resistance to ceftazidime. Worldwide, the emergence of ceftazidime-resistant *Klebsiella* strains began when the usage of this antibiotic was increased. Because of the numerous multiply resistant *Klebsiella* outbreaks that have been reported in the last few years, the ques-

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TABLE 1. Hospital-acquired bacterial infections caused by *Klebsiella* spp.

Infection	%	Rank
Urinary tract infections[a]	6–17	5–7
Pneumonia[a]	7–14	2–4
Septicemia[a]	4–15	3–8
Wound infections[a]	2–4	6–11
Nosocomial infections in intensive care unit patients[a]	4–17	4–9
Neonatal septicemia[b]	3–20	2–8

[a] Data are from references 12, 13, 21, 22, 27, 30, 39, 52, 62, 66, and 76.
[b] Data are from references 9, 39, 74, 94, 97, and 101.

tion has arisen whether it is necessary to determine whether each isolated *Klebsiella* isolate is an extended-spectrum β-lactamase producer. The answer depends upon the epidemiologic situation of a country or a hospital, but it should definitely be positive if a high percentage of ceftazidime-resistant strains are to be expected. Recent investigations report a 14 to 16% incidence of extended-spectrum β-lactamase producers among clinical *Klebsiella* isolates in France and England (88), but the incidence can reach 25 to 40% in particular regions or hospitals (14, 46).

Emergence of *K. oxytoca* K55 in neonatal bacteremia. In pediatrics, too, nosocomial *Klebsiella* infections become troublesome, particularly in premature infants and neonatal intensive care units. *Klebsiella* species are often isolated from the blood of patients with neonatal septicemia, including those with early-onset and late-onset infections. They are among the top four pathogens causing infections in neonatal intensive care units and represent the second most common causative agent of gram-negative neonatal bacteremia (Table 1). Preemptive antimicrobial therapy of suspected neonatal septicemia, however, led to increased rates of carriage of *Klebsiella* and, subsequently, to the emergence of multiresistant strains (11, 47). Outbreaks of infections caused by extended-spectrum β-lactamase-producing *Klebsiella* species in neonatal units have become a serious problem (23, 80). Remarkably, *K. oxytoca* has been isolated with increasing frequency from patients with neonatal septicemia. Epidemiologic analyses of these isolates demonstrated a highly virulent, multiresistant *K. oxytoca* clone showing capsular type K55. This strain apparently has an extraordinary capability to spread, leading to colonization of infants as well as to epidemic outbreaks in several countries (70, 89, 96). At present, *K. oxytoca* K55 is distributed nationwide in Swedish neonatal wards.

New *Klebsiella* species. In 1981, two new *Klebsiella* species, *Klebsiella terrigena* and *Klebsiella planticola*, were described. Originally considered to be without clinical significance and to be restricted to aquatic, botanic, and soil environments, recent reports describe them as occurring in human clinical specimens (71, 78, 79). While *K. terrigena* is rarely found among clinical *Klebsiella* strains (0.4%), *K. planticola* accounts for up to 20% of all clinical *Klebsiella* isolates. The findings of our group (79) revealed that 14 of 85 clinical *K. planticola* isolates were from patients with monomicrobial infections. Because a number of these isolates could be associated with corresponding diseases, *K. planticola* may be regarded as a causative agent of nosocomial infections. This species occurs predominantly in the respiratory tract; further studies are needed to evaluate whether a new respiratory pathogen has emerged.

KLEBSIELLA AND ANKYLOSING SPONDYLITIS

One of the most fascinating aspects of *Klebsiella* pathogenicity is the proposed role of this microorganism in the etiopathology of the HLA-B27-associated rheumatic disorder ankylosing spondylitis (AS). In the late 1970s the first reports of a possible linkage between *Klebsiella* and AS appeared. Since then, particular attention has been focused on the association of HLA-B27 and *Klebsiella* antigens in AS. Just recently, however, new epidemiologic evidence of the role of *Klebsiella* in AS has been gained by demonstration of the significance of particular *Klebsiella* capsular types. It is suggested that these findings point to an as yet undefined role of *Klebsiella* capsular polysaccharides in AS. A comprehensive summary of the recent developments in this field is given below.

Clinical and epidemiological aspects of HLA-B27 and AS. AS, also known as Bechterew's disease, is the prototype of the group of spondarthritides which comprises the numerically largest group of inflammatory rheumatic diseases after rheumatoid arthritis. The initial stage of the disease is characterized by sacroiliitis and enthesopathy of the musculotendinous insertion, especially along the lumbar spine (6); after a course sometimes lasting decades, the end stage of full-blown ankylosis, usually of the spinal and vertebral joints, is reached. The disease is often accompanied by a number of visceral manifestations such as iridocyclitis and mesaortitis. AS is characterized by a number of laboratory findings, which correlate with disease activity. The levels of total immunoglobulin A (IgA) have been shown to be significantly elevated in the sera of patients with active AS compared with those in the sera of patients with inactive disease and healthy controls. Moreover, it was demonstrated that clinically assessed disease activity correlates with elevations in nonspecific biochemical parameters of inflammation, e.g., C-reactive protein and erythrocyte sedimentation rate (24, 25). AS primarily affects males between 15 and 30 years of age (1) and approximately 0.1 to 1.5% of the Caucasian population. While the pathologic mechanism of the disease is unknown, the strong association with HLA class I antigen B27 is one of the common features of AS. Approximately 96% of patients with AS possess HLA-B27, while this genetic marker occurs in less than 8% of the healthy Caucasian population (15, 85). This strong restriction of the disease to those who possess HLA-B27 has led many researchers to investigate the racial and geographic heterogeneity of these antigens. Studies of families have shown that first-degree relatives of HLA-B27-positive AS patients have a much higher risk of developing AS than other relatives of HLA-B27-positive individuals (16, 99). The high frequency of HLA-B27 in some racial groups is associated with an unusually high incidence of AS. Approximately 29% of the Haida Indians of British Columbia and Navajo Indians of Arizona are HLA-B27 positive (41, 42), with the prevalence of AS in these populations being 6.2%. By contrast, AS has rarely been reported in populations in which HLA-B27 is absent, such as South American Indians, Australian aborigines, and Bantus and Sans of equatorial and southern Africa (56). So far, nine different HLA-B27 subtypes have been described. Of these, only HLA-B*2702, HLA-B*2703, HLA-B*2704, HLA-B*2705, and HLA-B*2706 are sufficiently prevalent to allow for meaningful analysis (56). The subtyping of various racial groups has revealed that HLA-B*2705 is the predominant subtype in almost all populations; it is believed, moreover, to be the progenitor for all other subtypes (61). A total of 85 to 90% of the Caucasian HLA-B27-positive population possesses this subtype. HLA-B*2702, which is restricted to the Caucasian population, is the second most frequent subtype, with a prevalence of 10%. HLA-B*2703, with an incidence of 61%, is found predominantly in West African and American blacks (19). HLA-B*2704 and HLA-B*2706 are restricted to Asians, in whom HLAB*2704, with a frequency of 55%, is the preponderant subtype. AS

occurs most frequently in patients with HLA-B*2702, HLB*2704, and HLA-B*2705 subtypes. Because of the low incidence of AS in individuals carrying the subtypes HLA-B*2703 and HLA-B*2706, it is has been suggested that these individuals are not susceptible to the disease (51). Recently, however, there have been reports of HLA-B*2703 and HLA-B*2706 AS patients (38). Therefore, the distribution of the serotypes in healthy individuals and in AS patients needs further verification.

Historical background of *Klebsiella* in AS. The well-documented association of acute reactive arthritis and infections with enterobacteria, e.g., *Yersinia enterocolitica*, *Shigella*, and *Salmonella*, led to the working hypothesis that AS might also be a sequela of infection with enteric microorganisms. A possible association between AS and *K. pneumoniae* was first pointed out by Ebringer et al. (34) in 1976. Since then attention has focused particularly upon *Klebsiella pneumoniae*, and in the last three decades a large number of studies underscoring the central role of this microorganism in the etiopathology of AS has been performed. In 1978 Ebringer and coworkers (36) reported an increased colonization of the bowel of AS patients with *Klebsiella* during the active phase of the disease. Subsequently, several investigators have also reported widespread *Klebsiella* colonization of the gut of AS patients (32, 53, 57). However, little is known about the distribution of *Klebsiella* serotypes in the bowels of these patients. Further isolation and serotyping of *Klebsiella* from the bowels of AS patients are therefore necessary. Studies with human HLA-B27 tissue typing sera and *Klebsiella* have shown increased binding of the latter by these sera (4). In further studies, increased cytolysis of HLA-B27-positive lymphocytes by rabbit anti-*Klebsiella* antibodies (103) and T-cell-independent polyclonal B-cell activation by *Klebsiella* antigens with development of autoimmune phenomena (45) have been demonstrated. In a serological study aimed at the detection of antibodies to various bacterial antigens in the sera of AS patients in 1983, Trull et al. (95) found titers of IgA antibodies to *Klebsiella* but not to other bacteria to be elevated in the sera of patients with active AS. Similar results of increased specific anti-*Klebsiella* IgA in the sera of AS patients have been reported by other groups (33, 63–65). Thus, an intestinal site of antigen presentation has been assumed. However, other groups have failed to confirm elevated titers of anti-*Klebsiella* antibodies in the sera of AS patients (90, 91, 98) or an increased isolation of *Klebsiella* from the feces of such patients (100, 102).

Various theories have been developed to explain the mode of association between HLA-B27 and *Klebsiella* and their contribution to the development of AS. The "modifying factor" theory initially proposed by Geczy et al. (40) is based on the observation that rabbit antisera raised against certain *Klebsiella* strains were cytolytic to HLA-B27-positive lymphocytes from AS patients but not to lymphocytes taken from HLA-B27-positive healthy individuals (87). Incubation of the lymphocytes from HLA-B27-positive healthy controls in filtrates from *Klebsiella* cultures results in cytolysis of these lymphocytes by the rabbit *Klebsiella* antisera (40). It has been suggested that a *Klebsiella* antigen, perhaps a plasmid, is responsible for the modification of the HLA-B27 molecule that renders it susceptible to an anti-self response (17). Attempts by different groups to reproduce the results of Geczy et al. (40) have been unsuccessful (10), and the concept of the modification of the HLA-B27-positive cells of the AS patients has never been clearly proved.

Another model to explain the association between *Klebsiella* and AS in an HLA-B27-restricted manner is the "chemotaxis theory" propounded by Repo et al. (81). According to this theory, the HLA-B27-positive polymorphonuclear leukocytes have an increased chemotactic activity compared with the chemotactic activity of polymorphonuclear leukocytes from HLA-B27-negative counterparts (81). An enhanced chemotaxis of HLA-B27-positive cells to certain gram-negative bacteria such as *Yersinia* or *Shigella* would explain the higher incidence of reactive arthritis in HLA-B27-positive patients after infections with these microorganisms. Such an increased responsiveness by HLA-B27-positive cells has been shown in HLA-B27-positive patients after *Yersinia*-reactive arthritis (59). In other studies, Pease et al. (75) could confirm an HLA-B27-linked chemotactic ability. It has been suggested that a similar response of the HLA-B27-positive cells to *Klebsiella* leads to the development of AS (60).

The molecular mimicry theory, first proposed by Ebringer et al. (34), implicates cross-reactivity between *Klebsiella* antigens and shared epitopes on the HLA-B27 molecule in the development of AS. This theory is supported by observations of increased binding of anti-*Klebsiella* antibodies to HLA-B27-positive cells and of anti-HLA-B27 antibodies to *Klebsiella* antigens and of increased binding of anti-HLA-B27 typing sera to *Klebsiella* (4, 103). Furthermore, an identical sequence of six amino acids (QTDRED) has been detected in both the *Klebsiella* enzyme nitrogenase reductase and certain HLA-B*2705 structures, and antibodies to this hexapeptide were detected in the sera of AS patients (86). By contrast, other groups were not able to confirm the existence of anti-B27 autoantibodies in AS patients (28).

The "receptor theory" is based on the hypothesis of Zinkernagel and Doherty that the class I major histocompatibility complex molecules present bacterial and viral antigens. It is suggested that the HLA-B27 molecule acts as a receptor for processed arthritogenic polypeptides, perhaps derived from *Klebsiella*. As a consequence, cytotoxic T cells directed against these peptides also attack structurally equivalent, joint-associated proteins physiologically presented by HLA-B27 molecules (8). Such an autoimmune response mediated by T cells against self-antigens requires a breaking up of the self-tolerance, which might result from a clonal deletion of the T-cell population that recognizes HLA during its maturation in the thymus. In a more recent study, *Klebsiella*-reactive T cells were found at a lower frequency in the peripheral blood of AS patients than in that of healthy HLA-B27-positive individuals. This might indicate an altered peripheral T-cell immune response to *Klebsiella* in AS patients. This response allows *Klebsiella* antigens to reach the synovial fluid and stimulate a specific T-cell-mediated immune response (49). Interestingly, CD8-positive cytotoxic T lymphocytes which recognize and kill antigen-presenting cells have been found in the synovial fluid of patients with reactive arthritis (50).

Recent immunological data linking immune response to *Klebsiella* capsular antigens and AS. Despite intensive research, the nature of the disease-relevant *Klebsiella* antigens remains unknown. The theories mentioned above have been partially refuted by contradictory findings of other groups (82). It must be pointed out, however, that previous reactivity studies applied different cell preparations containing only 2 of the 77 known *Klebsiella* serotypes (serotypes K21 and K43). The reactivity to specific capsule antigens has not been investigated, despite clear indications that these antigens play a central role in the pathogenesis of many infectious diseases. Moreover, there have been no epidemiologic studies of the 77 known *Klebsiella* serotypes in AS patients, although the individual capsule types differ markedly in their pathogenicities and epidemiologic relevance. Hence, it could not be excluded at that

TABLE 2. Incidence of reactive sera to *Klebsiella* capsular types K26, K36, and K50 in patients and controls

Patient[a]	% Sera positive for reactivity to the following *Klebsiella* CPS[b]:			
	K26	K36	K50	Total
AS^+B27^+	32[c]	51[c]	54[c]	90[c]
AS^+B27^-	15	30	23	37
SLE	8	12.5	25	40
PA	0	8	25	32
ReA	16	20	25	51
RA	0	25	12.5	33
AS^-B27^+	5	11	22	33
AS^-B27^-	10	7.5	27	40

[a] AS^+B27^+, HLA-B27-positive AS; AS^+B27^-, HLA-B27-negative AS; SLE, systemic lupus erythematosus; PA, psoriatic arthritis; ReA, reactive arthritis after *Y. enterocolitica* infection; RA, rheumatoid arthritis; AS^-B27^+ and AS^-B27^-, healthy individuals who are either HLA-B27-positive and HLA-B27-negative, respectively.

[b] CSP, capsular polysaccharide.

[c] Significantly higher antibody frequencies to *Klebsiella* capsular polysaccharides ($P < 0.01$).

point that other *Klebsiella* serotypes play a role in the etiopathology of AS.

Recent enzyme-linked immunosorbent assay studies of the antibody response to *Klebsiella* capsular polysaccharides in the sera of patients with AS and other rheumatic disorders were the first that involved all 77 *Klebsiella* serotypes. Sera from HLA-B27-positive AS patients showed increased IgG responses to the capsular polysaccharides of *Klebsiella* serotypes K26, K36, and K50 compared with the IgG responses of sera from HLA-B27-negative AS patients and sera from patients with systemic lupus erythematosus, psoriatic arthritis, reactive arthritis after *Y. enterocolitica* infections, or rheumatoid arthritis or sera from HLA-B27-positive or HLA-B27-negative healthy controls (83, 84) (Table 2). This finding can be taken to indicate an epidemiologic predominance of these serotypes in AS and might indicate an as yet undefined role of these capsular polysaccharides in the pathologic mechanism of AS. It is remarkable, however, that these three serotypes are rarely isolated from human clinical specimens, reflecting an absence of these types in human infections.

To date, it is not clear whether AS-associated *Klebsiella* serotypes are clonal. While it is generally assumed that infecting isolates of the same species from a single patient are clonally related (2), the question of whether particular *Klebsiella* infections can be assigned to clonal groups is the subject of a controversy. In a study on uropathogenic *K. pneumoniae* and *K. oxytoca* strains, Tarkkanen et al. (93) could not identify clonal substructures similar to those found in pyelonephritogenic *E. coli* strains. Other studies, however, observed a particular capsular antigen, antigen K2, to be prevalent in uropathogenic (77) as well as bacteremic (26) *Klebsiella* isolates.

Nonopsonic phagocytosis as a model for a possible role of the capsular polysaccharides in AS. The bacterial capsule is generally thought to have a virulence-enhancing, antiphagocytic effect. The phagocytic process initially requires an interaction between the bacterium and the phagocyte. Two modes of interaction have been described, opsonin-dependent and opsonin-independent interactions, also termed lectinophagocytosis or nonopsonic phagocytosis. The latter is especially important in a serum-poor environment and involves recognition of bacterial surface carbohydrates (e.g., capsule polysaccharides) by specific receptors (lectins) on the macrophage surface or recognition of the binding of carbohydrate structures on the macrophage surface with corresponding lectins of the bacterium (73). Athamna et al. (3) have shown that capsule polysaccharides of certain *Klebsiella* serotypes with the sequences Manα2/3Man and/or Rhaα2/3Rha bind specifically to the mannose–*N*-acetylglucose receptor (Man/GlcNAc-lectin) of macrophages, leading to phagocytosis and destruction of the bacterium. This feature may explain why certain capsule types can be isolated more frequently from clinical material than others.

It is worth noting that all three capsule types (types K26, K36, and K50) which we regard as dominant for AS contain polysaccharides recognized by the macrophage lectin (Fig. 1). This type of binding to macrophages could play an initial role in the pathogenesis of AS. Of the 77 known *Klebsiella* serotypes, only 16 capsule types contain sequences which allow for a specific interaction with the mannose receptor of the macrophage. In a second stage, it is conceivable that, in contrast to the other 13 serotypes mentioned above, bacteria expressing the three serotypes K26, K36, and K50 contain specific antigens, perhaps peptides, which elicit arthritogenic activity after ingestion and killing of the bacterium by the macrophage. Processing and presentation of this antigen might activate a specific and as yet undefined immunological cascade inducing reactive arthritis and, later, the full syndrome of AS. However, further studies aimed at elucidating the interaction of these serotypes with relevant cells from HLA-B27-positive AS patients and from healthy B-27-positive and -negative individuals are required.

Since the antibodies that we demonstrated are of the IgG type, it can be assumed that T cells are involved. This is in contrast to the generally accepted theory that, as polysaccha-

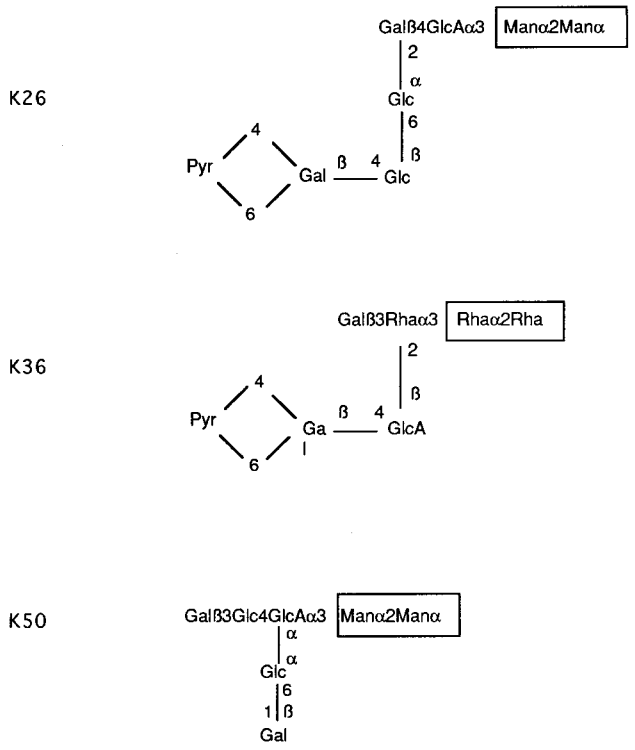

FIG. 1. Capsular polysaccharide structures of *Klebsiella* serotypes K26, K36, and K50 (31). Man, mannose; Gal, galactose; Glc, glucose; GlcA, glucuronic acid; Rha, rhamnose; Pyr, pyruvyl. Disaccharides considered to mediate binding to the mannose receptor are in boxes.

ride structures, capsules can induce the formation of IgM antibodies independently of T cells (5). Findings by various groups, however, indicate that an antibody response against pneumococcal polysaccharides is regulated by T cells on an antigen-specific and major histocompatibility complex-associated basis (44, 68). Since pneumococci and *Klebsiella* capsule polysaccharides have some antigens in common, it is conceivable that *Klebsiella* capsule antigens also elicit a similar immune response. No studies on T-cell involvement in the immune response to *Klebsiella* capsule polysaccharides in patients with AS have yet been published.

CONCLUDING REMARKS

Klebsiellae are enterobacteria that normally produce prominent polysaccharide capsules. These bacteria are considered to be a paradigm for systemic infections caused by capsulated microorganisms. Apart from community-acquired pneumonia, they are commonly associated with nosocomial infections. Over the past 10 years some new trends have been observed with respect to *Klebsiella* infections, such as the emergence of extended-spectrum β-lactamase-producing strains, neonatal septicemia caused by *K. oxytoca* capsule type K55, and new *Klebsiella* species as causative agents of human infection (*K. planticola* and *K. terrigena*).

Moreover, klebsiellae are thought to play a crucial role in the pathogenesis of HLA-B27-associated AS. The mode of association between *Klebsiella*, HLA-B27, and AS is unclear. We especially need to know to what extent HLA-B27-associated AS is characterized by an abnormal immunoreaction to *Klebsiella*, analogous to that in other pathogen-associated spondarthritides (e.g., chlamydial or yersinial arthritis). We also need to establish a pathologic immune response to *Klebsiella* as a diagnostic criterion in AS.

Optimization of the armamentarium (enzyme-linked immunosorbent assay and PCR) for the diagnosis of *Klebsiella* infections caused by specific *Klebsiella* serotypes would open new prospects for the treatment of AS. As in *Yersinia*-associated arthritis, early application of such measures as antibiotic agents (65) or restriction of dietary starch intake to reduce *Klebsiella* colonization in the gut could become an integral part of therapeutic planning (35).

Because of its apparent association with *Klebsiella* infection, AS is an excellent model for conducting a targeted search for pathogen-induced pathologic mechanisms in spondylarthritis. The knowledge thus gained could serve as a basis for the development of new therapeutic strategies, including T-cell vaccination to induce an immune response against autoreactive T cells. If increased colonization of the bowel by certain *Klebsiella* capsule types causes acute disease flare-ups, the use of monoclonal antibodies against certain capsule polysaccharides during acute phases of infection would represent another possible therapeutic approach. The effectiveness of such immunization against the pathogenetic process in experimental pneumonia has been demonstrated in animal models by other groups (48).

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