Factors associated with airway colonisation and invasion due to *Klebsiella* spp.

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Abstract **The clinical significance of a heavy growth of *Klebsiella* spp. in sputum was studied in 54 patients. All but 3 patients had significant factors potentially associated with respiratory tract colonisation or invasion. Risk factors identified for colonisation of the airway and for invasive disease were similar. Patients with community-acquired *Klebsiella* infections were more likely to have underlying chronic respiratory diseases. Prior antibiotic use was a risk factor for nosocomial infections which occurred more commonly with antibiotic-resistant organisms.**

The most common diagnoses were airway colonisation, acute community-acquired chest infections, and nosocomial chest infections. Primary acute community-acquired pneumonia was uncommon.

The sensitivity and specificity of the sputum Gram stain (in the setting of positive sputum cultures) in suggesting the presence of invasive disease due to *Klebsiella* spp. were 42% and 69% respectively.

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Acute respiratory tract infections, including bacterial pneumonia, are common world-wide.[1-3] While *Streptococcus pneumoniae* predominates among the community-acquired causes,[2-4] Gram-negative organisms such as *Klebsiella* spp. are frequent causes of nosocomial infections.[5,6] The latter organisms are also a recognised cause of community-acquired Gram-negative bacillary pneumonia.[2-4] Both for anecdotal reasons and as a result of previous studies at our hospital, we have noted that *Klebsiella* spp. are common sputum culture isolates[7] and important causes of pulmonary infection.[8,9]

The aim of the present investigation was to study the clinical significance of a positive sputum culture of *Klebsiella* spp., in particular to determine associated medical conditions which could serve as risk factors for colonisation of the respiratory tract with this organism. We compared such factors in patients with airway colonisation and invasive disease, in those with community-acquired and nosocomial infection, and in patients colonised with antibiotic-sensitive and resistant organisms.

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Patients and methods

This was a prospective study undertaken at Hillbrow Hospital in Johannesburg during a 3-month period. All patients from whose sputum cultures *Klebsiella* spp. were isolated in significant growth on primary blood agar plates following culture of fresh sputum specimens were entered into the study (2+ growth was equal to 10 - 100 colonies and 3+ growth to more than 100 colonies).

The quality of each specimen was assessed according to the Bartlett classification, based on the presence or absence of polymorphonuclear leucocytes and epithelial cells, the ratio of one to the other and the presence or absence of mucus on Gram-stained microscopy.[10] Good quality specimens were those of Bartlett grade ≥ 1. Sputum specimens were Gram-stained and cultured, and *Klebsiella* spp. were identified according to standard microbiological techniques.[11] Any large Gram-negative bacillus that was oxidase-negative and grew on MacConkey agar in the form of large mucoid, lactose-fermenting colonies within 24 - 48 hours of inoculation, was presumptively identified as *Klebsiella*.[11] Confirmation as a *Klebsiella* species was based on whether the organism was a non-motile, gas-producing glucose fermenter, with certain specific biochemical properties including decarboxylation of ornithine, and positive utilisation of citrate (95%).[11]

The presence of numerous (noted as 3+ quantity) large Gram-negative bacilli on sputum Gram-staining was recorded as a positive Gram's stain. The antimicrobial susceptibility of the *Klebsiella* organisms was determined by means of the disc diffusion method, according to the specifications of the National Committee for Clinical Laboratory Standards (NCCLS).[12] The presence of associated micro-organisms in sputum or blood culture was documented.

The demographic data of each patient were recorded, as were all associated factors which may have served as possible predisposing factors to respiratory tract colonisation or infection with *Klebsiella* spp. Specific factors recorded included the age of each patient, occupation, place of residence, diet and nutritional status, presence of any underlying lung, cardiac or systemic disease (including diabetes mellitus), any condition likely to be associated with immunosuppression in general or nosocomial infections, recent prior hospitalisation, duration of present hospitalisation, and current use of antibiotics, corticosteroids, and chemo- or radiotherapy.

Each patient was assigned a clinical diagnosis based on a consideration of several factors. 'Colonisation of the airway' was the term applied to those patients without evidence of invasive disease, from whose sputum *Klebsiella* spp. were cultured. 'Infection' was the term assigned to those patients with invasive disease. The latter diagnosis was based on a consideration of the patient's history, the clinical features of illness, including temperature and chest examination, laboratory data such as white cell count and chest radiographic findings, and also took into account the time of the sputum sample and its relationship to antibiotic therapy, associated organisms cultured from blood and/or sputum, and the antimicrobial agent used in individual patients and their response to such therapy.

Possible risk factors for airway colonisation with *Klebsiella* spp. were determined for the group as a whole. However, multivariate analysis with logistic regression (to document the relative importance of the individual risk factors) was not possible as incomplete data would have invalidated several cases. Risk factors were compared between colonised and infected patients, between those with community-acquired and those with nosocomial infections, and between patients colonised with antibiotic-susceptible and resistant organisms. Fisher's exact (two-tail) test was used for this purpose.

Clinical prediction rules (modified after Selker[13]) were applied to the sputum Gram stain in order to determine its accuracy (in the setting of positive sputum cultures) in differentiating patients colonised or infected with *Klebsiella* spp.

Results

Forty men (74%) and 14 women (26%) with a mean age of 49,9 ± 14,5 years (range 15 - 76 years) were entered into the study. Fifteen patients were older than 60 years. Most patients were city dwellers (92%), while 2 patients had no fixed abode and 1 patient lived on a farm. Three were goldminers, but occupation was unhelpful in predicting colonisation or infection.

Diet was adequately assessed in 32 cases and was found to be satisfactory in 62,5% and poor in 37,5%. Sixteen patients drank alcoholic beverages regularly, and a further 16 had previously done so on a regular basis. Eighteen patients were current cigarette smokers and a further 9 were ex-smokers.

Twelve patients had had blood cultures taken and only 1 of these (8,3%) grew *K. pneumoniae*. The majority of cases was identified during March and April. Possible predisposing conditions to respiratory tract colonisation or invasive disease are shown in Table I. Twelve patients had been admitted to the same or another hospital for various reasons during the preceding year. There were no significant differences in the risk factors noted in patients with airway colonisation and invasive disease.

TABLE I.
Possible factors predisposing to airway colonisation and invasive disease with *Klebsiella* spp. in 54 patients (sometimes multiple)

Pulmonary disorders	
Old fibrocavitatory lung changes	11
Bronchogenic carcinoma	5
Active sputum-positive tuberculosis	4
Asthma	3
Chest trauma	3
Chronic obstructive airways disease	2
Aspiration	1
Cardiac disorders (chronic)	8
Hospitalisation	
Current	7
Preceding 12 mo.	12
Diabetes mellitus	5
Carcinoma (other than lung)	4
Other	
Nephrotic syndrome	1
Infection with human immunodeficiency virus	1
Liver cirrhosis	1
Mixed connective tissue disease	1
Chemotherapy	1
Age > 60 yrs	15

When community-acquired and hospital-acquired infections were compared, the following were noted. The former occurred more commonly in patients under underlying chronic respiratory diseases (67,9% v. 18,2%; $P = 0,007$). The definition of nosocomial infections (occurring in patients hospitalised for more than 48 hours) was borne out by the statistical analysis which confirmed such infections as occurring in patients who had been hospitalised for as little as 2 days (or longer), but particularly in patients who had been on various antimicrobial agents during this time (90,9% v. 10,7%; $P < 0,0001$). The latter group of infections occurred more commonly with antibiotic-resistant organisms (63,6% v. 28,6%; $P = 0,207$).

Airway colonisation or invasive disease with antibiotic-resistant organisms was most commonly nosocomial (53,8% v. 16%; $P = 0,02$), and occurred in patients who had bene hospitalised and on antibiotic therapy for more than 2 days preceding the culture ($P < 0,005$), and in patients with underlying systemic disorders (62,5% v. 18,9%; $P = 0,032$). As a group, patients with underlying lung disease were more commonly colonised with susceptible organisms when compared with the other patients (64,7% v. 33,3%; $P = 0,06$).

Associated organisms (sometimes multiple) were isolated from 28 of the 54 sputum specimens and included *Candida* spp. (10 cases), *Pseudomonas* spp. (5), *Haemophilus parainfluenzae* (5), *S. pneumoniae* (3), *H. influenzae* (2), *Proteus mirabilis* (2), and *Staphylococcus aureus* and *Aspergillus* spp. (1 each). *Mycobacterium tuberculosis* was isolated concomitantly from 4 patients. Two patients with acute community-acquired pneumonia had pneumococci isolated from blood culture. The antimicrobial susceptibilities of the *Klebsiella* organisms are shown in Table II. Seventeen organisms were sensitive to all antimicrobial agents tested except for ampicillin and/or tetracycline.

TABLE II.
Antimicrobial susceptibility (%) of 53 isolates of *Klebsiella* spp. (disc method)*

Ciprofloxacin	100
Imipenem/cilastatin sodium†	100
Amikacin	87
Ceftazidime	87
Cefotaxime	85
Ceftriaxone	85
Tobramycin	79
Netilmicin	77
Piperacillin	75
Cefazolin	74
Trimethoprim	74
Tetracycline	32
Ampicillin	4

* One organism failed to grow on subculture.
† Only 8 cases tested.

The diagnoses are shown in Table III. In 44 cases these were made with relative confidence. In 10 cases the significance of the *Klebsiella* isolate was difficult to determine. Four of these patients had active pulmonary tuberculosis, 2 with pneumonia had pneumococci isolated from blood culture, and the remaining 4 had confounding factors of delay in sputum collection and submission in patients already on antibiotics, and/or associated organisms on sputum culture, and/or a good response to inappropriate antibiotics. A total of 11 patients died, 5 of whom had nosocomial chest infections.

Of the sputum specimens, 37 (68,5%) were of good quality and 17 (31,5%) of poor quality. There was no significant difference between the colonised and infected patients with regard to the number of good and poor quality sputum specimens. Fifteen of the good quality specimens had a positive Gram stain showing Gram-negative bacilli (40,5%) compared with 6 of the poor quality specimens (35,5%; not significant). While 80% of the former and 66,7% of the latter came from patients who were infected rather than colonised, this difference was not significant.

The accuracy of a positive or negative sputum Gram stain in the setting of a positive sputum culture of *Klebsiella* spp. in determining colonisation or invasive disease, as assessed by the clinical prediction rules, was as follows: sensitivity 42%, specificity 69%, predictive value of a positive test 76% (increasing to 80% for good quality specimens only), predictive value of a negative test 30%, false-positive rate 31%, false-negative rate 58%, false-positive diagnosis rate 24%, false-negative diagnosis rate 67%. There was no significant difference in the clinical prediction rules if only good quality sputum specimens were analysed and/or the 10 patients in whom the diagnosis was uncertain were included or excluded.

Discussion

This study confirms the relative frequency with which *Klebsiella* spp. are isolated from sputum specimens in our experience, and identifies a patient population who are at risk from airway colonisation or invasive disease due to *Klebsiella* spp.

All but 3 patients had significant factors predisposing to airway colonisation or invasive disease due to *Klebsiella* spp. (Table I). The most common predisposing factors were chronic underlying cardiac/respiratory disease. Fifteen patients were older than 60 years, and 12 had been hospitalised at some time during the preceding 12 months. The latter phenomenon may be the result either of patients with chronic diseases requiring repeated hospitalisation, or patients with nosocomial colonisation. Several of the latter patients were colonised with antibiotic-resistant strains (40%).

There were no significant differences in risk factors between patients with airway colonisation and invasive disease. Community-acquired infections occurred more commonly in patients with chronic underlying lung disease, and nosocomial airway colonisation or infection was more common in patients with chronic underlying systemic illness.

The sensitivity and specificity of the sputum Gram stain (in association with a positive sputum culture) in suggesting invasive disease due to *Klebsiella* spp. were 42% and 69% respectively. The predictive value of a positive test was 76% and of a negative test 30%.

The diagnoses are shown in Table III. Community-acquired and nosocomial pneumonia or chest infections were relatively common. In the current study *Klebsiella* spp. were a less common cause of primary acute community-acquired pneumonia. While this was also documented in a previous study from South Africa among less seriously ill patients with pneumonia,[14] the same was not found in studies of severely ill patients with pneumonia, in whom a much higher prevalence of *Klebsiella* infections, including both primary and bacteraemic infections, occurs.[8,15] Among the present patients were 4 with active sputum-positive pulmonary tuberculosis in whom *K. pneumoniae* was isolated concomitantly. The role of the latter organism was uncertain, although all patients were on antituberculosis and general antibiotic therapy.

TABLE III.
Diagnoses in 54 patients from whose sputum *Klebsiella* spp. were cultured

Airway colonisation without infection	15
Acute community-acquired chest infection	
Pneumonia	
Primary	3
Secondary	10
Aspiration	1
Endobronchial infection or bronchopneumonia	10
Nosocomial infection	
Pneumonia	9
Chest infection	2
Organism isolated in patients with pulmonary tuberculosis	4

The antimicrobial susceptibility of the organisms (disc method) is shown in Table II. The importance of such studies is that antibiotic resistance among *K. pneumoniae* organisms is becoming an increasingly common problem world-wide.[16,17] While 17 organisms were fully sensitive to all agents except ampicillin and/or tetracycline, the remainder were resistant to additional agents.

In conclusion, the findings of this study suggest that airway colonisation with *Klebsiella* spp. is common at Hillbrow Hospital. Not all cases represent invasive disease, which has to be determined according to the clinical setting. Colonisation is not easily differentiated from invasive disease on the basis of risk factors alone. Patients with community-acquired infection often have underlying chronic respiratory disease, and nosocomial infections occur with antibiotic-resistant organisms in patients who have been hospitalised for several days while receiving antibiotic therapy, particularly in the presence of systemic disorders.

While a positive sputum Gram stain in the correct clinical setting may be helpful in suggesting invasive disease due to *Klebsiella* spp., a negative test does not exclude such infection with any confidence. Thus in the correct clinical setting, particularly in seriously ill

patients, Gram-negative cover may need to be instituted before more complete microbiological results can be obtained, particularly since it has been shown that *Klebsiella* chest infections are common in such patients[8,15] and that the outcome of bacteraemic *Klebsiella* infections may be directly related to the early institution of combined β-lactam and aminoglycoside therapy.[9]

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