Klebsiella pneumoniae liver abscess: a new invasive syndrome

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Klebsiella pneumoniae is a well known human nosocomial pathogen. Most community-acquired _K pneumoniae_ infections cause pneumonia or urinary tract infections. During the past two decades, however, a distinct invasive syndrome that causes liver abscesses has been increasingly reported in Asia, and this syndrome is emerging as a global disease. In this Review, we summarise the clinical presentation and management as well the microbiological aspects of this invasive disease. Diabetes mellitus and two specific capsular types in the bacterium predispose a patient to the development of liver abscesses and the following metastatic complications: bacteraemia, meningitis, endophthalmitis, and necrotising fasciitis. For patients with this invasive syndrome, appropriate antimicrobial treatment combined with percutaneous drainage of liver abscesses increases their chances of survival. Rapid detection of the hypervirulent strain that causes this syndrome allows earlier diagnosis and treatment, thus minimising the occurrence of sequelae and improving clinical outcomes.

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Introduction

Klebsiella pneumoniae is a well known human pathogen. However, a distinct invasive syndrome has been detected in southeast Asia in the past two decades.[1,2] Liver abscesses in patients infected with *K pneumoniae* were first described in the 1980s in anecdotal reports and case series from Taiwan.[2,3] Extrahepatic complications resulting from bacteraemic dissemination, including endophthalmitis,[3] meningitis,[4] necrotising fasciitis,[5] and other illnesses,[6] have also been recorded. The invasive syndrome was subsequently reported in many southeast Asian countries, including Singapore,[7,8] Hong Kong,[9,10] Korea,[11,12] and Vietnam.[13,14] Few cases were reported from China.[15] Findings from a meta-analysis showed that the prevalence of *K pneumoniae* infection has been increasing since the late 1980s, and that it is now the main cause of liver abscess in Hong Kong,[10] Singapore,[8] South Korea,[11] and Taiwan.[2]

The reasons for the predominance of this syndrome in Asian people are unclear. In 2002, Ko and colleagues[16] showed that the major factor was the microbe itself. *K pneumoniae* isolated from Asian patients with the invasive syndrome had distinct phenotypic and genotypic features—eg, when assessed in mouse models, it was much more virulent than were strains isolated from patients from outside Asia.[16] Moreover, a genotype strongly associated with this highly invasive disease is widespread worldwide.[17–19]

In the past two decades, this syndrome has been described in anecdotal reports from North America.[20,21] Most patients from outside Asia with this invasive syndrome were of Asian descent. However, in the past decade, cases in patients of non-Asian descent are now being reported in North America and South America, and the isolated strains of *K pneumoniae* have been classified as serotypes K1 and K2.[17,19] In this Review, we describe the epidemiology, clinical manifestations, diagnosis, and treatment of liver abscesses caused by *K pneumoniae*.

Definition of the invasive syndrome

First, we propose a case definition for this newly described invasive liver abscess syndrome, to allow clear identification of cases. As knowledge about this distinct aspect of infection with *K pneumoniae* accumulates, this definition can be modified (panel).

The invasive nature of some *K pneumoniae* strains includes a hypermucoviscous phenotype associated with serotypes K1 and K2 and the regulator of mucoid phenotype A gene (*rmpA*). A loss or reduction of capsule synthesis will decrease a strain's virulence because of the loss of antiphagocytic effect against macrophages and neutrophils.[22,23] Almost all patients with severe infection with bacteraemia, liver abscess, and extrahepatic infections are infected exclusively with *K pneumoniae* serotypes K1 or K2, but not all infections with K1 or K2 serotypes result in liver abscess with extrahepatic infection. Fulfilment of both the clinical and microbiological definitions of the invasive syndrome portends a poor prognosis and warrants immediate and aggressive treatment.

Epidemiology and risk factors

In the past decade, 38 patients were diagnosed as having a liver abscess caused by *K pneumoniae* in two case series in the USA.[21,24] South Korea has the second highest prevalence of *K pneumoniae* liver abscesses (Taiwan has the highest prevalence), with 321 patients identified in

Panel: Definitions of invasive liver abscess syndrome

Clinical definitions

Definite invasive syndrome: *Klebsiella pneumoniae* liver abscess with extrahepatic complications, especially CNS involvement, necrotising fasciitis, or endophthalmitis

Probable invasive syndrome: *K pneumoniae* liver abscess as the sole presenting clinical manifestation

Microbiological definitions

Definite invasive syndrome: *K pneumoniae* liver abscess caused by the K1 or K2 serotype

Probable invasive syndrome: the hypermucoviscous phenotype is defined by the string test, which monitors the formation of a viscous string of greater than 0·5 cm in length stretched by the inoculation loop two national studies.[11,12] We reviewed the demographic and clinical characters of 512 patients from four large-scale studies in Taiwan (table 1).[25–28] Nearly all patients had community-acquired infections.

Diversity in terms of ethnic origin was greater in patients in the USA than it was in South Korea or Taiwan, with about half of US patients being non-Asian (table 1). Diabetes mellitus seems to be a risk factor for the invasive syndrome (table 1),[7,12,29–33] and it is associated with poor visual outcome in patients with endophthalmitis.[34] Strict glycaemic control might prevent the development of metastatic complications caused by *K pneumoniae* serotypes K1 and K2.[35] An abscess located in the right lobe of a patient's liver was the most common presentation (table 1). Worldwide, 43 (5%) of 813 patients with this invasive syndrome died in the past decade (table 1).

Several studies have shown that these invasive strains infect the liver from the gastrointestinal tract.[36,37] Fung and colleagues[37] have noted that *K pneumoniae* strains isolated from patients with a liver abscess and from otherwise healthy carriers of *K pneumoniae* had an identical pulsed-field gel electrophoresis profile with the same virulence-associated genes and similar median lethal dose values.[37] This finding indicates that the healthy adults carried the virulent strains in their intestines. Liver abscess might occur when bacteria translocates across the intestinal epithelium. Findings from a previous study done in animals suggest that *K pneumoniae* strains can cross the intestinal barrier and cause liver abscesses.[38] Faecal–oral transmission, gastrointestinal colonisation, and environmental exposure are possible routes of acquisition. Liver abscess might develop after leakage of *K pneumoniae* from a patient's bowel into their liver via the portal circulation. Findings from seroepidemiological studies of faecal carriage of *K pneumoniae* in healthy Chinese people, in populations in China as well as in other Asian countries, have shown that prevalence of *K pneumoniae* in healthy adults was 75%, with a high prevalence (23%) of serotype K1 or K2 isolates in typeable strains in Taiwan.[39] In European studies, the prevalence of *K pneumoniae* in faecal samples have differed substantially, ranging from 10% (eight of 79 samples) to 19% (seven of 36 samples).[40,41] Thus, the high prevalence of virulent *K pneumoniae* strains in patients of Asian descent is probably why the prevalence of this invasive syndrome is so high in this population.

	USA (n=38[21,24])	South Korea (n=321[11,12])	Taiwan (n=512[25–28])
Mean age (years)	53·6	59·9	57·4
Men	68% (26/38)	42% (136/321)	63% (321/512)
Ethnic origin			
Asian	50% (16/32)*	100% (58/58)†	100% (512/512)
Hispanic	25% (8/32)*	..	..
Black	13% (4/32)*	..	..
White	9% (3/32)*	..	..
Underlying disorder			
Diabetes mellitus	29% (11/38)	38% (122/321)	63% (323/512)
Hepatobiliary disease	18% (7/38)	20% (64/321)	25% (127/512)
Cancer	3% (1/38)	6% (20/321)	7% (38/512)
Alcoholism	0	16% (50/321)	8% (40/512)
Chronic renal failure	0	<1% (1/321)	3% (16/512)
Bacteraemia	74% (28/38)	48% (153/321)	61% (312/512)
Single abscess	74% (28/38)	62% (198/321)	77% (392/512)
Multiple abscesses	26% (10/38)	38% (123/321)	23% (120/512)
Location of abscess			
Right hepatic lobe	65% (24/37)‡	64% (37/58)§	65% (333/512)
Left hepatic lobe	24% (9/37)‡	24% (14/58)§	25% (129/512)
Both lobes	11% (4/37)‡	12% (7/58)§	10% (50/512)
Metastatic infection	24% (9/38)	8% (26/321)	15% (62/428)¶
Lung	16% (6/38)	3% (2/58)§	4% (16/428)¶
Eye	11% (4/38)	..§	4% (18/428)¶
CNS	8% (3/38)	2% (1/58)§	5% (21/428)¶
Muscular and skeletal system	3% (1/38)	..§	2% (9/428)¶
Urinary system	3% (1/38)	..§	<1% (1/428)¶
Mortality	8% (3/38)	4% (10/263)||	6% (30/512)

Data are % (n/N; some denominators do not add up to the total in some cohorts because of missing data for some patients). *The ethnic origin of six patients was not reported in reference 24. †Patients' ethnic origin was not described in reference 11. ‡One patient's abscess location was not reported in reference 24. §The locations of liver abscess and number of patients with metastatic infection were not given in reference 11. ¶Metastatic infection was not mentioned in reference 25. ||There were no data for mortality in reference 12.

Table 1: **Demographic and clinical characteristics of patients with *Klebsiella pneumoniae* liver abscesses, by country**

Virulence factors

Several virulence factors have been described for *K pneumoniae*, and include the presence of the capsular serotype, mucoviscosity-associated gene A (*magA*), *rmpA*, and aerobactin (table 2).[43] *K pneumoniae* strains expressing capsular type K1 or K2 antigen are especially virulent. These serotypes have a high prevalence of resistance to phagocytosis and intracellular killing by neutrophils and bactericidal complements in a patient's serum. Mutant strains without a capsule are highly susceptible to phagocytosis and serum killing and show reduced virulence in mice.[22,29] Although *K pneumoniae* serotypes K1 and K2 isolated from patients with liver abscess usually show hypermucoviscosity, hypermucoviscosity is not confined to only these two serotypes.[17] This mucoid phenotype might be indicative of the extent of capsular polysaccharide expression, which is related to resistance to phagocytosis. In animal models, the resistance of K1 and K2 strains to intracellular killing by neutrophils and in serum might promote inflammation and dissemination.[44,45]

magA has been described as the causative gene for *K pneumoniae* liver abscess and septic metastatic complications.[46] Similar to mutant strains without a capsule, the *magA* mutant strain does not show hypermucoviscosity (figure).[46,47] The enzyme encoded by *magA*, also named *wzy* in accordance with the bacterial polysaccharide gene nomenclature scheme, functions as a polymerase involved in capsule synthesis, and this

	rmpA	Aerobactin	Resistance		Virulence*
			Phagocytic	Serum	
K1[18]	+	+	+	+	+++
K1[18]	+	+	+	–	V(+++,+)
K1[18]	+	+	–	–	+
K1[18]	+	–	+	+	+
K1[18]	+	–	+	–	+
K1[42]	+	+	ND	ND	V(+++,+)
K1[42]	–	–	ND	ND	–
K2*	+	+	+	+	+++
K2*	+	+	+	–	V(+++,+)
K2*	+	+	–	+	V(+++,+)
K2*	+	–	+	–	+
K1[42]	+	+	ND	ND	V(+++,+)
K1[42]	–	–	ND	ND	V(+,–)
Non K1 or K2[42]	+	+	ND	ND	V(+++,+)
Non K1 or K2[42]	–	–	ND	ND	–

+=virulent strains with a 50% lethal dose (LD_{50}) of $\geq1\times10^3$ colony-forming units (CFU) and $>1\times10^6$ CFU are less likely to induce complications in mice. +++=hypervirulent strains with an LD_{50} of less than 1×10^3 CFU are more likely to induce complications in mice. –=non-virulent strains with an LD_{50} of 1×10^6 CFU of greater (do not cause complications). ND=no data. V=variable. *Chang F-Y, unpublished data.

Table 2: **Microbiological features of *Klebsiella pneumoniae* associated with virulence, by serotype**

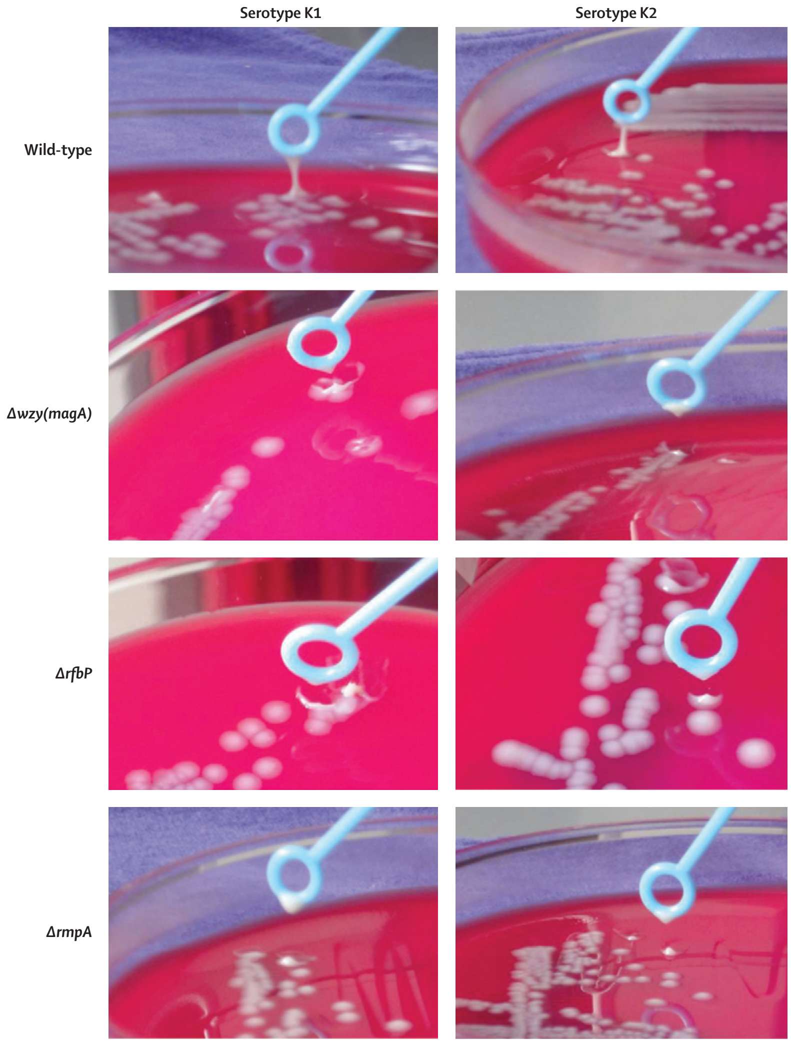

Figure: **String tests of *Klebsiella pneumoniae* serotypes K1 and K2**
Wild-type *K pneumoniae* strains with normal capsule expression have positive string test results. Loss of extreme mucoid phenotype mutants, capsular polymerase gene mutant (Δ*wzy*), capsular glycosyltransferase gene mutant (Δ*rfbP*), and regulator of mucoid phenotype A gene mutant (Δ*rmpA*) have negative string test results. Δ=deletion.

function is restricted to the capsular gene cluster of serotype K1 only.[48,49] Silencing of genes surrounding *magA* (figure) in the same cluster of genes needed for capsular polysaccharide synthesis resulted in hypermucoviscosity and virulence.[23]

In 2006, *rmpA* was proposed as a virulent factor in addition to *magA* and capsular serotypes K1/K2.[50] *rmpA* is not an independent factor contributing to liver abscess but aids capsule synthesis.[7] One report showed that all *K pneumoniae* strains that cause liver abscesses and abscesses at other sites are *rmpA*-positive.[50] *rmpA* has been confirmed as a gene that regulates capsular polysaccharide synthesis.[51] Ablation of this gene results in the loss or thinning of the *K pneumoniae* capsule and weak positivity to the anti-serum antibody due to very low capsule synthesis. One important phenotype of *rmpA*-negative strains is the loss of hypermucoviscosity or a negative string test (figure). Aerobactin, a type of siderophore, is an iron chelator that enhances the virulence *K pneumoniae* by 100 times in mouse models, and is an essential factor of pathogenicity in *K pneumoniae*.[52] Aerobactin genes in combination with *rmpA* play an important part in the virulence of *K pneumoniae* isolates other than those of serotype K1 and K2. The mucoid phenotype is often concomitant with aerobactin production.[53] Because aerobactin is involved in iron acquisition, the growth of bacteria in a human being has a restricted supply of iron if a siderophore is absent. Thus, bacteria that produce siderophores are more virulent. Aerobactin's involvement in *K pneumoniae*'s virulence has been confirmed in several studies.[7,37,53] Non-serotype K1 and K2 isolates that express *rmpA* and aerobactin genes show a similar virulence to serotype K1 and K2 isolates from patients with liver abscesses.[42]

Clinical manifestations and diagnosis

The most common clinical manifestations in patients with *K pneumoniae* liver abscesses are fever, chills, and abdominal pain.[25–28] Nausea and vomiting occur in about a quarter of patients.[25–28] However, these symptoms are not characteristic for the *K pneumoniae* invasive syndrome. Leucocytosis, thrombocytopenia, increased concentrations of C-reactive protein and glucose in blood, and abnormal results of liver function tests were common.[27]

In terms of clinical diagnosis, in patients, especially those who are Asian or of Asian descent, with diabetes mellitus who present with *K pneumoniae* bacteraemia, endophthalmitis, meningitis, or other extrahepatic infections, a search for an occult liver abscess is indicated. CT scans are more sensitive than sonography in the diagnosis of liver abscess.[54] In terms of microbiological diagnosis, a *K pneumoniae* isolate taken from a blood or liver abscess with the hypermucoviscous phenotype is suggestive of an invasive *K pneumoniae* strain, and the attending clinician should be notified as soon as possible. Multiplex PCR might be a useful rapid test for detection of the *K pneumoniae* serotype that causes liver abscesses.[55]

Lungs, CNS, and eyes are the most common metastatic sites in a patient.[27,56,57] Only a third of metastatic infections were seen on admission and most metastatic infections were diagnosed within 3 days of presentation.[27] Meningitis and endophthalmitis are two of the main metastatic presentations; others include septic pulmonary emboli and empyema. High mortality was seen in patients with meningitis.[58] *K pneumoniae* endophthalmitis, often occurring in patients with diabetes mellitus, can present without hepatic involvement at disease onset.[59] A poor outcome with a high mortality was also seen for patients with septic pulmonary emboli or empyema.[60] Thus, for a patient with a liver abscess, an abnormal chest radiograph might portend the development of complications. In the musculoskeletal system, osteomyelitits or subcutaneous or muscular abscesses are more common than is necrotising fasciitis.[5,26]

Management

Because of the potential for metastatic infection, clinicians should assess patients for such complications when clinical response is poor. Strict glycaemic control can prevent the development of metastatic complications.[35]

The selection of antimicrobial treatment should be based on in-vitro susceptibilities and clinical response. Cephalosporins are the antibiotic mainstay of treatment in Asia for *K pneumoniae* abscesses (table 3).[11,12,25,28] Patients in the USA were treated successfully with combination treatment (table 3). In the 36 patients treated, the combinations included aminopenicillins (six patients [17%]), antipseudomonal penicillins (six patients [17%]), first-generation or second-generation (three patients [8%]) and third-generation (18 patients [50%]) cephalosporins, carbapenems (one patient [3%]), fluoroquinolones (11 patients [31%]), aminoglycosides (eight patients [22%]), and metronidazole (11 patients [31%]; table 3).[21,24]

Although liver abscesses caused by extended spectrum β-lactamase (ESBL)-producing *K pneumoniae* have been reported in Taiwan,[31,62] it is a rare occurrence. Carbapenems are the drug of choice for ESBL-producing *K pneumoniae*. Carbapenem-resistant *K pneumoniae*, such as strains producing NDM-1, is of serious concern because of the few treatment options for these hyper-resistant strains.[63]

Because ESBL-producing *K pneumoniae* has been detected very rarely in patients with liver abscesses, antibiotics such as ampicillin–sulbactam, a third-generation cephalosporin, aztreonam, and a quinolone can be used. Clinicians often add an aminoglycoside unless a third-generation cephalosporin is used, although no randomised controlled trials have assessed the effectiveness of such a combination regimen. A third-generation cephalosporin is preferable to a first-generation cephalosporin for 2–4 weeks for solitary single abscess and 6 weeks for multiple abscesses.[6] The duration of treatment can be determined by response to treatment, as shown by ultrasound of the abscess and resolution of fever and leucocytosis. Adequate drainage of the abscess is recommended for better clinical response. Although percutaneous drainage was more

	Liver abscess						Endophthalmitis (Taiwan; Yang et al[61])
	USA		South Korea[11]	Taiwan			
	Lederman et al[24]	Pastagia et al[21]		Lee et al[27]	Chen et al[26]	Cheng et al[6]	
Aminopenicillins	..	30% (6/20)	..	..	..	..	9% (2/22)
Antipseudomonal penicillins	38% (6/16)	..	..	..	..	..	..
First-generation and second-generation cephalosporins*	13% (2/16)	5% (1/20)	..	95% (104/110)	70% (59/84)	55% (59/107)	18% (4/22)
Third-generation cephalosporins†	44% (7/16)	55% (11/20)	83% (217/263)	4% (4/110)	18% (15/84)	45% (48/107)	73% (16/22)
Carbapenems‡	6% (1/16)	..	..	..	..	..	..
Fluoroquinolones§	56% (9/16)	10% (2/20)	..	..	7% (6/84)	..	5% (1/22)
Aminoglycosides¶	50% (8/16)	..	..	95% (104/110)	..	69% (74/107)	32% (7/22)
Metronidazole	69% (11/16)	..	..	..	..	..	5% (1/22)

Data are % (n/N). *Cefazolin, cefotetan. †Cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone. ‡Imipenem. §Levofloxacin, ciprofloxacin. ¶Amikacin, gentamicin, kanamycin.

Table 3: **Antibiotic treatment in patients with *Klebsiella pneumoniae* liver abscess and complications of endophthalmitis**

> **Search strategy and selection criteria**
>
> We searched PubMed for papers published between Jan 01, 1970, and June 30, 2012, by using combinations of the following keywords: "*Klebsiella pneumoniae*", "liver abscess", "endophthalmitis", and "meningitis". We selected articles published in English or Chinese. We selected reports of large case series for inclusion in this Review in favour of anecdotal reports, of which we identified many. Data surveyed included ethnic origin, underlying diseases, clinical manifestations, treatments, and clinical outcome.

widely used because of advances in interventional radiology, aggressive hepatic resection resulted in a better outcome than did conventional percutaneous drainage for patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of 15 or greater (ie, those with more severe disease and higher risk of death).[64]

Metastatic infections of the CNS and eyes are severe and difficult to treat. In the absence of ESBL production, third-generation cephalosporins are the drugs of choice for *K pneumoniae* meningitis in view of their better penetration into the cerebrospinal fluid (compared with first-generation and second-generation cephalosporins).[65] Both cefotaxime and ceftriaxone are effective for treatment of meningitis.[66] Large doses are used for both cefotaxime (up to 2 g every 4 h) and ceftriaxone (2 g twice a day). 3 weeks of treatment has been recommended because of a high rate of relapse in individuals treated with shorter courses of treatment. Imipenem and meropenem can be given to patients instead of third-generation cephalosporins (when ESBL strains are suspected).[67]

The prognosis for patients with endophthalmitis caused by *K pneumoniae* is very poor; more than 85% of patients had a severe visual deficit.[3,59,68–72] Prognosis for visual recovery is improved if a diagnosis is made early and the patient is given early antibiotic treatment.[68,71] *K pneumoniae* endophthalmitis can present days after appropriate treatment for *K pneumoniae* bacteraemia has begun or a hepatic abscess has formed.[68] Both intravitreal and intravenous routes should be used for endophthalmitis.[68,69,71] Intravenous ceftazidime plus amikacin has been the most widely used combination. Combination intravitreal treatment with cephalosporins (cefazolin 2 g and ceftazidime 2·25 g) and aminoglycosides (gentamicin 4 g, amikacin 0·5 g) have been used successfully.[73]

Antibiotics, when given systematically, penetrate into the vitreous humour of a patient's eye with variable success. Third-generation cephalosporins have the fastest penetration of all antibodies and can achieve peak vitreous concentrations of at least 2 mg/L.[74] Aminoglycosides penetrate the vitreous quite well after repetitive systemic dosing.[75] Oral ciprofloxacin can achieve vitreous concentrations of 0·2–0·5 mg/L.[76,77] An imipenem dose of 0·5 g resulted in mean vitreous concentrations of 0·2 mg/L, 2–4 h after infusion; concentrations increased to about 2 mg/L after a 1 g dose.[78]

Conclusions

This invasive syndrome seems to be spreading to countries outside Asia. Presentation of liver abscess with bacteraemia in patients infected with *K pneumoniae* strains that have a positive string test result (figure) can be the first clinical clue. Rapid diagnosis followed by appropriate treatment should improve a patient's outcome and prevent metastatic complications, which are severe. Further research should aim to find out why Asian populations (particularly Taiwanese people) are especially prone to this disorder, to confirm that gastrointestinal colonisation is the mechanism for infection, and to elucidate the reason for the detection of the K1 and K2 serotypes in North America and Europe. Further investigation is urgently needed to identify the source or environmental reservoir for these highly virulent *K pneumoniae* strains.

Contributors

LKS and FYC had the idea for and designed the Review. LKS and K-MY wrote early drafts of the paper. LKS, F-YC, and J-CL critically reviewed the final draft. LKS, F-YC, K-MY, and C-PF proofread and edited the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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