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ARTICLE

Role of K1 capsule antigen in cirrhotic patients with *Escherichia coli* spontaneous bacterial peritonitis in southern Taiwan

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Abstract Spontaneous bacterial peritonitis (SBP) is one of the most serious complications in patients with cirrhosis. This study aimed to investigate the prevalence of SBP caused by *Escherichia coli* isolates with or without the K1 capsule antigen in cirrhotic patients and the outcome. From January 2004 to January 2012, a total of 54 and 41 *E. coli* strains derived from patients with SBP and intestinal perforation (IP), respectively, were included for comparison in this study. Bacterial characteristics including phylogenetic groups, K1 capsule antigen, and 14 virulence factor genetic determinants, as well as data regarding patient characteristics, clinical manifestations, and in-hospital deaths, were collected and analyzed. The prevalence of the K1 capsule antigen gene *neuA* was more common in SBP isolates compared to IP isolates (28 % vs. 10 %, $p=0.0385$). Phylogenetic groups B2 and group D were dominant in *E. coli* isolates with and without the K1 capsule antigen, respectively. The prevalence of virulence factors genes *papG II*, *ompT*, and *usp* was higher in *E. coli* K1 strains. There were 26 deaths (48 %) during hospitalization. Presence of the K1 capsule antigen in *E. coli* isolates was significantly associated with in-hospital death in cirrhotic patients with SBP (42 % vs. 14 %, $p=0.0331$). This study demonstrates a higher prevalence of the K1 capsule antigen in *E. coli* SBP compared to *E. coli* peritonitis caused by IP. There were significant associations between the K1 capsule antigen and in-hospital mortality and bacterial virulence in cirrhotic patients with *E. coli* SBP.

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Introduction

Spontaneous bacterial peritonitis (SBP) is one of the most serious complications in patients with cirrhosis. Among the causative pathogens, *Escherichia coli* is the most common Gram-negative bacillus [1, 2]. In the pathogenesis of SBP, bacterial translocation from the intestine into the mesenteric lymph nodes, followed by bacteremia and ascitic fluid inoculation due to impaired local and systemic immunity are considered to be two important steps [3, 4].

E. coli isolates causing SBP and bacteremia were genetically diverse and exhibited varying virulence profiles [5]. Phylogenetic group B2 was the most common [5, 6]. Outcome was not influenced by the phylogenetic group or the virulence

profile [6]. Nosocomial SBP, severity of liver cirrhosis, and an antimicrobial profile with resistance to third-generation cephalosporins or extended-spectrum β-lactamases (ESBLs) were associated with poorer outcomes [2, 6, 7].

The K1 capsule of *E. coli* is believed to reduce the bacterial susceptibility to phagocytosis and complement the host defense system, and increase invasiveness [8, 9]. The K1 capsule antigen contributes to breach of the blood–brain barrier and subsequent neonatal meningitis and bacteremia [10–12]. Information is scarce about the outcomes of SBP caused by *E. coli*, with or without K1 capsular polysaccharide, in cirrhotic patients. Soriano et al. reported that the incidence of complications and mortality was similar in SBP patients infected with encapsulated *E. coli* strains with or without K1 [13].

The aims of this study were to examine and compare the prevalence and distribution of *E. coli* isolates among SBP and intestinal perforation (IP) with regard to K1 capsule antigen, phylogenetic grouping, and virulence factors. We further investigated the association between K1 capsule antigen and clinical manifestations and outcomes in *E. coli* SBP in cirrhotic patients.

Materials and methods

Patients and bacterial strains

From January 2004 to January 2012, *E. coli* isolates from peritoneal fluid were collected from patients at National Cheng Kung University Hospital in Taiwan. Data regarding patient characteristics, clinical manifestations, and in-hospital mortality were collected and analyzed. Only one isolate per patient was accepted. *E. coli* was obtained from aspirates of peritoneal fluid during surgery for IP or from ascites of cirrhotic patients.

SBP was defined by an ascitic fluid polymorphonuclear leukocyte count ≥250 cells/mm^3 and a positive culture result in cirrhotic patients [2, 14]. The severity of liver cirrhosis was assessed according to the Child–Pugh score/classification and model for end-stage liver disease (MELD) score [15, 16]. IP was diagnosed by the surgical findings and/or imaging studies in patients with peritonitis. The causes of IP included trauma, ulcer, diverticulitis, infection (tuberculosis), ischemia, malignancy, or unknown.

Antimicrobial susceptibility

The susceptibility of *E. coli* strains, investigated using the disk diffusion method and interpretive criteria according to the Clinical and Laboratory Standards Institute (CLSI) guidelines 2011 [17], was determined for ampicillin, gentamicin, cefazolin, second-generation cephalosporins (cefuroxime, cefoxitin, or cefmetazole), third-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefixime, or cefpodoxime), fourth-generation cephalosporins (cefepime or cefpirome), and fluoroquinolones (ciprofloxacin, levofloxacin, or lomefloxacin).

The *E. coli* strains from peritoneal fluid were identified using standard methods [18] and stored in 20 % glycerol at −70 °C until its use in all subsequent analyses.

Phylogenetic analysis and detection of virulence determinants

The phylogenetic grouping of the *E. coli* isolates was determined by a polymerase chain reaction (PCR)-based method, as previously described [19]. K1 capsule antigen and 14 uropathogenic virulence factor genes of *E. coli* were detected using PCR. Primer pairs specific for the K1 capsule gene, *neuA*, were K1-F: ATGATTACTCGACACTGTC; K1-R: AACAATCTCCGCTATTTCG. The size of the PCR products was 812 bp. Primer pairs specific for *papG* classes I to III, *fimH*, *sfa*, *foc*, *afa*, *iha*, *hlyA*, *cnf1*, *iroN*, *iutA*, *ompT*, and *usp* have been described previously [19, 20].

Statistical analysis

The Chi-square test or Fisher's exact test (two-tailed) was used for the comparison of categorical variables, whereas the Wilcoxon rank-sum test was used for the comparison of continuous variables. A p-value <0.05 was considered to be statistically significant. All statistical analyses were performed using JMP software (SAS Institute Inc., Cary, NC, USA).

Results

A total of 54 and 41 *E. coli* strains derived from patients with SBP and IP, respectively, were included. Bacterial characteristics in relation to the source of *E. coli* strains are shown in Table 1. There were no significant differences in the distribution of phylogenetic groups and most of the virulence factors between the two groups. Phylogenetic groups D and B2 were the two most common groups in the SBP group. The prevalence of the K1 capsule antigen gene, *neuA*, was more common in SBP isolates compared to IP isolates.

The host characteristics of the 54 cirrhotic patients with SBP included 33 males (61 %) and had a mean age of 61±12 years. The major causes of cirrhosis were hepatitis B virus (14, 26 %) and hepatitis C virus (17, 31 %). The median Child–Pugh score was 11 (range 6–14); the Child–Pugh classifications of A, B, and C were 1 (2 %), 9 (17 %), and 44 (81 %), respectively; and the median MELD score was 11 (range 7–22). There were no significant differences in age,

Table 1 Comparison of the bacterial characteristics of *Escherichia coli* isolates derived from spontaneous bacterial peritonitis (SBP) and intestinal perforation (IP)

Characteristic	SBP (n=54)	IP (n=41)	p-value, SBP vs. IP
Phylogenetic groups			0.0745
A	5 (9)	11 (27)	
B1	10 (19)	9 (22)	
B2	19 (35)	13 (32)	
D	20 (37)	8 (20)	
K1 capsule antigen, *neuA*	15 (28)	4 (10)	0.0385
Adhesin			
papG I	0	0	–
papG II	10 (19)	6 (15)	0.7834
papG III	6 (11)	3 (7)	0.7274
fimH	49 (91)	36 (88)	0.7412
sfa	4 (7)	1 (2)	0.3857
foc	0	1 (2)	0.4316
afa	39 (72)	34 (83)	0.3262
iha	11 (20)	10 (24)	0.8034
Toxin			
hlyA	5 (9)	2 (5)	0.6949
cnf1	3 (6)	1 (2)	0.6314
Siderophore			
iroN	20 (37)	9 (22)	0.1234
iutA	32 (59)	20 (49)	0.4055
Miscellaneous			
ompT	32 (59)	23 (56)	0.8349
usp	21 (39)	13 (32)	0.5218

Data are presented as mean ± standard deviation (SD) or number (percentage)

gender, cause of cirrhosis, and presentations of SBP between patients in the K1 and non-K1 groups. The bacterial characteristics of the 54 *E. coli* isolates in relation to the K1 capsule antigen are shown in Table 2. Phylogenetic groups B2 and D were dominant in *E. coli* isolates with and without the K1 capsule antigen, respectively. The prevalence of virulence factors genes *papG II*, *ompT*, and *usp* was higher in *E. coli* isolates with the K1 capsule antigen. The antimicrobial resistance profile was similar between both groups.

Host and *E. coli* bacterial characteristics in relation to in-hospital death in cirrhotic patients with SBP are shown in Table 3. Twenty-six patients (48 %) died during hospitalization. There was a higher MELD score in the in-hospital death group (P=0.0269), whereas there was no difference in the Child–Pugh score or classification between both groups. Presence of the *E. coli* K1 capsule antigen was significantly associated with in-hospital death, whereas a history of SBP in cirrhotic patients was inversely associated with in-hospital death.

Table 2 Bacterial characteristics of *Escherichia coli* isolates derived from cirrhotic patients with spontaneous bacterial peritonitis (SBP) in relation to the K1 capsule antigen

Characteristic	K1 capsule antigen		p-value
	Negative (n=39)	Positive (n=15)	
Phylogenetic group			0.0003
A	4 (10)	1 (7)	
B1	9 (23)	1 (7)	
B2	7 (18)	12 (80)	
D	19 (49)	1 (7)	
Adhesin			
papG I	0	0	–
papG II	3 (8)	7 (47)	0.0027
papG III	5 (13)	1 (7)	1.0000
fimH	34 (87)	15 (100)	0.3064
sfa	3 (8)	1 (7)	1.0000
foc	0	0	–
afa	30 (77)	9 (60)	0.3094
iha	6 (15)	5 (33)	0.2558
Toxin			
hlyA	3 (8)	2 (13)	0.6099
cnf1	2 (5)	1 (7)	1.0000
Siderophore			
iroN	14 (36)	6 (40)	1.0000
iutA	22 (56)	10 (67)	0.5509
Miscellaneous			
ompT	19 (49)	13 (87)	0.0139
usp	9 (23)	12 (80)	0.0003
Antimicrobial resistance			
Ampicillin	29 (74)	6 (40)	0.0268
Gentamicin	12 (31)	1 (7)	0.0830
Cefazolin	15 (38)	2 (13)	0.1056
Cefuroxime, cefoxitin, or cefmetazole	14 (36)	2 (13)	0.1823
Cefotaxime, ceftriaxone, ceftazidime, cefixime, or cefpodoxime	14 (36)	2 (13)	0.1823
Cefepime or cefpirome	6 (15)	1 (7)	0.6601
Ciprofloxacin, levofloxacin, or lomefloxacin	14 (36)	2 (13)	0.1116

Data are presented as mean ± standard deviation (SD) or number (percentage)

Discussion

In patients with IP, *E. coli* bacteria escape the intestinal tract directly through a bowel perforation and enter the abdominal cavity. K1 capsular antigen predisposes to *E. coli* bacteremia in male infants with urinary tract infection (UTI) [12]. The pathogenic *E. coli* in cirrhotic patients with SBP is considered to be derived from bacterial translocation from intestinal flora [3, 4]. It is a pathogenesis different from

Table 3 Host and *Escherichia coli* bacterial characteristics in relation to in-hospital mortality in cirrhotic patients with spontaneous bacterial peritonitis (SBP)

Characteristic and manifestation	In-hospital death		*p*-value
	Negative (*n*=28)	Positive (*n*=26)	
Host factor			
Age (years)	60±11	62±13	0.5333
Gender (male)	16 (57)	17 (65)	0.8158
Cause of cirrhosis			0.7984
Hepatitis B	7 (25)	7 (27)	
Hepatitis C	10 (36)	7 (27)	
Hepatitis B and C	4 (14)	2 (8)	
Alcohol	2 (7)	3 (12)	
Others	5 (18)	7 (27)	
Child–Pugh score (median, range)	11 (6–14)	11 (8–15)	0.1972
Child–Pugh class			0.3643
A	1 (4)	0	
B	6 (21)	3 (12)	
C	21 (75)	23 (88)	
MELD score (median, range)	11 (7–17)	14 (7–22)	0.0269
Concomitant HCC	13 (46)	13 (50)	1.0000
Community acquired	19 (68)	12 (46)	0.1683
Presentation of septic shock	3 (11)	8 (31)	0.0947
Presentation of acute kidney injury (*n*=51, 3 patients with ESRD)	8/25 (32)	13/26 (50)	0.2581
History of SBP	14 (50)	3 (12)	0.0032
Presence of bacteremia	13 (46)	12 (46)	1.0000
Bacterial factor			
Phylogenetic group			0.1683
A	3 (11)	2 (8)	
B1	4 (14)	6 (23)	
B2	7 (25)	12 (46)	
D	14 (50)	6 (23)	
K1 capsule antigen, *neuA*	4 (14)	11 (42)	0.0331
Adhesin			
papG I	0	0	–
papG II	3 (11)	7 (27)	0.1689
papG III	3 (11)	3 (12)	1.0000
fimH	25 (89)	24 (92)	1.0000
sfa	2 (7)	2 (8)	1.0000
foc	0	0	
afa	21 (75)	18 (69)	0.7638
iha	5 (18)	6 (23)	0.7411
Toxin			
hlyA	3 (11)	2 (8)	1.0000
cnf1	2 (7)	1 (4)	1.0000
Siderophore			
iroN	12 (43)	8 (31)	0.4083
iutA	17 (61)	15 (58)	1.0000
Miscellaneous			
ompT	14 (50)	18 (69)	0.1761
usp	8 (29)	13 (50)	0.1065
Antimicrobial resistance			
Ampicillin	17 (61)	18 (69)	0.5770
Gentamicin	7 (25)	6 (23)	1.0000
Cefazolin	7 (25)	10 (38)	0.3821
Cefuroxime, cefoxitin, or cefmetazole	6 (21)	10 (38)	0.2358
Cefotaxime, ceftriaxone, ceftazidime, cefixime, or cefpodoxime	6 (21)	10 (38)	0.2358
Cefepime or cefpirome	2 (7)	5 (19)	0.2501
Ciprofloxacin, levofloxacin, or lomefloxacin	6 (21)	10 (38)	0.2358

Data are presented as mean ± standard deviation (SD) or number (percentage)

MELD model for end-stage liver disease; *HCC* hepatocellular carcinoma; *ESRD* end-stage renal disease

that in IP. Our data showed a higher prevalence of the K1 capsule antigen in SBP compared to that in IP (28 % vs. 10 %, $p=0.0385$), whereas there were no significant differences in phylogenetic grouping or other virulence factors. We speculate that the K1 capsule antigen is helpful in the escape from phagocytic clearance and complement activation in the lymphatic system and bloodstream following bacterial translocation. Therefore, the *E. coli* strain can reach the ascitic fluid as a result of bacteremia and then induce SBP.

The role of the K1 capsule antigen in different *E. coli* extraintestinal infections has not been well established. *E. coli* K1-related neonatal bacterial meningitis was associated with considerable mortality and morbidity [21, 22]. Male infants with *E. coli* bacteremic UTI have a higher prevalence of K1 capsular antigen than those with nonbacteremic UTI [12]. In a study of 137 adults with *E. coli* bacteremia, 16 (12 %) were caused by *E. coli* K1. There were no patient deaths from *E. coli* K1 bacteremia, while 16 of 48 patients with non-K1 bacteremia died [23]. Soriano et al. reported that encapsulated *E. coli* was identified in 27 of 37 cirrhotic patients with SBP, and they were associated with a higher complication rate than patients with nonencapsulated strains (93 % vs. 50 %, $p<0.01$). However, the mortality rate was similar in SBP patients infected with encapsulated *E. coli* with or without K1 [13]. Our data showed that in-hospital death in cirrhotic patients with *E. coli* SBP was associated with a higher prevalence of the K1 capsule antigen. This result might suggest the role of the K1 capsule antigen in the outcome of cirrhotic patients with *E. coli* SBP.

papG II adhesin recognizes a specific receptor on uroepithelial cells [24]. Studies have shown that the *papG II* gene had a close association with *E. coli* upper UTI and bacteremia [20, 25]. *ompT* is a protease present in the outer membrane of *E. coli*; it confers resistance to urinary and antimicrobial cationic peptides [26, 27]. *ompT* and *usp* were frequently associated with UTI [19, 28], and a close association among *ompT*, *usp*, and *kpsMT* genes may be explained by co-selection and is beneficial for pathogenicity in UTI [28], whereas data on the relationships among K1 capsule antigen, *papG II*, *ompT*, and *usp* in *E. coli* infections is scarce. This study showed that *E. coli* strains with K1 capsule antigen were associated with a higher prevalence of *papG II*, *ompT*, and *usp*.

Our data showed that there were no associations between in-hospital death and most of the host factors, *E. coli* phylogenetic grouping, or other virulence factors, except the MELD score and K1 capsule antigen. Patients with a history of SBP were associated with less in-hospital death. It may be related to patient characteristics, in that those who survived the previous SBP may have earlier awareness of illness or better host immunity, nutrition status, or response to antimicrobial treatment. These may contribute to a better outcome in the following SBP episode. However, this is a single-center retrospective study with a small sample size. The small population analyzed may limit the statistical power of the results and their extrapolability.

In conclusion, we find a higher prevalence of the K1 capsule antigen in *E. coli* from SBP compared to *E. coli* from peritonitis caused by IP. We demonstrate a significant association between the K1 capsule antigen and in-hospital mortality in cirrhotic patients with *E. coli* SBP, and *E. coli* isolates with the K1 capsule antigen were more virulent and dominated by phylogenetic group B2. This observation suggests that the K1 capsule antigen may contribute to the development of *E. coli* SBP and poor outcome in cirrhotic patients.

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Conflict of interest No conflict of interest declared.

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