Obtaining drug plasma levels above the MIC for a sufficient period of time is critical for β-lactams to effect optimal activity. For carbapenems, a target exposure of 25–40% $T >$ MIC is considered sufficient to achieve significant antibacterial activity [9,10]. Both of the treatment regimens used in the present study maintained drug plasma levels above the MIC for >30% of the time for all three imipenem-susceptible isolates. By meeting this requirement, imipenem produced an antibacterial effect on the susceptible control isolate that is maximal in this model [7]. Despite these favourable pharmacokinetic parameters, imipenem had inferior activity against the VPKP isolates. The antibacterial effect of the drug on the two susceptible VPKP isolates was significantly augmented by doubling the dosage, as has also been reported for aztreonam in an experimental rat model of pneumonia caused by VIM-1-producing *Pseudomonas aeruginosa* [11]. Nevertheless, imipenem activity remained lower than that obtained against the susceptible control. A possible explanation for the low-to-moderate activity of imipenem against the susceptible VPKP isolates is the operation of an in-vivo inoculum effect, similar to that observed *in vitro*. While the present data cannot provide firm conclusions regarding the treatment of infections caused by VPKP strains with imipenem MICs in the susceptible range, they clearly suggest that the administration of imipenem at higher doses may prove to be of some benefit.

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RESEARCH NOTE

Patient and bacterial determinants involved in symptomatic urinary tract infection caused by *Escherichia coli* with and without bacteraemia

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ABSTRACT

Risk-factors for bacteraemia were determined in a case-control study of patients with *Escherichia coli* urinary tract infection. Cases were defined as patients with *E. coli* urinary source bacteraemia, and controls were chosen from among patients with *E. coli* urinary tract infection without bacteraemia. Patient characteristics were collected prospectively and the bacterial traits were determined. The phylogenetic background and virulence factors of *E. coli* isolates did not differ between cases and controls. In multivariate

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analysis, being female and having a urinary catheter were significantly less prevalent among patients with urinary source bacteraemia than among patients with uncomplicated urinary tract infection.

Keywords Bacteraemia, *Escherichia coli*, phylogenetic groups, risk-factors, urinary tract infection, virulence factors

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Extra-intestinal infections caused by *Escherichia coli*, such as urinary tract infections and bacteraemia, are a major cause of morbidity, mortality and increased costs for hospital treatment [1,2]. The virulence genotype and phylogenetic background have been correlated with the pathogenicity of *E. coli* strains responsible for extra-intestinal infections [2–4]. *E. coli* strains fall into four main phylogenetic groups (A, B1, B2 and D) [5], with virulent extra-intestinal strains belonging primarily to group B2 and, to a lesser extent, group D, whereas most commensal strains belong to groups A and B1 [6]. The role of virulence traits and phylogenetic background in the pathogenesis of urinary source bacteraemia (USB) is not completely understood. Moreover, patient characteristics, such as the underlying disease and the type of care, e.g., the use of an invasive device or antimicrobial treatment, are likely to be involved. This study investigated the determinants involved in the occurrence of *E. coli* USB at the University Hospital, Besançon, France.

Between 1 October 2002 and 1 March 2003, 28 patients with clinical signs of bacteraemia yielded *E. coli* from both blood and urine. Of these, 24 were included for analysis in the present study, comprising patients with *E. coli* bacteraemia caused by a strain with a similar pulsed-field gel electrophoresis (PFGE) pattern to that of the strain isolated from the UTI. Controls were chosen from among patients with *E. coli* UTI, but without bacteraemia. Controls were chosen from the same unit as the cases, and were paired with cases according to their antimicrobial resistance pattern.

The multiplex PCR technique described by Clermont *et al*. [7] was used to categorise the *E. coli* isolates into one of the four principal *E. coli* phylogenetic groups (A, B1, B2 or D). All isolates were tested for seven *E. coli* virulence genes using multiplex PCR [8], i.e., *papC*, *papEF*, *sfa*, *afa*, *hly*, *aer* and *cnf*. Patient characteristics were also recorded. Univariate and multivariate statistical analysis were performed using Systat software v.8.0 (SPSS Inc., Chicago, IL, USA) and LogXact software (CYTEL Software Corp., Cambridge, MA, USA).

The 24 cases were paired with 46 controls (22 cases were paired with two controls each, and two cases with one control each). Cases were not significantly older than controls (p 0.25), with a mean age of 71.0 ± 15.8 years and 64.5 ± 26.8 years, respectively. Patient characteristics are listed in Table 1. Univariate analysis revealed that cases were significantly more often male than were controls (p 0.01). None of the other characteristics recorded was associated with bacteraemia. The number of virulence genes did not differ significantly between cases and controls, with an average of 2.0 ± 1.6 and 1.84 ± 1.6 virulence genes, respectively (p 0.70). Four variables with a p value ≤0.2 in the univariate analysis were introduced into the multivariate model, i.e., gender, alcoholism, presence of a urinary catheter device, and presence of the *hly* virulence gene. The final multivariate model revealed that being female (p 0.005) and having a urinary catheter (p 0.019) were linked with fewer cases of bacteraemia secondary to *E. coli* UTI.

There are few data available concerning the virulence characteristics of *E. coli* isolates from patients with USB, or concerning the association between molecular determinants and invasiveness in this condition. Therefore, the virulence characteristics and phylogenetic background of *E. coli* isolates causing USB were assessed and compared with those of *E. coli* isolates responsible for non-bacteraemic UTI. No significant differences in bacterial determinants were revealed between these two types of isolates. These results are concordant with those of Bonacorsi *et al*. [9]. In contrast, Moreno *et al*. [10] reported that the virulence genes *sfa* and *cnf* were significantly more prevalent among isolates causing USB than among isolates causing pyelonephritis with a negative blood culture. This discrepancy may be related to the case mix and inclusion design. Thus, in the present study, age and frequency of the underlying disease were similar for cases and controls, whereas there was a large difference in

Table 1. Comparison between cases (patients with *Escherichia coli* urinary source bacteraemia) and controls (patients with *E. coli* urinary tract infection only). showing the results of univariate analysis

	Variables				
	Cases (n = 24) n (%)	Controls (n = 46) n (%)	OR	95% CI	p
Patient characteristics					
Male	10 (41.6)	5 (10.8)	5.69	1.47–25.15	0.01
Underlying diseases	13 (54.2)	19 (41.3)	1.67	0.55–5.11	0.44
Cancer	4 (16.7%)	5 (10.8%)	1.62	0.28–8.50	0.73
Diabetes	4 (16.7%)	7 (15.2%)	1.10	0.21–5.02	0.90
Renal insufficiency	2 (8.3%)	5 (10.8%)	0.79	0.07–4.80	0.80
Hepatic insufficiency	1 (4.2%)	1 (2.2%)	2.00	0.12–31.9	0.62
Alcoholism	4 (16.7%)	1 (2.2%)	7.12	0.79–64.3	0.08
Cardiac insufficiency	3 (12.5%)	5 (10.8%)	1.16	0.16–6.70	0.89
Respiratory insufficiency	2 (8.3%)	2 (6.5%)	1.29	0.10–12.21	0.99
Immunodeficiency	5 (20.8%)	5 (15.2%)	1.77	0.39–8.03	0.46
Transplant	3 (12.5%)	3 (6.5%)	2.02	0.25–196.4	0.67
AIDS	0 (0.0%)	0 (0.0%)	–	–	–
Pregnancy	1 (4.2%)	1 (2.2%)	1.93	0.02–1.56	0.99
Corticosteroids	1 (4.2%)	3 (6.5%)	0.63	0.01–8.31	0.99
Invasive device	2 (8.3%)	13 (28.3%)	0.23	0.02–1.19	0.09
Peripheral vascular catheter	0 (0.0%)	3 (6.5%)	0.48	0.00–4.64	0.55
Central vascular catheter	0 (0.0%)	2 (4.4%)	0.78	0.00–10.25	0.86
Urinary catheter	2 (8.3%)	12 (26.1%)	0.26	0.03–1.35	0.14
Invasive respiratory device	0 (0.0%)	2 (4.4%)	0.78	0.00–10.25	0.85
Antibiotic treatment before UTI	3 (12.5%)	8 (17.4%)	–	–	0.79
***E. coli* characteristics**					
Phylogenetic group					
Group A	3 (12.5%)	9 (19.6%)	–	–	0.53
Group B1	3 (12.5%)	4 (8.7%)	–	–	
Group B2	12 (50.0%)	27 (58.7%)	–	–	
Group D	6 (25.0%)	6 (13.0%)	–	–	
Virulence genes					
papC	14 (58.3%)	20 (43.5%)	1.80	0.59–5.60	0.26
papEF	15 (62.5%)	26 (56.5%)	1.28	0.41–4.05	0.82
sfa	5 (20.8%)	10 (21.7%)	0.94	0.22–3.60	0.99
afa	2 (8.3%)	6 (13.0%)	0.61	0.05–3.79	0.87
hly	5 (20.8%)	4 (8.7%)	2.71	0.52–15.3	0.20
aer	1 (4.2%)	4 (8.7%)	0.50	0.01–5.05	0.87
cnf	6 (25.0%)	15 (32.6%)	0.69	0.18–2.32	0.70

TI, urinary tract infection.

age between the two groups of patients in the study by Moreno *et al.* [10]. In addition, in contrast to Moreno *et al*. [10], the present study checked specifically that the isolates from blood and urine were identical. Using PFGE, it was shown that most (85.7%; 24 of 28) isolates from blood were identical to the corresponding isolates from urine. Previous studies have reported similar findings [11,12].

Female gender and the presence of a urinary catheter were associated with fewer cases of *E. coli* bacteraemia once the bacteria have infected the urinary tract. A urinary catheter bypasses the normal host defences and allows the entry of pathogens into the bladder. The presence of a foreign body also leads to the formation of a biofilm, which helps pathogens to proliferate and cause infection. Because of the different mechanisms involved in infection, the *E. coli* isolates responsible for catheter-associated UTI harbour fewer virulence factors than isolates causing classical UTI [13]. It is likely that these isolates are less invasive, and are thus less able to invade the bloodstream once they have infected the urinary tract.

There were some limitations to the present study. First, only a limited number of virulence genes were characterised, and it is possible that other known virulence factors [14,15] may also be involved in bloodstream invasion. However, studies including additional risk-factors (e.g., *ibeA*, *malX* or *kspM II*) have also failed to reveal an association between these factors and the invasiveness of the strains studied [13,14]. Second, the diagnosis of bacteraemia in symptomatic UTI depends on the time at which blood cultures are taken, and a positive blood culture may not be a clear-cut factor that allows discrimination. Nevertheless, the findings suggest that *E. coli* strains of urinary tract origin, which also cause bacteraemia, do not differ significantly from those responsible for UTI only, with respect to their phylogenetic background and virulence determinants. These data should be confirmed by

additional studies, but factors other than bacterial virulence are probably more important in the development of a symptomatic UTI into USB.

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RESEARCH NOTE

A comparison of phylogenetic group, virulence factors and antibiotic resistance in Russian and Norwegian isolates of *Escherichia coli* from urinary tract infection

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ABSTRACT

Isolates of *Escherichia coli* from 31 Norwegian and 31 Russian females with significant bacteruria who presented with clinical signs of urinary tract infection (UTI) were tested for antimicrobial sensitivity, the presence of virulence genes, phylogroup distribution and clonal affinity. Twenty isolates, representing the full clonal diversity of a collection of 138 intestinal isolates of *E. coli* from healthy Norwegian females, served as a reference group. Russian UTI isolates belonged more often to phylogroup A and possessed fewer virulence genes than did Norwegian isolates. UTI isolates of *E. coli* were genetically heterogeneous and had a high degree of antimicrobial sensitivity.

Keywords Antimicrobial sensitivity, clonal diversity, *Escherichia coli*, phylogenetic groups, urinary tract infection, virulence factors

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