Escherichia coli bacteraemia in pregnant women is life-threatening for foetuses

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Abstract

In order to improve knowledge on *Escherichia coli* bacteraemia during pregnancy, we studied clinical data and performed molecular characterization of strains for 29 *E. coli* bacteraemia occurring in pregnant women. Bacteraemia mostly occurred in the third trimester of pregnancy (45%) and was community-acquired (79%). Portals of entry were urinary (55%) and genital (45%). *E. coli* strains belonged mainly to phylogroups B2 (72%) and D (17%). Four clonal lineages (i.e. sequence type complex (STc) 73, STc95, STc12 and STc69) represented 65% of the strains. The strains exhibited a high number of virulence factor coding genes (10 (3–16)). Six foetuses died (27%), five of them due to bacteraemia of genital origin (83%). Foetal deaths occurred despite adequate antibiotic regimens. Strains associated with foetal mortality had fewer virulence factors (8 (6–10)) than strains involved in no foetal mortality (11 (4–12)) (p 0.02). When comparing *E. coli* strains involved in bacteraemia with a urinary portal of entry in non-immunocompromised pregnant vs. non-immunocompromised non-pregnant women from the COLIBAFI study, there was no significant difference of phylogroups and virulence factor coding genes. These results show that *E. coli* bacteraemia in pregnant women involve few highly virulent clones but that severity, represented by foetal death, is mainly related to bacteraemia of genital origin.

Keywords: Bacteraemia, chorioamnionitis, *Escherichia coli*, foetal mortality, phylogenetic group, pregnancy, virulence
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Introduction

Bacterial infections during pregnancy remain a relevant complication, even in developed countries [1]. Sepsis is now the most common cause of direct maternal death [2], with 1.1 maternal deaths for 100 000 pregnancies in the UK between 2006 and 2008. The incidence of bacteraemia during pregnancy varies from 3 to 7.5 for 1000 pregnancies [3,4]. Bacteraemia during pregnancy is also life-threatening for fetuses, with 10% of foetal death in a retrospective study [4].

Escherichia coli is one of the most common organisms involved in bacteraemia in the general population [5,6] and during pregnancy [3,4,7–10]. This bacterium was involved in 44% of bacteraemia during pregnancy in a recent study by Surgers *et al.* [4]. The *E. coli* species is classified in at least seven phylogenetic groups (A, B1, B2, C, D, E and F) [11]. Classically, extra-intestinal virulent strains belong to phylogroups B2 and, to a lesser extent, D [12]. The intrinsic virulence of the strains, assessed in a mouse model of sepsis, is mostly determined by the presence of virulence genes [12]. However, the contribution of these bacterial determinants of

E. coli to patient mortality was found to be low regarding host factors or portal of entry in a prospective study of *E. coli* bacteraemia in adults [13]. Because little is known about *E. coli* bacteraemia in pregnant women, we conducted a study to describe clinical and microbiological characteristics of bacteraemia during pregnancy and to compare clinical and bacterial characteristics of bacteraemia: (i) according to the portal of entry, (ii) according to the severity of bacteraemia evaluated by foetal mortality, and (iii) in pregnant women vs. non-pregnant women with a urinary portal of entry.

Materials and Methods

Studied patients

This analysis focused on pregnant women with *E. coli* bacteraemia included in two previous studies. The first one was the multicentre prospective COLIBAFI study [13]. This study enrolled 1051 adults with *E. coli* bacteraemia and was carried out in France between January 2005 and November 2007. The second study was a multicentre retrospective study of bacteriaemic pregnant women conducted in France between 2005 and 2009 [4]. Women were included until 7 days post-delivery. All *E. coli* strains were centralized in one laboratory (INSERM, UMR 1137) for molecular epidemiological studies.

For the case-control analysis, cases were non-immunocompromised pregnant women with a urinary portal of entry. Each case was matched to two controls. Controls were chosen from the original COLIBAFI cohort [13]. Eligible controls were non-pregnant women aged from 18 to 51 years, who had a urinary portal of entry of bacteraemia and were not immunocompromised. Patients were matched for age using a greedy algorithm (http://mayoresearch.mayo.edu).

Clinical data

The following demographic characteristics and underlying conditions were collected: age, place of birth, antibiotherapy within 2 weeks, tobacco addiction, diabetes including gestational diabetes and history of previous bacteraemia. Patients were considered to be immunocompromised if they had at least one of the following conditions: solid or bone-marrow transplantation, immunosuppressive therapy, solid cancer, haemopathy and HIV infection.

The portal of entry of bacteraemia was established after review of each medical record conjointly by obstetricians and infectious disease specialists through a careful evaluation of all possible sources according to clinical and microbiological features (i.e. *E. coli* had to be isolated in the blood culture and in the sample from the presumed source of bacteraemia).

Bacteraemia episodes were classified according to the gestational age at occurrence: first trimester (T1) (before 15 weeks' gestation), second trimester (T2) (between 15 and 28 completed weeks' gestation), third trimester (T3) (after 28 weeks' gestation) and post-partum until 7 days post-delivery (PP). They were considered to be community-acquired if the first positive blood culture was obtained within the first 48 h after admission. All patients were followed-up until hospital discharge (up to 28 days maximum).

Bacterial strains

Strains were conserved with glycerol shortly after isolation and stored at −80°C. Genomic DNA was extracted using the WIZARD® DNA genomic kit from Promega (Madison, WI, USA). All strains were characterized in terms of phylogenetic group with the new quadruplex PCR method, which allows the delineation of the seven main phylogenetic groups [11]. Ten main B2 phylogenetic subgoups (I–X) were detected by allele-specific PCRs [14,15]. They correspond to clonal lineages or sequence type complexes (STc) 131, 73, 127, 141, 144, 12, 14, 452, 95 and 372, respectively, according to the Achtman multilocus sequence typing (MLST) scheme [16]. Among the D phylogroup strains, clonal group A (CGA), which corresponds to STc69, was identified as previously described [17]. O-types were determined by allele-specific PCR or by the classical serological method when necessary [18]. PCR was used to detect the presence of genes encoding 18 virulence factors, including adhesins (*papC*, *papG*, including *papG* alleles, *sfa/foc*, *iha*, *hra* and *ibeA*), toxins (*hlyC*, *cnf1* and *sat*), iron capture systems (*fyuA*, *irp2*, *iroN*, *iucC* and *ireA*), protectins (*neuC*, chromosomal *ompT* and *traT*) and *usp,* a gene encoding for a uropathogenic-specific protein. Virulence factors were clustered on genomic islands called pathogenicity-associated islands (PAIs) as in Lefort *et al.* [13].

Antimicrobial susceptibilities were determined for 18 antibiotics with the disk-diffusion method with Mueller-Hinton agar, as recommended by Comité de l'Antibiogramme de la Société Française de Microbiologie standards (www.sfm-microbiologie.org). A strain was considered to be multidrug resistant if it was resistant to amoxicillin, ofloxacin and cotrimoxazole. For each strain, a resistance score was computed as the number of antibiotics to which it was resistant among the following: amoxicillin, cefotaxime, gentamicin, ofloxacin and cotrimoxazole [13]. The empirical antimicrobial therapy was considered to be adequate if the results of susceptibility testing revealed that the isolate was susceptible to the empirical antimicrobial therapy prescribed.

Statistical analysis

We first performed a descriptive analysis. Descriptive statistics were expressed as number and percentage and as median and interquartile range, as appropriate. We then performed a univariate comparison of clinical and bacterial characteristics for urinary vs. genital portal of entry of bacteraemia. Clinical characteristics studied included immunosuppression, antibiotic treatment within 2 weeks before the diagnosis of bacteraemia, tobacco addiction, diabetes mellitus, a previous history of bacteraemia, nosocomial bacteraemia and adequacy of empirical antibiotics. Bacterial characteristics included resistance to the 18 antibiotics tested, resistance score, multidrug resistance, phylogroup (for simplicity, the only F strain was considered to belong to the D phylogroup as it appears D using the triplex PCR phylogrouping method) [11] and presence of 18 virulence genes with characterization of six PAIs.

A second univariate analysis was performed to analyse the factors associated with foetal death. We performed this comparison in bacteraemia occurring during pregnancy, and post-partum bacteraemia were excluded. We analysed the same clinical and bacterial characteristics as those used above in the first univariate analysis. Comparisons between groups were performed using the non-parametric Wilcoxon or Fisher's exact tests, as appropriate.

We finally performed a matched case-control analysis to identify factors associated with *E. coli* bacteraemia during pregnancy using a univariate conditional logistic regression. The same clinical and bacterial characteristics as in previous analyses were studied.

All analyses were performed with SAS v9.3 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided with a type-I error fixed to 0.05.

Results

Global clinical characteristics

Twenty-nine women with *E. coli* bacteraemia during pregnancy and the early postpartum (PP) period were included (Table 1). Fourteen patients were from the COLIBAFI cohort, and 15 women were included from the retrospective study. The median age was 31(20–46) years. One patient was considered to be immunocompromised because she was receiving a long-term corticosteroid treatment (prednisone 10 mg/day) for an unknown reason. Bacteraemia mostly occurred during the third trimester (n = 13, 45%). Seven bacteraemias occurred postpartum (24%). Gestational age of occurrence was unknown for two patients. Bacteraemia was mostly community-acquired (n = 23, 79%). Two portals of entry were reported: urinary tract infections (n = 16, 55%) and genital tract infections (chorioamnionitis during pregnancy and endometritis PP) (n = 13, 45%). No maternal death was observed during the period of sepsis or up till day 28. Nevertheless, two pregnant non-immunocompromised women were transferred to the intensive care unit (ICU) for septic shock due to genital tract infections (i.e. chorioamnionitis) occurring during T1/T2 of pregnancy.

TABLE 1. Clinical characteristics of the 29 pregnant women with *E. coli* bacteraemia

Demographics	
Age in years median (range)	31 (20–46)
	***n* (%)**
Place of birth	
Europe	15 (51.7)
Africa	9 (31.0)
Asia	1 (3.5)
Unknown	4 (13.8)
Clinical	
Immunosuppression	1 (3.5)
Antibiotics within 2 weeks	1 (3.5)
Tobacco addiction	5 (17.2)
Diabetes	4 (13.8)
Previous bacteraemia	1 (3.5)
Community-acquired bacteraemia	23 (79.3)
Empirical antibiotic inadequate	8 (28.6)
Foetal death	6 (20.7)
ICU admission for mother	2 (6.9)
Portal of entry	
Urinary tract	16 (55.2)
Genital tract	13 (44.8)
Gestational age at the time of bacteraemia	
First trimester	1 (3.5)
Second trimester	6 (20.7)
Third trimester	13 (44.8)
Unknown	2 (6.9)
Post-partum	7 (24.1)

Among the 22 bacteraemias occurring during pregnancy, six foetuses died (27%). Five out of the six foetal deaths occurred in a context of chorioamnionitis following preterm prelabour rupture of the membranes. No neonates died and global mortality associated with bacteraemia during pregnancy and the early post-partum period was 21%.

Bacterial strain characteristics

The 29 *E. coli* strains are described in Table 2. Twenty-one belonged to the B2 phylogroup (72%), five to the D phylogroup (17%), five to the A phylogroup (7%) and one to phylogroup F (3%). Among the B2 group strains, seven belonged to B2 subgroup II (33%), four to subgroup IX (19%), four to subgroup VI (19%), three to subgroup I (14%) and two to subgroup IV (10%), whereas only one strain was unassignable to any subgroup tested (5%). All except one D strain belonged to the CGA clone (80%). We observed 14 different O-types. Most represented O-types were O6a (n = 8, 28%), O4 (n = 4, 14%) and O1 (n = 3, 10%). The median virulence score was 10 (3–16). The frequency of PAIs ranged from 10% for PAI_{gimA} to 90% for PAI_{IV536}, with values of

TABLE 2. Phylogroups and subgroups, O-type, virulence and resistance scores of the 29 *E. coli* strains isolated from pregnant women

Strain ID	Phylogroup	Clonal group[a]	O type	Virulence score	Resistance score
R1B6F18	A	/	O77	8	0
HFE7	A	A_1	O6a	4	1
HFE3C	B2	B2-I	O120	8	2
HFE2	B2	B2-I	O25b	8	2
R1B5C13	B2	B2-I	O6a	9	1
R1B4E1	B2	B2-II	O22	9	0
R1B9C4	B2	B2-II	O4	6	0
HFE10	B2	B2-II	O6a	10	2
HFE12	B2	B2-II	O6a	16	2
HFE15	B2	B2-II	O6a	11	2
HFE8	B2	B2-II	O6a	15	0
R1B12B17	B2	B2-II	O6a	12	1
HFE1	B2	B2-IV	O2b	12	0
HFE5	B2	B2-IV	O2b	9	2
HFE11	B2	B2-IX	O1	10	1
R1B3J4	B2	B2-IX	O1	15	0
R1B4F3	B2	B2-IX	O1	12	0
R1B8D18	B2	B2-IX	O2a	10	1
HFE16	B2	B2-UA	O75	12	0
R1B6E1	B2	B2-VI	O21	11	1
HFE9	B2	B2-VI	O4	12	1
R1B1G3	B2	B2-VI	O4	13	1
R1B6J15	B2	B2-VI	O4	13	1
R1B6G4	D	/	O7	3	0
R1B13H4	D	CGA	O17	3	1
HFE6	D	CGA	O6a	9	2
R1B5D10	D	CGA	O73	6	1
HFE4	D	CGA	O77	7	3
HFE13	F	/	O7	10	0

[a]A_1 and CGA correspond to STc10 and 69 of the Achtman MLST scheme, respectively [16]. Within the B2 group, sub-groups I, II, IV, VI and IX correspond to STc131, 73, 141, 12 and 95, respectively [16]. B2-UA = B2 unassignable using our allele-specific assay [15].

21%, 34%, 41% and 72% for $PAI_{ICFT073}$, PAI_{IIJ96}, PAI_{III536} and PAI_{USP}, respectively.

Eighteen strains were resistant to amoxicillin (62%) and 14 to amoxicillin-clavulanate (48%). No strain exhibited extended-spectrum β-lactamase (ESBL) and one strain (3%) was resistant to quinolones (i.e. nalidixic acid, ofloxacin and ciprofloxacin). The median resistance score was 1 [0–3]) and one strain was multidrug resistant (3%). Antibiotic therapy was inadequate for eight patients (28%), consisting of an initial prescription of amoxicillin or amoxicillin-clavulanate.

Portal of entry

No significant difference was observed between urinary and genital portals of entry for bacteraemia in terms of host characteristics, nosocomial/community-acquired infection, trimester of occurrence and bacterial characteristics.

Severity of mother sepsis and foetal death

Of the 29 patients included, two were transferred to the ICU during hospitalization. Neither of these two women was immunocompromised. Empirical antibiotic therapy was not adapted for one patient; the second patient lost the foetus. Both isolated strains belonged to the B2 phylogroup, with a virulence score of 12 and 8, respectively.

Among the six foetal deaths due to the 22 bacteraemias occurring during pregnancy, five were observed in patients with a genital portal of entry (83%) and one observed in a patient with a urinary portal of entry (17%) (p 0.06). When comparing bacterial characteristics according to the occurrence of foetal death, no significant difference in phylogenetic group and antimicrobial susceptibility profile was observed. However, virulence score was significantly higher in the group of surviving foetuses than in the group with foetal death (11 [4–12] vs. 8 [6–10], p 0.02). Strains associated with foetal death carried less frequently the *papC* or *papG* genes (p 0.04 for both virulence factor genes). Empirical antibiotic therapy was adapted due to susceptibility testing for all bacteraemias associated with foetal death (6/6, 100%) but not adapted for seven of the 16 patients without foetal death (44%) (p 0.05) (Table 3).

Comparison of bacteraemia in pregnant and non-pregnant women

Among the 29 pregnant women included in this analysis, 16 had a urinary portal of entry, one of whom was immunocompromised. Fifteen pregnant women were thus matched to 30 controls from the COLIBAFI study. No significant difference was observed between cases and controls for any of the clinical or bacterial characteristics studied in the univariate case control analysis (Table 4).

Discussion

We report here the results of the largest study ever published focusing on *E. coli* bacteraemia during pregnancy, a rare but severe event [4]. Bacteraemia occurred mostly during T3 and was mostly community acquired. No maternal death was observed. The most remarkable result of our study is the very

TABLE 3. Comparison of clinical and microbiological characteristics according to foetal death

	Foetal death		
	No *n* = 14	Yes *n* = 6	p-value
Clinical characteristics			
Genital portal of entry	1	5	0.06
Empirical antibiotic inadequate *n* (%)	7 (50)	0	0.05
Bacterial characteristics			
Resistance score, median (range)	1 (0–3)	1 (0–2)	0.5
Phylogroup *n* (%)			
A	1 (7.1)	0 (0)	
B2	12 (85.7)	4 (66.7)	1
D	1 (7.1)	2 (33.3)	
Virulence score, median (range)	11 (4–12)	8 (6–10)	0.02
Virulence factor, *n* (%)			
papC	10 (71.4)	1 (16.7)	0.04
papG	10 (71.4)	1 (16.7)	0.04

TABLE 4. Comparison of urinary portal of entry bacteraemia in pregnant women ('Cases') vs. non-pregnant women ('Controls')

	Cases $n = 15$	Controls $n = 30$	OR (IC 95%)	p	p-value (Fisher)
Type of infection					
Community acquired	11 (78.6)	23 (85.2)	1	–	0.7
Nosocomial	3 (21.4)	4 (14.8)	1.6 (0.2–20.5)	1	
Empirical antibiotic inadequate					
No	5 (33.3)	6 (20)	1.9 (0.4–10.0)		0.5
Yes	10 (66.7)	24 (80)	1	–	
Multidrug resistance					
No	15 (100)	28 (93.3)	1	–	0.5
Yes	0 (0)	2 (6.7)	–	–	
Phylogroup					
A	1 (6.7)	0 (0)	–	–	0.7
B1	0 (0)	1 (3.3)	–	–	
B2	11 (73.3)	23 (76.7)	1	–	
D	3 (20)	6 (20)	1 (0.1–16.0)	1	
Virulence score, median (range)	10 (1–16)	12 (6–15)	0.9 (0.7–1.1)	0.4	0.5

high rate of foetal mortality (27%), confirming the poor foetal outcome of bacteraemia during pregnancy [4]. Foetal mortality was not due to inadequate antibiotherapy or related to a specific clone or virulence factor. Paradoxically, strains associated with foetal death exhibited a lower virulence score than strains associated with no foetal death. In fact, the severity of the disease is not linked to the intrinsic virulence of the strain assessed by the number of virulence genes but, probably, to host factors and the portal of entry. All foetal deaths except one were associated with a genital portal of entry (p 0.06). This result was non-significant but it might be due to a lack of power. Indeed, chorioamnionitis often occurs on a particular obstetrical background, such as cervical incompetence requiring emergency cervical cerclage or in a context of preterm prelabour rupture of the membranes. The only way to treat clinically obvious chorioamnionitis in this case is to induce delivery because antibiotics have a poor diffusion at the site of infection in the case of chorioamnionitis. It could explain the severity of genital tract bacteraemia for foetuses. Foetal death is then related to a particular obstetrical background. Poor outcome in non-urinary portal of entry bacteraemia has already been shown in adults and children [13,19]. In the same way, we have recently reported that in 60 *E. coli* strains isolated from bacteraemic patients, a correlation was observed between the number of virulence genes and the severity in a mouse sepsis model but not with the severity in the patients [20].

Strains causing bacteraemia overwhelmingly belonged to phylogroup B2 (72%). Such a high proportion was only observed in infants younger than 3 months with neonatal meningitis or bacteraemia, in whom it reached more than 80% [19,21–24]. In children older than 3 months and adults, phylogroup B2 *E. coli* strains were isolated in 58% and 52% of bacteraemia, respectively [13,19]. A clear decreasing trend in the proportion of B2 phylogroup strains is thus observed in bacteraemia from pregnant women and young infants compared with older infants and adults. As compared with the other groups, B2 phylogroup strains were shown in a mouse model of sepsis to possess high intrinsic extra-intestinal virulence. This property was linked to the presence of numerous extra-intestinal virulence genes [12]. This indicates that a high virulence potential is needed to induce extra-intestinal infection in pregnant women and young infants, whereas in older infants and adults, strains of other phylogroups can cause the disease, probably as a result of the pathophysiology of the disease underpinned by the host status and the portal of entry [25]. This was not expected, as pregnancy induces immunological variations that could increase susceptibility to bacterial infection [26]. However, a recent study highlighted variations of bactericidal activities of the genital tract secretions during pregnancy compared with non-pregnant women [27]. During pregnancy, there is an increase of bactericidal activities and a decrease in *E. coli* colonization. Strains from the B2 phylogroup seem to be better suited to colonizing the vagina in particular if they possess more virulence factor genes [28]. Accordingly, in our study, the median virulence score was significantly higher in strains isolated from pregnant women than in strains isolated from non-pregnant patients from the COLIBAFI study (10 vs. 9, p 0.05) [13].

Among the B2 phylogroup, we observed a clear oligoclonality, with STc73 (subgroup II) and STc95 (subgroup IX) representing more than half of the strains. In fact, these lineages are also preeminent in various extra-intestinal infections such as newborn meningitis [23], infant [19,24] and adult bacteraemia [15,29] and urinary tract infections in adults [29,30]. Interestingly, we also observed a high proportion (19%) of STc12 (subgroup VI), which is not frequent in adult infections but had been found to be relatively frequent in a cohort of young infants with bacteraemia [24]. This oligoclonality was also observed at the O-type level with a predominance of O6 and O4 types. Lastly, all but one D-group strain belonged to the clonal A group (STc69) [31].

This study has several limitations. First, we pooled two studies with different designs, but with the same data recorded during the same time period. Second, strains were collected before the spread of ESBL in the community [32]. Lastly, the number of studied patients is rather low, leading to a small power for most comparisons. However, this is the first study focusing on clinical and microbiological *E. coli* bacteraemia in pregnant women. We demonstrate that bacteraemia in pregnant women is due to a few highly virulent clones but

severity, represented by foetal death, is mainly related to the genital portal of entry.

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Transparency Declaration

We don't have any conflict of interest for this study.

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Appendix 1: Members of the COLIBAFI Group

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