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Incidence, risk factors and outcomes of *Escherichia coli* bloodstream infections in a large Canadian region

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ABSTRACT

Although *Escherichia coli* is the most common cause of bloodstream infection, its epidemiology has not been well defined in non-selected populations. We sought to describe the incidence of risk factors for, and outcomes associated with, *E. coli* bacteraemia. Population-based surveillance for *E. coli* bacteraemia was conducted in the Calgary Health Region (population 1.2 million) during the period 2000–2006. In total, 2368 episodes of *E. coli* bacteraemia were identified for an overall annual population incidence of 30.3/100 000; 15% were nosocomial, 32% were healthcare-associated community-onset and 53% were community-acquired bacteraemias. The very young and the elderly were at highest risk for *E. coli* bacteraemia. Sixty per cent of the episodes occurred in females (relative risk 1.5; 95% CI 1.4–1.6). Dialysis, solid organ transplantation and neoplastic disease were the most important risk factors for acquiring *E. coli* bacteraemia. Rates of resistance to ampicillin, trimethoprim–sulphamethoxazole, gentamicin, ciprofloxacin, cefazolin and ceftriaxone increased significantly during the period 2000–2006. The case-fatality rate was 11% and the annual population mortality rate was 2.9/100 000. Increasing age, ciprofloxacin resistance, non-urinary focus and a number of comorbid illnesses were independently associated with an increased risk of death, and community acquisition and urinary focus were associated with a lower risk of death. This study documents the major burden of illness associated with *E. coli* bacteraemia and identifies groups at increased risk for acquiring and dying from these infections. The emergence of ciprofloxacin resistance and its adverse effect on patient outcome is a major concern.

Keywords Bacteraemia, epidemiology, mortality, population, resistance

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INTRODUCTION

Escherichia coli ranks first and second as the most common cause of community-acquired and hospital-acquired bloodstream infection, respectively [1–7]. *E. coli* bloodstream infections usually arise as a complication of focal infections of the urinary or gastrointestinal tracts, although occasionally they also cause primary bacteraemia without a defined source. *E. coli* is also a major cause of invasive infections, including bacteraemic sepsis and meningitis in the neonatal period [1,8]. Rates of antimicrobial resistance in *E. coli* have increased in recent years. Resistance to a number of classes of antimicrobials has been observed, and the emergence of strains with AmpC-type β-lactamases and extended-spectrum β-lactamases (ESBLs) [9–13] is of most concern. Several studies have reported on the clinical features and outcomes of *E. coli* bacteraemia within selected populations [7,14–23]. Case-fatality rates in these predominantly hospital-based studies have ranged broadly from 5% to 30%, probably reflecting, at least in part, the selected case mix of cohorts studied and the impact of resistant organisms.

Despite the paramount importance of *E. coli* bloodstream infections, their epidemiology has rarely been evaluated in a non-selected population [24]. Although population-based studies

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investigating the epidemiology of bloodstream infections in general have been conducted, specific risk factors and outcomes associated with *E. coli* bacteraemia are not well defined or described [2–6,24]. The objective of this study was to conduct population-based surveillance in a large Canadian region during the period 2000–2006 in order to define the incidence, risk factors for acquisition and outcomes of *E. coli* bloodstream infections.

METHODS

Study population

The Calgary Health Region (CHR) provides virtually all medical and surgical care to the residents of the cities of Calgary and Airdrie and a large surrounding area (population 1.2 million) in the Province of Alberta, Canada. Only patients requiring acute liver, heart or lung transplantation surgery are routinely referred elsewhere for care. All persons who resided in the CHR and who developed bacteraemic *E. coli* infection during the period 1 January 2000 to 31 December 2006 were included in the study. The Conjoint Health Research Ethics Board at the University of Calgary and the CHR approved this study and waived the requirement for individual written informed consent.

Study protocol

An active, population-based surveillance cohort design was utilized. Surveillance for bacteraemic *E. coli* infections was conducted by Calgary Laboratory Services, a regional laboratory system that receives more than 95% of all blood samples submitted for culture from hospitals, nursing homes and clinics in the CHR. Further clinical and outcome details were obtained concerning all patients admitted to any of the four major acute-care hospitals (representing ≥95% of the CHR admissions), using data available from the regional corporate data warehouse.

Definitions

Bacteraemic *E. coli* infection was defined on the basis of the isolation of *E. coli* from one or more sets of aseptically inoculated blood culture bottles. Clinical isolates were cultured, confirmed as *E. coli*, and tested for antimicrobial susceptibility by standard techniques. At Calgary Laboratory Services, all *E. coli* isolates are routinely screened for ESBL and AmpC production, as previously described [9,10]. The presence or absence of *E. coli* cultures obtained from non-blood sites within *c.* 48 h of the index incident blood culture draw was also assessed. Incident cases were defined as those of the initial isolation of *E. coli* from blood of a CHR resident; repeated isolation within 365 days after the first isolation was deemed to represent the same incident infection. Residency status was established using the 2003 boundaries of the CHR (http://www.calgaryhealthregion.ca/newslink/publications/regionhealth/pdf/health_region_report_06.pdf). Neonatal infections were defined as those yielding a positive culture in children aged less than 90 days, and they were considered to be of early onset in children less than 7 days old.

Nosocomial bacteraemias were defined as those with first culture-positivity ≥48 h following hospital admission or within 48 h of discharge. Community-onset infections were defined as those with first culture-positivity within <48 h of admission or >48 h after discharge from hospital. A healthcare-associated community-onset *E. coli* bacteraemia was in addition associated with at least one of the following: (i) discharge from an adult home parenteral therapy clinic within 2–30 days before bloodstream infection [25]; (ii) attendance at a hospital clinic or emergency room within 2–30 days before bloodstream infection; (iii) admission to a CHR acute-care hospital for two or more days within the 90 days before bloodstream infection; (iv) sample submission from a patient who previously sent a sample from a nursing home or a long-term-care facility; and (v) outpatient haemodialysis.

Data on adult home parenteral therapy clinic assessment and dialysis were not available for children, and in these cases they were assumed to be non-existent. Community-acquired infections were defined as community-onset bacteraemias that were not healthcare-associated.

Statistical analysis

Analysis was performed using Stata Software version 9.0 (Stata Corp., College Station, TX, USA). Non-normally distributed variables were reported as medians with interquartile ranges (IQRs), and compared using the rank sum test for pairs or median test for multiple groups. Differences in proportions among categorical data were assessed using Fisher's exact test for pairwise comparisons and the chi-squared test for multiple groups. The incidence of bacteraemic *E. coli* infections was calculated by dividing the number of incident cases by the total regional population. The neonatal infection rate was also expressed as a rate per 1000 live births (106 752). Population-based risk factors for developing *E. coli* bacteraemia were quantified by dividing the incidence of these infections among those with a given factor by those without the factor. Regional demographic data were used to determine the population at risk according to age and gender. For other potential risk factors, the population at risk was ascertained or estimated using local patient registry data [26], regional or Canadian survey data (http://www.statcan.ca/english/freepub/82-570-XIE/intro.htm), or published North American epidemiological data [27–29]. Risks were expressed as incidence rate ratios (RRs) and reported with 95% CIs. A logistic regression model was developed to assess independent factors associated with in-hospital deaths. Factors found to be significant to the $p < 0.1$ level were included in the initial model, and backward stepwise variable elimination was then performed to develop the final model. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, and discrimination was assessed using the area under the receiver operator characteristic curve. For all statistical comparisons, a p-value <0.05 was deemed to represent statistical significance.

RESULTS

During the 7-year study, 2368 incident bacteraemic *E. coli* infections occurred among 2316 CHR residents; 47 patients had two incident episodes, and five patients had three incident episodes.

Basic demographic (age, gender, residency) and microbiological data were available for all patients, and further clinical and outcome information was available for the 2041/2368 (86%) incident cases managed at one of the four major acute-care centres in the CHR. Among the 2368 incident bacteraemic *E. coli* infections, 364 (15%) were classified as nosocomial, 758 (32%) as healthcare-associated community-onset, and 1246 (53%) as community-acquired. The overall annual population incidence of bacteraemic infection among residents of the CHR was 30.3/100 000. A relatively stable incidence was observed during the 7 years of the study, as shown in Fig. 1.

The median age of the patients was 67.3 years (IQR, 49.9–79.0 years); it was significantly ($p < 0.001$) lower in patients with community-acquired infections (65.0 years; IQR, 46.9–76.6 years) than in patients with nosocomial (69.6 years; IQR, 51.5–80.3 years) and healthcare-associated (71.5 years; IQR, 53.5–81.6 years) infections. The risk of development of *E. coli* bacteraemia was closely related to age, with the very young and the elderly being at highest risk, as shown in Fig. 2. Sixty-seven neonates (<90 days) developed *E. coli* bacteraemia at a rate of 0.63/1000 live births. Rates of early-onset and late-onset disease (19 and 48 cases) were 0.18 and 0.45/1000 live births, respectively. Sixty per cent (1415) of incident episodes overall occurred in females (RR 1.5; 95% CI 1.4–1.6; $p < 0.0001$). However, the excess risk in females was only observed in the age range 1–59 years (Fig. 2; RR 2.3; 95% CI 2.0–2.7), with there being no significant excess risk in the group of less than 1-year-old or over 60-year-old patients (RR 1.0; 95% CI 0.9–1.1). However, among 48 late-onset neonatal cases, 37 (77%) occurred in males (RR 3.2; 95% CI 1.6–7.0).

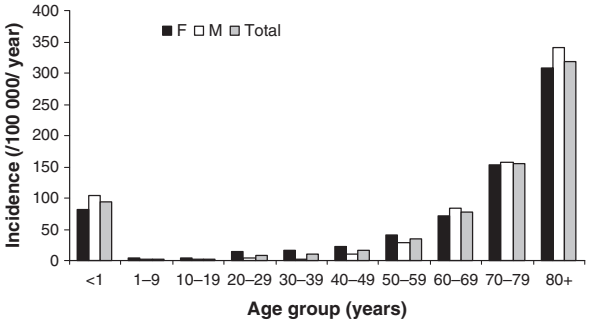

Fig. 2. Age-specific incidence of *Escherichia coli* bloodstream infections in the Calgary Health Region, Canada, 2000–2006.

A number of selected conditions were assessed as risk factors for acquiring *E. coli* bacteraemia, and these are shown in Table 1. Solid organ transplantation, renal dialysis and neoplastic disease were the most important risk factors. Among transplant patients, 27 were kidney recipients, two were lung recipients, and one each received a kidney/pancreas, liver or heart transplant. Among the 422 patients with neoplastic disease, 270 (64%) had malignant tumours, 96 (23%) had haematological malignancies, one patient had both a tumour and a haematological malignancy, and 55 (13%) patients had neoplastic disease in

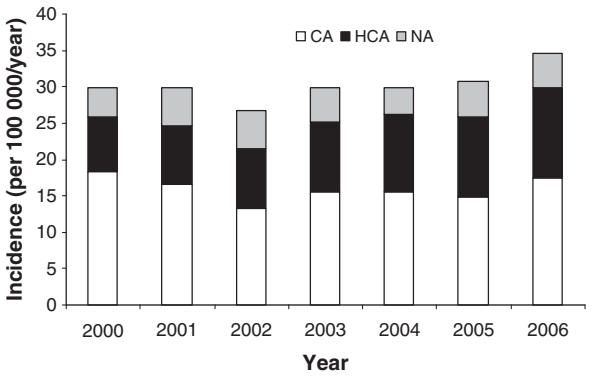

Fig. 1. Annual incidence of *Escherichia coli* bloodstream infections in the Calgary Health Region, Canada, 2000–2006. CA, community-acquired; HCA, healthcare-associated community-onset; NA, nosocomial-acquired.

Table 1. Risk of *Escherichia coli* bacteraemia associated with selected underlying conditions

Factor	Age group[a]	Number (%)	RR (95% CI)	p-value
Dialysis	20+	28 (1)	29.6 (19.6–43.0)	<0.0001
Organ transplant	All	33 (2)	20.3 (13.9–28.6)	<0.0001
Cancer	20+	422 (22)	14.9 (13.4–16.7)	<0.0001
Diabetes	12+	370 (19)	7.2 (6.4–8.0)	<0.0001
Heart disease	12+	399 (21)	6.2 (5.6–7.0)	<0.0001
HIV infection	All	6 (<1)	4.2 (1.5–9.2)	0.0042
Stroke	12+	63 (3)	3.3 (2.5–4.3)	<0.0001
COPD	12+	159 (8)	2.9 (2.4–3.4)	<0.0001
Crohn's disease	All	11 (1)	1.9 (1.0–3.4)	0.049
Rheumatoid arthritis	20+	36 (2)	1.9 (1.3–2.6)	0.0005
Ulcerative colitis	All	7 (<1)	1.9 (0.7–3.8)	0.13
Alcoholism	20+	129 (7)	1.7 (1.4–2.1)	<0.0001
Systemic lupus erythematosus	20+	12 (1)	1.7 (0.9–3.0)	0.089
Hepatitis C	All	26 (1)	1.4 (0.9–2.1)	0.087
Asthma	12+	47 (2)	0.3 (0.2–0.4)	<0.0001

RR, rate ratio; COPD, chronic obstructive pulmonary disease.
[a]Number of cases in age groups: all ages, $n = 2041$; 12 + (12 years and older), $n = 1935$; 20 + (20 years and older), $n = 1916$.

remission. Among the 270 malignant tumours, gastrointestinal tract (115; 43%), genitourinary tract (53; 20%) and lung (31; 11%) cancers were most frequently observed, and 145 (54%) were metastatic.

Among the incident 2368 cases, cultures of *E. coli* were positive from a non-blood site within 48 h of the index blood culture draw in 1121 (47%) cases. These cultures were obtained from urine in 1070 (45%) cases, intra-abdominal samples in 25 (1%), lower respiratory tract samples in 21 (1%), soft tissue in five (<1%), bone/joint samples in three, and central nervous system samples in two; one sample each was from the upper respiratory tract and the genitourinary tract.

Antimicrobial susceptibility testing results were available for 2355 (99%) of incident blood isolates. Reduced susceptibility (intermediate susceptibility or resistance) to ampicillin occurred in 986 (42%) cases, to trimethoprim–sulphamethoxazole in 508 (22%), to gentamicin in 212 (9%), and to cefazolin in 172 (7%). Among isolates tested, reduced susceptibility to amoxycillin–clavulanate was observed in 428/2226 (19%) cases, to ciprofloxacin in 257/2204 (12%), to ceftriaxone in 81/2192 (4%), to piperacillin–tazobactam in 60/2197 (3%), and to imipenem in 0/1482. AmpC- and ESBL-producing isolates were identified in 32 (1%) and 50 (2%) cases, respectively, predominantly of community-onset infections (25/32; 78% and 41/50; 82%). During the 7 years of the study, rates of resistance to all of the antimicrobials tested, except imipenem, trimethoprim–sulphamethoxazole and piperacillin–tazobactam, increased significantly ($p < 0.05$), as shown in Fig. 3.

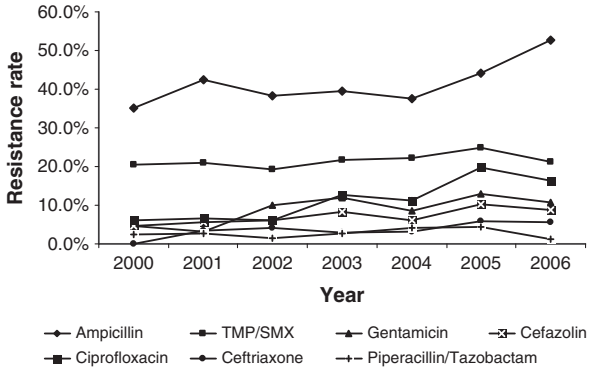

Fig. 3. Rates of antimicrobial resistance among *Escherichia coli* isolates from bloodstream infections in the Calgary Health Region, Canada, 2000–2006. TMP/SMX, trimethoprim–sulphamethoxazole.

The overall median length of hospital stay was 8.3 days (IQR, 4.8–16.5 days) and was significantly ($p < 0.0001$) longer for patients with nosocomial (25.8 days; IQR, 14.3–50.4 days) infections than for those with healthcare-associated (7.8 days; IQR, 4.7–13.4 days) and community-acquired (6.6 days; IQR, 4.1–11.0 days) infections. The median time from admission to development of nosocomial bacteraemia was 9.3 days (IQR, 4.2–18.9 days). The case-fatality rate was 230/2041 (11%) for an annual population mortality rate of 2.9/100 000. A multivariable logistic regression model was developed ($n = 1896$) to assess factors associated with death, and had both good discrimination (area under receiver operator characteristic = 0.794) and calibration (Hosmer–Lemeshow goodness-of-fit test p 0.66). Increasing age, ciprofloxacin resistance, nosocomial acquisition, non-urinary focus and a number of comorbid illnesses were independently associated with an increased risk of death, as shown in Table 2.

DISCUSSION

In this article, novel population-based data describing the incidence, risk factors for and outcome of *E. coli* bacteraemia in a large Canadian population (*c.* 8 million person-years of observation) are reported, and a contribution is made to the body of literature concerning factors associated with death due to these infections.

Population-based studies minimize selection bias, enable incidence rate calculations, and facilitate standardized comparisons among different regions and time periods. Few contemporary studies are available for comparison of the inci-

Table 2. Logistic regression modelling of risk factors for death in patients with *Escherichia coli* bacteraemia.

Factor	OR (95% CI)	p-value
Age 0–39 years	1.0 (reference)	
Age 40–64 years	2.9 (1.3–6.7)	0.011
Age 65+ years	5.0 (2.3–11.3	<0.001
Cancer	2.4 (1.6–3.6)	<0.001
Haematological malignancy	2.4 (1.3–4.5)	0.005
Community-acquired	1.0 (reference)	
Healthcare-asssociated	1.7 (1.1–2.4)	0.010
Nosocomial	2.7 (1.8–4.0)	<0.001
No focus	1.0 (reference)	
Urinary tract focus	0.4 (0.3–0.6)	<0.001
Focus other than urinary tract	5.6 (2.9–11.1)	<0.001
Stroke	2.1 (1.1–4.4)	0.035
Chronic lung disease	1.6 (1.0–2.7)	0.048
Alcoholism	7.3 (4.4–12.2)	<0.001
Heart disease	1.6 (1.1–2.3)	0.014
Ciprofloxacin resistance	1.8 (1.2–2.8)	0.008

dence rate of 30/100 000/year as reported here. Uslan *et al.* [2] reported a population-based analysis of bloodstream infections occurring in Olmstead County, USA, during the period 2003–2005. They found that *E. coli* was the most frequent isolate (163/650), with an approximate unadjusted rate of 40.5/100 000/year (calculated from data in their report) [2]. Skogberg *et al.* [4] observed a rate of approximately 30/100 000 for *E. coli* bacteraemias in Finland during the period 1995–2002. Madsen *et al.* [6] reported a rate of 32/100 000 in North Jutland County in Denmark during the period 1981–1994. Most recently, Kennedy *et al.* [24] reported a rate of 28/100 000 for *E. coli* bacteraemias in Canberra, Australia during the period 2000–2004. Putting this in context with other aetiologies, the incidence rate for *E. coli* bloodstream infections is 1.5-fold higher than that for either *Staphylococcus aureus* or *Streptococcus pneumoniae*, and ten-fold higher than that for group A and B streptococcal bacteraemias [2,4,30–37].

There are no other studies for direct comparison with the mortality rate of 2.9/100 000 reported here, because previous population-based investigations have either reported only aggregate data for all bloodstream infections [2,4,6] or have follow-ups limited to only 7 days [24]. Kennedy *et al.* [24] found a 5% 7-day case-fatality rate in their population-based study from Australia. Hospital-based studies have reported variable case-fatality rates, broadly ranging from 5% to 29%. Melzer and Petersen [18] studied 354 adults with *E. coli* bacteraemia at a hospital in Essex, UK, and found a case-fatality rate of 29%. A 21% case-fatality rate for *E. coli* bacteraemia was observed by both Gransden *et al.* among 861 patients in London, UK, and Olesen *et al.* in 433 episodes in a Danish university hospital [17,20]. Vazquez *et al.* [21] reported a slightly lower case-fatality rate of 18% among 474 cases in Oviedo, Spain. In contrast, Kuikka *et al.* found a case-fatality rate of 9% at a Finnish university hospital, and Peralta *et al.* a rate of 5% at an adult acute-care community teaching hospital in Torrelavega, Spain [15,22]. The wide variability in case-fatality rates observed in these studies probably reflects, at least in part, differences in case mix among investigations, as well as the effect of selection bias in studies from major referral centres [38–40] Population-based studies, by including all cases occurring in residents of a defined geographical region, minimize this important bias.

Previous population-based studies have documented the excess risk of all bloodstream infections in association with advancing age [2,4]. Uslan *et al.* identified an increased risk of *E. coli* bacteraemia in females across all age ranges which contrasts with the current observation of an excess risk in only 1–59-year-old females (Fig. 2). In contrast, Kennedy *et al.* [24] found that elderly males were at highest risk. Several hospital-based studies have suggested that a number of comorbid illnesses, including diabetes, malignancy, chronic lung disease, cirrhosis and heart disease, may increase the risk of *E. coli* bacteraemia [15,18,20]. However, to our knowledge, the present study is the first designed to quantify actual risk factors for the development of *E. coli* bacteraemia in a general, non-selected population (Table 1). There are several potential risk factors for *E. coli* bacteraemia that were not assessed in this study, e.g. chronic urinary catheterization, urinary incontinence and other urinary tract abnormalities, and this is a limitation of the study. Jackson *et al.* [19] conducted a case–control study nested within a large-cohort study of community-onset *E. coli* bacteraemias in seniors. They found that urinary catheterization and incontinence were risk factors in males, and that cancer, renal failure, heart disease and urinary incontinence were risk factors in females [19].

The rate of resistance to antimicrobials and its effect on rates of mortality merits discussion. As compared to most other large contemporary series of *E. coli* bacteraemia [14,15,18,24], overall lower rates of resistance to most antimicrobials tested were observed in this study; however, they are increasing (Fig. 3).

Previous studies have identified advancing age, hospital acquisition, comorbid illnesses, presence of shock, non-urinary focus and antimicrobial resistance in conjunction with inadequate treatment as being associated with death [15,17,18,20,41]. Melzer and Petersen [18] found that the adjusted OR for death associated with ESBL-producing isolates was 3.6 (95% CI 1.5–8.6). Peralta *et al.* [15] found that resistance to each antibiotic, except gentamicin, was associated with increased crude risk of death, and that multidrug-resistant (ESBL- or AmpC-producing, or resistant to three or more standard antimicrobials) *E. coli* accounted for an adjusted 3.1-fold (95% CI 1.3–7.4) increased risk of death.

These authors identified the effect of antimicrobial resistance as being an increased risk of receiving inadequate therapy. These findings contrast with those of the present study, in which only ciprofloxacin resistance was associated with a crude and adjusted risk of death (Table 2). It is notable that neither the presence of AmpC or ESBL enzymes, nor multidrug resistance or resistance to antimicrobials other than ciprofloxacin, was associated with adverse outcome in this study. Unfortunately, antimicrobial utilization data were not available for this study, and therefore it was not possible to assess the potential effect of adequacy of therapy on outcome.

Although a rigorous population-based design was utilized, there are some study limitations that merit discussion. Only patients who had a positive blood culture for *E. coli* were included in this study. Patients who may have had *E. coli* bacteraemia but from whom no sample was submitted for culture would not have been identified in this study. The rates presented should therefore be viewed as conservative estimates of all true *E. coli* bloodstream infections in the population studied. Another limitation is that each patient was not clinically assessed to determine a potential focus of infection; this was based, crudely, on the presence of *E. coli* at other sites. Finally, the assessment of factors associated with rates of mortality did not include a number of potentially important variables not limited to adequacy and timing of antimicrobial therapy and markers of severity of illness [15,41,42]. Although the present model had good discrimination, inclusion of these variables would probably improve the model further.

In summary, this novel study documents the major burden of illness associated with *E. coli* bacteraemia and identifies groups at increased risk for acquiring and dying from these infections. Ongoing surveillance for *E. coli* bacteraemia will be important to track the burden of disease and the adverse impact of antimicrobial resistance.

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TRANSPARENCY DECLARATION

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