J Microbiol Immunol Infect
2002;35:103-108

Invasive *Escherichia coli* infection in infancy: clinical manifestation, outcome, and antimicrobial susceptibility

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Received: August 1, 2001 Revised: August 29, 2001 Accepted: September 20, 2001

Escherichia coli is the second most common bacterium isolated from the blood of neonates with sepsis. During a 12-year period from January 1988 through December 2000, *E. coli* sepsis or central nervous system infections were diagnosed in a total of 46 infants (M/F ratio, 3.6:1) in a tertiary care medical center. These infants were stratified into 3 groups according to age at disease onset. Group A include infants at birth to 7 days old; Group B, 7 days to 1 month old; and Group C, beyond 1 month old. Among them, 13 had sepsis, 24 had urosepsis, and 9 had meningitis or meningoencephalitis. All patients with central nervous system infections were younger than 40 days old. In the urosepsis group, 22 (91.7%) of 24 patients were younger than 6 months old with a male predominance (M/F ratio, 20:4), and 7 (29.2%) of 24 had urinary tract anomaly. Nine (68%) of 13 patients with sepsis had underlying disease. The most common clinical signs and symptoms were fever (89.1%), followed by tachycardia (71.7%), ill looking (50%), poor feeding (30.4%), and tachypnea (23.9%). The significant laboratory findings were elevated C-reactive protein (60.9%), and leukocytosis (56.5%) with left shifting (43.5%). Antimicrobial susceptibility test of the isolates showed a 67.7% resistant rate to ampicillin and a 35.5% resistant rate to chloramphenicol between 1994 and 2000. No significant increase in the resistance rate of the strains was noted compared with results from 2 studies conducted at different periods of time (1988-1993 and 1994-2000). Two infants with central nervous system infection died and 5 experienced major neurological sequelae. The clinical spectrum of invasive *E. coli* infections is age-related and associated with the underlying conditions. The prognosis was related to the development of central nervous system complications.

Key words: Central nervous system infection, *Escherichia coli*, infant, sepsis, urosepsis

Escherichia coli is one of the most important pathogens of newborns and young infants causing sepsis, meningitis, and urinary tract infection [1-9]. The source of early-onset *E. coli* neonatal infection is usually the maternal genitourinary or gastrointestinal tract, particularly in pregnancies complicated by perinatal urinary tract infection, prolonged rupture of membranes, and chorioamnionitis [1]. Neonatal risk factors include prematurity, skin breakdown, and immunological and metabolic disorders. Late-onset infections are commonly associated with indwelling catheters, surgical procedures, and prolonged use of antibiotics; the latter may enhance selection of antimicrobial-resistant *E. coli* strains [1]. In Taiwan, *E. coli* and group B *Streptococcus* are the 2 most frequent bacteria isolated from neonates with sepsis and meningitis [2,3,6,10].

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The objectives of this retrospective study were to delineate the clinical presentations, laboratory findings, outcome, and antimicrobial susceptibility of invasive *E. coli* infections in Taiwan infants treated in a tertiary care medical center.

Patients and Methods

The medical records of all infants (age, <1 year) with invasive *E. coli* infections admitted to the National Cheng Kung University Hospital from 1988 through 2000 were retrospectively reviewed and analyzed. Invasive *E. coli* infection was defined as a positive blood culture and/or cerebrospinal fluid culture in the presence of clinical signs compatible with infection. Microbiological identification of *E. coli* and determination of antimicrobial susceptibilities were accomplished by standard laboratory methods. According to the age at disease onset, these patients were divided into 3 age groups. Group A include infants at birth to 7 days old; Group B, 7 days to 1 month old; and Group C, beyond 1 month old. These patients were further categorized

by disease entity into sepsis, urosepsis, and central nervous system (CNS) infection groups. Sepsis was diagnosed in patients with a blood culture positive for the presence of *E. coli* with one or more of the following symptoms: fever, hypothermia, apnea, lethargy, irritability, poor feeding, vomiting, and abdominal distension. Urosepsis was defined as isolation of *E. coli* from both blood culture and urine culture with associated clinical symptoms. Central nervous system infection was defined as isolation of *E. coli* from cerebrospinal fluid culture. Data on demographic characteristics, clinical manifestations, laboratory results, and outcome were collected and analyzed. Laboratory records were reviewed for *E. coli* isolates and the antimicrobial susceptibility test was performed by the disk diffusion method using BBL Sensi-Disc antimicrobial susceptibility test disks (Becton-Dickson, Cockeysville, MD, US) according to the manufacturer's instructions and in accordance with the criteria of the National Committee on Clinical and Laboratory Standards [11]. The antimicrobial agents tested were ampicillin (10 μg), gentamicin (10 μg), tobramycin (10 μg), ampicillin/sulbactam (10 μg/10 μg), amikacin (30 μg), cefamandole (30 μg), cefmetazole (30 μg), cefoxitin (30 μg), ceftazidime (30 μg), ceftriaxone (30 μg), cefuroxime (30 μg), cephalothin (30 μg), chloramphenicol (30 μg), moxalactam(30 μg) , netilmicin (30 μg), tetracycline (30 μg); cefoperazone (75 μg), and trimethoprim/sulfamethoxazole (1.25 μg/ 23.75 μg). The statistical analyses were performed by using Fisher's exact test or chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

Demographics

A total of 46 infants or neonates, including 36 males and 10 females with a male/female ratio of 3.6:1 ($p<0.001$) were included in the study. There were 5, 10, and 31 cases in groups A, B, and C, respectively. The disease was classified as sepsis in 13 patients, urosepsis in 24, and meningitis or meningoencephalitis in 9. All patients with CNS infections were younger than 40 days old with a male/female ratio of 7:2 ($p=0.096$). The majority (66.7%, 16/24) of patients with urosepsis were younger than 3 months old, and 91.7% (22/24) were younger than 6 months old. The male/ female ratio was 20:4 ($p=0.001$) in the urosepsis group and 9:4 ($p=0.166$) in the sepsis group. The associated underlying conditions in patients with invasive *E. coli* infections are summarized in Table 1.

Clinical presentations and laboratory results

The major clinical symptoms and signs of invasive *E. coli* infections presented at admission were fever (89.1%, 41/46), tachycardia (71.7%, 33/46), ill looking (50%, 23/46), poor feeding (30.4%, 14/46), tachypnea (23.4%, 11/46), abdominal distension (13%, 6/46), cyanosis (13%, 6/46), and seizure (11.2%, 5/46) (Table 2). In groups B and C, the main symptoms and signs were fever, tachycardia, ill looking, and poor feeding. The symptoms and signs in younger patients varied more greatly. Besides, multiple non-specific symptoms and signs were presented in Group A, especially gastrointestinal features. The significant laboratory abnormalities included elevated C-reactive protein (>20

Table 1. Congenital anomalies and underlying diseases in patients with invasive *E. coli* infection (n = 46)

Disease	Congenital anomaly and underlying disease	No. of cases
Urosepsis		24
	No congenital anomaly	17
	Hydronephrosis/hydroureter	5
	Left-side urinary-pelvic junction stenosis	1
	Posterior urethral valve	1
Sepsis		13
	No underlying disease	4
	Down syndrome with endocardial cushion defect	1
	Cerebral palsy	1
	Chronic diarrhea since birth	1
	Laryngeal malacia	1
	Chromosome anomaly	1
	Right kidney agenesis	1
	Biliary atresia	1
	Acute lymphocytic leukemia in chemotherapy	1
	Prematurity with a gestational age of 33 weeks, perinatal infections	1
Central nervous system infection		9
	No underlying disease	9

Table 2. Clinical symptoms or signs of invasive *E. coli* infection in different age groups[a]

Symptom/sign	Group A n = 5	Group B n = 10 (%)	Group C n = 31 (%)
Fever[b]	2	10 (100)	29 (93.5)
Fever >3 days	0	0	1 (3.2)
Tachycardia[c]	1	8 (80)	24 (77.4)
Tachypnea[d]	1	5 (50)	5 (16.1)
Ill looking	3	5 (50)	15 (48.4)
Poor feeding	1	3 (30)	10 (32.2)
Hypotension[e]	2	3 (30)	1 (3.2)
Abdominal distension	3	1 (10)	2 (6.4)
Seizure	1	3 (30)	1 (3.2)
Diarrhea	1	0	2 (6.4)
Jaundice	0	2 (20)	1 (3.2)
Cyanosis	1	2 (20)	3 (9.7)
Vomiting	2	0	1 (3.2)
Apnea[f]	1	0	0

[a]Group A = at birth to 7 days old; Group B = 7 days to 1 month old; Group C = beyond 1 month old.
[b]Temperature (38oC.
[c]Heart rate >200/min in neonates and >150/min in infants.
[d]Respiratory rate >60/min in neonates and >50/min in infants.
[e]Systolic blood pressure measurement >2 standard deviations below the mean for age.
[f]Cessation of breathing for longer than 20 s.

20 mg/L, 60.9%), leukocytosis (>30 000 /mm^3 in Group A, >20 000 /mm^3 in groups B and C, 56.5%) with left shifting (neutrophil-band form >10 % of leukocyte count, 43.5%), and unexplained metabolic acidosis (base excess >–7 mmol/L, 21.7%) (Table 3). Bandemia was more frequently noted in neonates compared with infants (p=0.001).

Antimicrobial susceptibility testing

The susceptibility testing of the isolates showed a high resistance rate to ampicillin (69.6%, 32/46) and chloramphenicol (43.5%, 20/46). Resistance rates to gentamicin, tobramycin, and first-generation cephalosporins were 19.6% (9/46), 15.2% (7/46), and 21.7% (10/46), respectively (Table 4). All strains were susceptible to netilmicin, amikacin, second- and third-generation cephalosporins, and tetracycline. Ampicillin/sulbactam and trimethoprim/sulfamethoxazole were also highly effective. Compared with the resistance rates found in 2 studies conducted at different periods (1988-1993 and 1994-2000), no significant increase of resistance was noted.

Prognosis

Empiric antibiotics, ampicillin, and gentamicin were initiated for neonatal infection. All patients with suspicion of CNS infection received ampicillin and third-generation cephalosporins, including cefotaxime, ceftriaxone, or moxalactam. The overall attributable mortality in infants with invasive *E. coli* infection was 4.3% (2/46). The clinical outcome was related to the existence of CNS infection. The CNS infection group

Table 3. Laboratory findings in different age groups of infants with invasive *E. coli* infection[a]

Laboratory finding	Group A n = 5	Group B n = 10 (%)	Group C n = 31 (%)
Leukocytosis (WBC >30 000/mm^3 in Group A, >20 000/mm^3 in Group B and C)	3	6 (60)	18 (58.1)
Bandemia (band form >10% WBC)	3	9 (90)	8 (25.8)
Leukopenia (WBC <4000 /mm^3)	1	2 (20)	1 (3.2)
Elevated CRP (>20 mg/L)	1	8 (80)	17 (54.8)
Thrombocytopenia (platelet <100 000 /mm^3)	1	2 (20)	3 (9.6)
Metabolic acidosis (BE <–7 mmol/L)	1	4 (40)	5 (16.1)
Hyponatremia (sodium <130 mmol/L)	1	1 (10)	3 (9.6)

[a]Group A = at birth to 7 days old; Group B = 7 days to 1 month old; Group C = beyond 1 month old.
Abbreviation: WBC = white blood cell; CRP = C-reactive protein; BE = base excess

Table 4. Antimicrobial susceptibility of the isolates of infants with invasive *E. coli* infection by disk diffusion method

Antimicrobial agent	No. of resistant isolates (%)	
	1988-1993 n = 15	1994-2000 n = 31
Ampicillin	11 (73.3)	21 (67.7)
Ampicillin/sulbactam	0	2 (6.5)
Chloramphenicol	9 (60)	11 (35.5)
Gentamicin	1 (6.7)	8 (25.8)
Tobramycin	1 (6.7)	6 (19.4)
Amikacin	0	0
1° cephalosporin[a]	4 (26.7)	6 (19.4)
2° cephalosporin[b]	0	0
3° cephalosporin[c]	0	0
Netilmicin	0	0
Tetracycline	0	0
Trimethoprim/sulfamethoxazole	0	1 (3.2)

[a] 1° cephalosporin: cephalothin.
[b] 2° cephalosporin: cefamandole, cefmetazole, cefoxitin, cefuroxime.
[c] 3° cephalosporin: cefotaxime, ceftriaxone, ceftazidime, cefoperazone, moxalactam.

had a high incidence of sequelae (55.5%, 5/9) such as subdural effusion and/or empyema, hydrocephalus, hearing impairment, brain edema, and infarct and mortality (22.2%, 2/9). No significant difference in mortality was found in relation to sex, predisposing factors, or initial appropriate antibiotic therapy. Patients with urosepsis and sepsis received ampicillin and gentamicin, whereas 3 patients in the sepsis group were treated with cephalothin, cefoxitin, or cefamandole in combination with gentamicin. According to the results of culture and susceptibility testing, the regimens were switched to responsive antibiotics. After adequate antimicrobial therapy, no mortality was noted in the sepsis and urosepsis groups.

Discussion

Although a number of gram-negative organisms cause primary neonatal infections, bacteria belonging to the family of *Enterobacteriaceae* are by far the most common. Within this family, *E. coli* is the bacterium isolated most frequently, causing approximately 10% to 35% mortality for sepsis and bacterial meningitis [4]. *E. coli* CNS infections almost always occur in the neonatal period. The outcome of the infectious process depends not only on the virulence of the invading microorganism but also on the defense mechanisms of the challenged host. In this study, 5 (55.5%) of 9 patients with CNS infection had concurrent bacteremia and none of these patients had associated urinary tract infection. The immaturity of the blood-brain barrier is a likely pathophysiological cause. While the role of K1 capsular polysaccharide antigen [5,12,13], impaired neutrophil function [14], and deficiency in opsonic activity against *E. coli* [15] have been explained, further investigation of *E. coli* CNS infection in neonates is needed. In comparison with the sepsis and urosepsis groups, no congenital anomaly or underlying diseases were noted in the CNS infection group. The high mortality and morbidity of CNS infections was not related to ampicillin resistance in this study, which is different from some prior reports [1,8].

In the CNS infection group, there were more males than females, but this difference did not reach statistical significance. Synnott *et al* [16] reported a male preponderance for *E. coli* meningitis compared with non-*E. coli* pathogens, which showed no sex significance. No relationship was noted in age or sex distribution among the sepsis group in this study. Ginsburg and McCracken [5] reported that 75% of patients with urinary tract infection younger than 3 months old were boys and 85% of urosepsis occurred in infants less than 2 months of age. Honkinen *et al* [17] found similar results in a recent study. But this study found different results in the age and sex distribution of urosepsis. Bachur and Caputo [9] reported that urosepsis (including non-*E. coli* pathogens) was limited to those younger than 6 months old and incidence is inversely related to age. However, in this study, there were 2 female patients older than 6 months (9 and 12 months old) and the distribution was not inversely related to age. The peak incidence (54%) was among infants of 1 to 3 months old. Among infants with urosepsis, 29.2% had a congenital urinary tract anomaly. The age-related incidence may not only stem from the relative immune immaturity of young children, but also from associated urinary tract anomaly.

In invasive *E. coli* infections, the clinical symptoms and signs were fever, tachycardia, ill looking, and poor feeding in the patients older than 1 month, whereas the neonates showed non-specific symptoms and signs, especially gastrointestinal presentations such as abdominal distension and vomiting. Fever and tachycardia are not the major signs of *E. coli* infection in neonates younger than 7 days compared with older infants. The signs and symptoms of *E. coli* infection are also indistinguishable from many different disease entities. During the past 2 decades, the main clinical manifestations of neonatal sepsis and probable sepsis shared similar presentations to those found in this study [18]. Invasive *E. coli* infections must always be considered in the differential diagnosis when evaluating an infant with similar presentations. Thorough physical examination and complete history are necessary to avoid misdiagnosis and delayed management when encountering a young neonate with suspicion of neonatal sepsis. Extreme values of any variables of laboratory findings such as elevated C-reactive protein, leukocytosis with left shifting, and unexplained metabolic acidosis should alert clinicians to a high likelihood of invasive infection.

Ampicillin and gentamicin have been recommended as the drugs of choice due to their synergistic effect in the treatment of *E. coli* infections [19]. Although this study found that resistance to ampicillin did not increase significantly during the periods from 1988 through 1993 and from 1994 through 2000, susceptibility to gentamicin and tobramycin decreased from 93.3% and 93.3% to 74.2% and 80.6% during these 2 periods, respectively. Since the source of *E. coli* isolates was limited to patients aged below 1 year, these isolates may not reflect the situation in the general population. In the era of increasing antimicrobial resistance, recent reports indicated that the rate of resistance to ampicillin and aminoglycoside were increased [1,8]. This study and a recent report of ampicillin susceptibility of *E. coli* in Taiwan showed a high resistance rate (67.7%-90.2%) [7]. These results may be related to the unnecessary usage of antibiotics in clinical practice. Periodic surveillance of antimicrobial resistance in clinical isolates is necessary for the detection of ampicillin-resistant *E. coli*. The appropriateness of using ampicillin and gentamicin as empiric antibiotics to treat neonatal infection needs to be further evaluated. Adjusting the antibiotic regimen according to the susceptibility results is essential.

In summary, this study showed that invasive *E. coli* infections in infancy had a male predominance, especially in patients with urosepsis. Urosepsis and CNS infections are age-related and sepsis is mainly associated with underlying conditions. Differential diagnosis is difficult because of non-specific symptoms and signs of invasive infection and of other mild diseases. Laboratory tests cannot accurately discriminate infants with invasive *E. coli* infections at the time of presentation. The prognosis of *E. coli* infection depends on the complications of CNS. Antimicrobial susceptibilities did not directly contribute to outcome. Susceptibility testing of the isolates of invasive *E. coli* infection in infancy showed a high resistance rate to ampicillin and chloramphenicol, whereas no significant increase in the resistance rate was found compared with different time periods (1988-1993 and 1994-2000).

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