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ORIGINAL ARTICLE

Escherichia coli in septic arthritis: prevalence and antibiotics susceptibility patterns

Masroora Ali Khan[1,2], Muhammad Kamran Taj[1*], Zahid Khan[3], Imran Taj[1], Muhammad Naeem[1], Saima Azam[1]

[1]Department of Microbiology, Center for Advanced Studies in Vaccinology and Biotechnology, University of Balochistan, Quetta, Pakistan
[2]Department of Microbiology, Sardar Bahadur Khan Women's University, Quetta, Pakistan
[3]Department of Orthopaedics Surgery, Sandeman Provincial Hospital, Quetta, Pakistan

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ABSTRACT

Background and Objectives: Septic arthritis (SA) is an orthopedic emergency mainly caused by bacteria. SA due to *Escherichia coli (E. coli)* is rare with a poor prognosis. This study aimed to assess the occurrence and antibiotic resistance patterns of *E. coli* in SA patients in Quetta, Balochistan, Pakistan.

Materials and Methods: A cross-sectional study was conducted from March 2021 to December 2023. 220 samples were collected from SA patients from tertiary care hospitals. Joint aspirates (2ml) and blood (5ml) were analyzed for microbial and hematological examination.

Results: There were 5.45% samples positive, and 94.5% negative for *E. coli*. SA due to *E. coli* was more common in male (6.2%) than female (4.6%) patients with the knee being the most affected joint (6.3%). *E. coli* was more common in patients aged 41-60 years (7.7%), lower socioeconomic (6.9%), and illiterate (8.6%) patients. Suspected patients showed a significant increase in the levels of white blood cells (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), notably, these levels were further elevated in *E. coli*-positive patients. The polymerase chain reaction (PCR) based identification of *E. coli* showed clear bands of 204bp of the 16S rRNA gene. Sequence analysis using the Basic Local Alignment Search Tool found high similarity with pathogenic *E. coli* from Egypt and China. The identified *E. coli* strain showed significant resistance to common antibiotics: amoxicillin, amoxicillin-clavulanate, ceftriaxone, sulfamethoxazole/trimethoprim, gentamicin, tetracycline, and erythromycin.

Conclusion: Antibiotic resistance in *E. coli* from SA patients suggests the need for accurate antibiotic selection to ensure prompt treatment.

Keywords: Antibiotic resistance; *Escherichia coli*; Septic arthritis; Sequence analysis

INTRODUCTION

Septic arthritis (SA) is inflammation of the joints usually caused by bacterial invasion (1). which requires prompt diagnosis, and treatment (2). Patients with fever, acute atraumatic joint pain, and swelling have to be evaluated. The main causes of SA are hip or knee prosthesis, skin infection, recent joint surgery, advanced age, diabetes mellitus, rheumatoid arthritis and use of immunosuppressive drugs. Advanced age, recent joint surgery, knee or hip prosthesis, skin infection, diabetes mellitus, rheumatoid ar-

*Corresponding author: Muhammad Kamran Taj, Ph.D, Department of Microbiology, Center for Advanced Studies in Vaccinology and Biotechnology, University of Balochistan, Quetta, Pakistan. Tel: +923337948111 Email: kamrancasvab@yahoo.com

thritis, and usage of immunosuppressive medications are the main risk factors of SA (3). The most common route of infection is the hematogenous spread of bacterial pathogens to the joints while penetrating inoculation or trauma are potential triggers (4). The most commonly affected sites are major joints, such as knees (affecting almost half of all cases), hips, shoulders, elbow, ankle, and sacroiliac joints (5). The use of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and leukocytosis can be reliable prognostic markers in SA (6).

The reported incidence of SA varies greatly between studies, with the literature suggesting 40 to 60/100,000 cases annually (4). The risk increases with age, the use of immunosuppressive drugs usage and lower socioeconomic status (7). The prevalence of this disease is higher in males than in females (8), Significant epidemiological, and microbiological differences exist in SA infections between developed and developing regions as well as across age groups (9). SA caused by *Escherichia coli (E. coli)* is uncommon but can lead to both polyarticular and monoarticular SA with a poor prognosis when diagnosis and treatment are delayed due to concurrent medical conditions (10). The extra-intestinal sepsis caused by *E. coli* is diverse but often results in more severe illness (11). SA caused by *E. coli* is uncommon because the aerobic Gram-Negative organism typically does not infect the synovium unless there is an underlying predisposing condition (12).

Antibiotic resistance in *E. coli*, like in other bacteria, is promoted by numerous mechanisms these include decreases in intracellular concentration of the antibiotics due to reduced uptake or active efflux, target modification or overexpression, and inactivation or destruction of antibiotic molecules (13). Multidrug-resistant (MDR) strains of *E. coli* are a global concern in industrialized, and developing nations (14).

E. coli-induced SA is very rare. As a result, limited studies have reported the epidemiological status of SA caused by this pathogen. Therefore, the current study aimed to determine the incidence of SA caused by *E. coli*, and its antibiotic resistance pattern in Balochistan.

MATERIALS AND METHODS

Study design, demographics and sample collection. A total of 220 samples were collected from March 1st, 2021 to December 31st, 2023 from patients visiting Sandeman Provincial Hospital (SPH) and Bolan Medical College and Hospital (BMCH) with tertiary medical healthcare facilities located in Quetta, the provincial capital of Balochistan, Pakistan. The study was conducted after approval (CAS/45/15-21) from the Ethical Committee of the University of Balochistan, SPH, and BMCH (CAS/45/15-21) according to the Helsinki Declaration. All ethical considerations were followed accordingly. Before the collection of the sample, oral, and written consent was taken from patients, and their guardians (in case, the patient is under 18 years of age). Demographic data such as gender, age, ethnicity, literacy, socioeconomic status, and history regarding affected joint(s) were collected from all the patients recruited in the study through a pre-designed questionnaire to identify the SA among the patients. Synovial fluid (~01-03 ml), and blood samples (~05 ml) were aseptically collected in sterile tubes by a physician from each patient with the signs and symptoms of warm, and swollen erythematous joint with compromised function, and a history of fever. The samples were transported to the Center for Advanced Studies in Vaccinology, and Biotechnology (CASVAB), University of Balochistan, Quetta, and immediately processed for further examination.

Haematological testing and microbiological identification. The blood samples collected from patients were to determine white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and elevation of C-reactive protein (CRP). Synovial fluid samples were inoculated in nutrient broth, and incubated at 37°C for 24/48 hours. If any bacterial growth was observed in the broth, a loop of inoculum from the broth was further streaked on MacConkey, and eosin methylene blue (EMB) agar for isolation, further identifying *E. coli* through different biochemical tests.

Molecular identification through PCR. Genomic DNA was extracted from bacterial culture using the kit method (Qiagen, USA) per manufacturer's instructions, and stored at -20ºC till further processing. The extracted DNA was amplified through polymerase chain reaction (PCR) according to the method described by Wang et al. (15), for the detection of *E. coli* using species-specific oligonucleotide primers: 5'-GGGAGTAAAGTTAATACCTTTGC-3' (Forward), and 5'-CTCAAGCTTGCCAGTATCAG-3' (Reverse), (Macrogen, South Korea) targeting 16S

rRNA gene. The extracted DNA, and oligonucleotides were mixed with the ready-to-use PCR reaction mix (Gene direX, Inc) to achieve a volume of 25 µl.

The initial denaturation was set for 2 minutes at 95°C during the PCR cycle conditions, 35 cycles of denaturation at 95°C for 30 seconds, annealing at 55°C for 15 seconds, extension at 72°C for 30 seconds, and the final extension at 72°C for 05 minutes. The amplified PCR product was loaded in 02% agarose gel stained with ethidium bromide and electrophoresed at 100 volts for 40 minutes. The separated amplicons were visualised, and documented using a UV (wavelength: 365 nm) transilluminator. The target amplicon size for *E. coli* was estimated using a 100-bp DNA marker as a reference.

Nucleotide sequencing and phylogenetic analysis. The PCR products were purified and the standard sequencing was carried out at a commercial facility (Macrogen, South Korea) using a high-throughput Sanger sequencing platform (ABI Genetic Analyzer 3730XL System). For analysis, the obtained FASTA sequence was subjected to BLAST on the NCBI database for the confirmation of species information, and submitted to the NCBI GenBank (accession ID: OR113046). The subsequent molecular, and phylogenetic analysis were conducted using Clustal-W, and MEGA tools.

Antibiotic susceptibility testing. The disc diffusion method was used to determine the antibiotic susceptibility pattern of each isolate against different antibiotics. The turbidity of each inoculum was matched with 0.5 McFarland standard, and the entire surface of each Mueller Hinton agar (MHA) plate was inoculated so that an even bacterial lawn could be achieved. The antibiotic discs (Oxoid) were dispensed on each plate using an antibiotic disc dispenser, and plates were incubated at 37°C for 16 to 18 hours. After incubation, the diameters of inhibition zones were measured, and documented. The Clinical and Laboratory Standards Institute's (CLSI) guidelines were followed in interpreting the results.

Statistical analysis. The data was entered into a Microsoft Excel sheet and analyzed using SPSS version 20.0. (Inc., Chicago IL, USA). The demographic, and clinical data were analysed by Pearson chi-square test. The median, and interquartile range (IQR) were calculated for continuous variables, and the *p*-value 0.05 was considered significant.

RESULTS

Microbiological and molecular testing. Out of 220 synovial fluid samples collected from SA patients, only 12 samples were found positive for *E. coli* through isolation on MacConkey agar, growth parameters, colony morphology on EMB agar, and through different biochemical tests. These isolates were further identified through PCR. All of the isolates produced *E. coli* species-specific 16S rRNA gene amplicons (204-bps, Fig. 1).

Demographics of patients. Among the 220 SA patients, 5.45% were found positive for *E. coli*, and 94.5% were negative. The percentage was higher in male patients (6.2%) as compared to female patients (4.6%). The proportion of SA induced by *E. coli* was also higher in patients aged between 41-60 years (7.7%) followed by over 60-year-old patients (5.2%), and the lowest in younger patients (<20 years, 2.9%). The joint most frequently affected was the knee (6.3%) followed by the hip (5.9%), sacroiliac joint (3.8%), and shoulder (3.1%). Patients from all ethnic groups including the Pashtoon, Baloch, Hazara, and settlers were observed to have SA caused by *E. coli.* The disease was more common in illiterate patients (8.6%) as compared to literate patients (3.6%), and in the lower socioeconomic class (6.9%) than the upper (3.0%) class (Table 1).

Clinical parameters and septic arthritis. Table 2 shows the clinical parameters of SA patients with, and

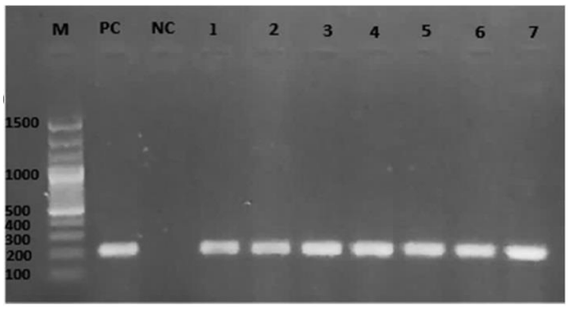

Fig. 1. Agarose gel electrophoresis of PCR products after amplification of the 16S rRNA gene (204bp). LANE M: DNA Marker; PC: Positive Control; NC: Negative Control; Lane 1 to 7 showing the amplicon of 204 bps: positive for *E. coli.*

Table 1. Epidemiological incidence of SA caused by *E. coli* in various population parameters in Balochistan

Demographic characteristics		Suspected SA cases		Total n (%)	*P*-value
		E. coli-positive n (%)	*E. coli*-negative n (%)		
Sex	Male	7 (6.2)	105 (93.8)	112 (50.9)	0.597
	Female	5 (4.6)	103 (95.4)	108 (49.1)	
Age	0-20 years	1 (2.9)	34 (97.1)	35 (15.9)	
	21-40 years	2 (4.1)	47 (95.9)	49 (22.3)	0.705
	41-60 years	6 (7.7)	72 (92.3)	78 (35.4)	
	> 60 years	3 (5.2)	55 (94.8)	58 (26.4)	
Joints affected	Knee	7 (6.3)	104 (93.7)	111 (50.5)	
	Hip	3 (5.9)	48 (94.1)	51 (23.2)	0.887
	Shoulder	1 (3.1)	31 (96.9)	32 (14.5)	
	Sacroiliac joint	1 (3.8)	25 (96.2)	26 (11.8)	
Ethnicity	Pashtoon	6 (7.1)	79 (92.9)	85 (38.6)	
	Baloch	3 (5.0)	57 (95.0)	60 (27.3)	0.858
	Settlers	2 (4.2)	46 (95.8)	48 (21.8)	
	Hazara	1 (3.7)	26 (96.3)	27 (12.3)	
Literacy	Illiterate	7 (8.6)	74 (91.4)	81 (36.8)	0.102
	Literate	5 (3.6)	134 (96.4)	139 (63.2)	
Socioeconomic class	Low	7 (6.9)	94 (93.1)	101 (45.9)	
	Middle	4 (4.7)	82 (95.3)	86 (39.0)	
	High	1 (3.0)	32 (97.0)	33 (15.0)	0.643

Table 2. Relationship of *E. coli* infection in SA patients with WBC count, ESR, and CRP

Clinical parameters (Cut-off values)	Suspected SA cases		*P*-value
	E. coli-positive (n=12)	*E. coli*-negative (n=208)	
WBC count (10^9/L)			
<15	3 (25.0%)	53 (25.5%)	0.970
≥15	9 (75.0%)	155 (74.5%)	
ESR (mm/hr)			
<10	0 (0.0%)	14 (6.7%)	0.353
≥10	12 (100.0%)	194 (93.3%)	
CRP (mg/L)			
<20	1 (8.3%)	26 (12.5%)	0.669
≥20	11 (91.7%)	182 (87.5%)	

WBC: White Blood Cell, ESR: Erythrosine Sedimentation Rate, CRP: C-reactive Protein

without *E. coli* infection. Patients were categorized into two groups based on *E. coli* infection, and the cut-off values of different variables. Patients in the group with a WBC count less than 15 × 10^9/L, ESR less than 10mm/hr, and CRP less than 20mg/L were considered normal, and patients in the group with higher cut-off values were regarded as not normal. The WBC count was elevated in 9 out of 12 *E. coli*-positive SA patients (median=39 × 10^9/L; range=12-65 × 10^9/L, Table 3). Similarly, a higher WBC count was observed in *E. coli*-negative SA patients (155/208, 75.4%). Notably, ESR level was observed to be elevated in all (100%) of *E. coli*-positive SA patients. (median=67.5 mm/hr, range=37-106 mm/hr, Table 3). However, a lower proportion of *E. coli*-negative SA patients were found to have abnormally higher ESR levels as compared to *E. coli*-positive SA patients. The CRP level was elevated in 87.5% of *E. coli*-negative SA patients but this level was further raised (91.7%) in *E. coli*-positive SA patients. The Median CRP level in SA patients infected with *E. coli* was 80.2 with a range of 10.8-201(Table 3). Statistically, no significant differences (p>0.05) were observed in the clinical parameters between *E. coli*-positive, and *E. coli*-negative SA patients (Table 2).

***E. coli* sequencing, and phylogenetic analysis.** The nucleotide sequence revealed 100% identity of our *E. coli* isolates (accession ID: OR113046) with the *E. coli* from Egypt (LC764402), and China (OQ919470)

Table 3. Mean, and interquartile range of clinical parameters in *E. coli*-positive SA patients (n=12)

Clinical parameters	*E. coli*-positive (n=12)
WBC (10^9/L)	
Median (range)	39 (12-65)
IQR	9 (75.0%)
ESR (mm/hr)	
Median (range)	67.5 (37-106)
IQR	45.0-81.5
CRP (mg/L)	
Median (range)	80.2 (10.8-201)
IQR	42-92

(Fig. 2). The constructed phylogenetic tree showed that the tree is divided into two branches.

Antimicrobial susceptibility patterns. The isolates of *E. coli* were tested for antimicrobial susceptibility against 10 antibiotics belonging to different groups, and results were interpreted according to CLSI (Table 4). All 12 isolates were found to be resistant to amoxicillin (100%). For amoxicillin/clavulanate, and ceftriaxone, 11 (92%) isolates showed resistance, and 01 (08%) was found to be susceptible. Out of 12 isolates, 10 (83%) isolates showed resistance, and only 02 (17%) were found to be susceptible to both: the tetracycline, and trimethoprim-sulfamethoxazole. Gentamicin, and erythromycin, showed a similar pattern, 09 (75%) isolates were resistant against both, and only 03 (25%) were found susceptible. The isolates showed a higher degree of susceptibility to fluoroquinolone (ciprofloxacin), with only 04 (33%) isolates showing resistance, and 08 (67%) being susceptible. In the case of chloramphenicol only 03 (25%) out of 12 isolates were resistant, while 09 (75%) were susceptible. However, in the case of Imipenem, none of the isolates showed resistance. All 12 (100%) isolates were found to be susceptible.

DISCUSSION

Our study aimed to find *E. coli*-induced SA, and its antibiotic-resistant pattern. SA is linked to severe morbidity, and mortality, and is a serious medical emergency (16). The findings in this study indicate that the incidence of *E. coli*-related SA is 5.45% in the population of Balochistan. SA caused by *E. coli* has also been reported by Cohen et al. (9), and a case report by Lee and Coleman. (10) described the contributing risk factors.

We observed a higher proportion of SA in males as compared to females which is consistent with a study by Momodu and Savaliya (8). SA is generally more common among older individuals (17), which was also notable in our study where most of the patients were between 41-60, and above 60 years of age. According to our study the knee joint was the most often impacted joint by SA which is in agreement with a similar study conducted by Alhaji et al. (18).

There is sufficient evidence in the literature to support the use of ESR, and CRP as reliable markers in the presumptive diagnosis of SA. ESR and CRP levels were observed to be higher in this study. Elevated levels of these two markers can precisely represent the severity of SA (19). About 75% of the patients had higher levels of WBC count (>15 × 10^9/L) in both *E. coli*-positive and *E. coli*-negative patients which indicates the occurrence of leucocytosis in SA patients regardless of *E. coli* infection. The ESR and CRP levels were elevated in all SA patients, and

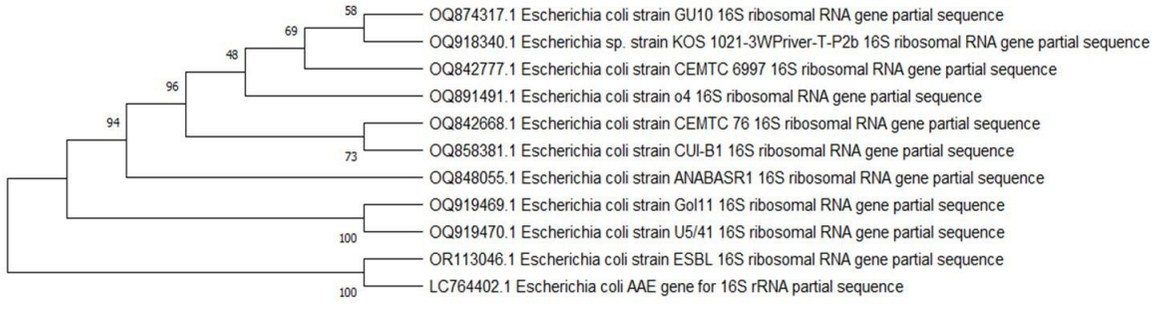

Fig. 2. Neighbour-joining phylogenetic tree showing the relationship between the *E. coli* strain OR113046, and other strains of *E. coli* based on the sequence of 16s RNA gene fragment (204bp).

Table 4. Drug resistance pattern of *E. coli* isolates from suspected SA patients

Antibiotics groups	Antibiotics used	Potency	Sensitive n=12 (%)	Resistance n=12 (%)
Penicillin	Amoxicillin (AML)	10ug	00 (00%)	12 (100%)
B-lactam combination agents	Amoxicillin-Clavulanate (AMC)	20/10 ug	01 (08%)	11 (92%)
Cephalosporin	Ceftriaxone (CRO)	30ug	01 (08%)	11 (92%)
Tetracycline	Tetracycline (TE)	30ug	02 (17%)	10 (83%)
Macrolide	Erythromycin(E)	15ug	03 (25%)	09 (75%)
Aminoglycoside	Gentamicin (CN)	10ug	03 (25%)	09 (75%)
Sulphonamide	Sulfamethoxazole/ Trimethoprim (SXT)	1.25 /23.75	02 (17%)	10 (83%)
Fluoroquinolone	Ciprofloxacin (CIP)	5ug	08 (67%)	04 (33%)
Carbapenem	Imipenem (IMP)	10ug	12 (100%)	00 (00%)
Phenicol	Chloramphenicol(C)	30ug	09 (75%)	03 (25%)

these clinical factors were notably further elevated in SA caused by *E. coli*. An increase in these clinical parameters is likely the most frequent indicator of SA. These findings are similar to a previous study reported by Holzmeister et al. (20).

The PCR is a highly effective diagnostic approach for rapid, and reliable diagnosis of SA (21). We also used PCR in this study for the confirmation of our culture isolates targeting species-specific *E. coli* 16S rRNA gene. PCR was shown to be a highly specific, and rapid method in the diagnosis of SA. In addition, nucleotide sequencing facilitated the identification of *E. coli* strains circulating in the region. The nucleotide sequence revealed 100% identity of our *E. coli* isolates (accession ID: OR113046) from Egypt by El-Sapagh et al. (22), and also to the strain from China by Zhao et al. (23).

The goal of the current study was to determine the resistance profile of clinical isolates from our local area against commonly prescribed antibiotics. Our *E. coli* culture isolates showed a higher level of antibiotic resistance which is consistent with the findings of the previous study reported by Nwafia et al. (24). The result of antibiotic susceptibility testing showed that *E. coli* has developed 100% resistance to Amoxicillin and more than >90% resistance to amoxicillin-clavulanate as well as to ceftriaxone. These findings are similar to a study conducted in Bangladesh by Islam et al. (25). Our study also showed that > 75% of *E. coli* isolates were resistant to erythromycin, tetracycline, sulfamethoxazole trimethoprim, and gentamicin which is also reported by Ramírez-Castillo et al. in Mexico (26).

CONCLUSION

Our study has provided insights that demographics like gender, age, literacy rate, and socioeconomics can be associated with SA. The study also identified that elevated levels of WBC, ESR, and CRP can be used as diagnostics markers for SA which were further increased when in association with *E. coli*, thus indicating the important role of *E. coli* in the disease severity. The diagnosis of SA presents challenges that require careful consideration. It is essential to identify the specific pathogen causing the infection by utilizing proper diagnostic methods such as joint fluid culture, and PCR. Moreover, the study revealed multiple drug-resistant *E. coli* causing SA, which suggests that antibiotic susceptibility testing is necessary to ensure the prescription of effective antibiotic treatment.

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