ISSN- (2584-265X) O

ORIGINAL ARTICLE

Evaluation of prevalence, predisposing factors, inter-species differences in clinical profile and outcome of Campylobacter blood-stream infections: A 7-year experience from north India

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CITATION

c, Krishnamoorthi S, Sreenivasan P, Verma S, Rana S, Pal L, Angrup A, Ray P. Evaluation of prevalence, predisposing factors, inter-species differences in clinical profile and outcome of Campylobacter blood-stream infections: A 7-year experience from north India. Journal of the Epidemiology Foundation of India. 2024;2(3):119-127.

DOI: https://doi.org/10.56450/JEFI.2024.v2i03.008

ARTICLE CYCLE

Received: 21/05/2024; Accepted: 25/08/2024; Published: 30/09/2024

Abstract

Purpose: A comprehensive study evaluating prevalence, risk factors and outcome of Campylobacter bloodstream infection (CBSI) in Indian population is lacking. **Methods**: A retrospective analysis of blood culture specimens positive for Campylobacter species over a 7-year period (September 2013 to August 2020) was conducted. Campylobacter species were identified using MALDI-TOF MS and patients' details were retrieved from hospital records. **Results**: 39 episodes from 38 patients were reported (0.15% of all BSI), with one case of recurrence. The median age was 10 years. 54.5% patients presented with gastrointestinal symptoms. Steroid-dependent nephrotic syndrome predisposed paediatric patients (27.3%) and liver cirrhosis predisposed adult patients (81.8%) to CBSI. **Conclusion**: C. jejuni was the most prevalent species (59%) followed by C. coli (25.6%) and C. fetus (15.4%). C. fetus infection was seen in immunocompetent patients (p=0.01) and was associated with longer hospital stay (p=0.01). Overall outcome of CBSI was good.

Keywords

Blood Culture; Bacteraemia; Infections in Immunosuppressed; Epidemiology; Campylobacter Fetus

Introduction

Campylobacter species are among the leading causes of bacterial enteritis and campylobacteriosis contribute to nearly 42% cases of travel-associated diarrhoea in the developed countries. (1) These gram-negative spiral bacteria reside naturally in the intestinal

tracts of birds and mammals. Eating or handling contaminated/undercooked meat, especially poultry, are major risk factors for acquiring human campylobacteriosis. Numerous cases of Campylobacter infection went unrecognized in the past due to its fastidious nature and lack of proper detection methods. (2)

Campylobacter associated bloodstream infection (CBSI) is a rare extra-intestinal complication. It is reported to occur in <1% of all cases of campylobacteriosis. (3) In a healthy host, the presence of campylobacter inside the bloodstream remains limited to transient bacteraemia that resolves with minimal or no therapy. However, underlying disorders leading to immunosuppression like hypogammaglobulinemia, malignancy, organ transplant, immunodeficiency disorders, and even human immunodeficiency virus (HIV) infection are known to predispose the host to CBSI. (3)(4) While the disease burden of campylobacteriosis is being continuously monitored by Food-Borne Diseases Active Surveillance Network (FoodNet) and European Food Safety Authority (EFSA) across the USA and Europe, respectively, (5) such nation-wide monitoring is lacking in several developing countries including India. Further, the global data on CBSI is limited to a few studies describing either cases of CBSI witnessed over prolonged observation periods or single case reports. (4–14) These studies report wide variations in number of CBSI episodes, ranging from 183 episodes over 4 years in France (11) to only 6 cases over 25 years in Chile. (13) Since wide variations have been observed in the epidemiology of CBSI in these studies, there is a definite need to generate local epidemiological data for better surveillance of CBSI in developing countries. To the best of our knowledge, the available literature reports no study evaluating CBSI among Indian population. Therefore, the present study was designed to determine the prevalence, clinical and microbiological features of Campylobacter BSI in a tertiary care hospital of north India.

Material & Methods

Study design: A retrospective analysis of all those patients whose blood culture specimen was processed in the department of Microbiology, PGIMER Chandigarh and was positive for Campylobacter species during the study period of seven years (September 2013 to August 2020) was performed. The patients were identified from the hospital information system and the medical records of these Campylobacter positive patients were reviewed with a pre-established protocol including demographic and epidemiological conditions, clinical presentation, presence of an underlying disease, duration of hospital stay and outcome. Ethical clearance was waived as the study does not reveal or use personal data of the patients.

Case definition: A case was defined as a patient with one or more blood culture specimen positive for spiral gram-negative organism identified as Campylobacter species by MALDI-TOF MS. Recurrence was defined as a positive blood culture with the presence of the same species of microorganism detected at least one month after the first episode, as described earlier. (15)

Microbiological processing: Blood culture bottles were processed using automated BACTEC™ 9240 system (Becton Dickinson, NJ, USA) and a standard incubation time of 5 days was given before reporting the specimen sterile. Once the blood culture bottle beeped positive for growth of the organism, it was retrieved from the machine and a drop of broth was smeared onto the slide for Gram stain. All those smears that showed presence of seagull-shaped or spiral gram-negative rods were presumptively identified as Campylobacter spp.-Helicobacter spp. Broth from those bottles was then inoculated onto 5% sheep blood agar and incubated for 48 hours at 370C inside candle jars with BD Campy-PAKTM (Becton Dickinson, NJ, USA) to generate microaerophilic environment. A faint greyish translucent growth observed on the blood agar plate was subjected to identification using MALDI-TOF MS Biotyper version 3.1 (Microflex LT, Bruker Daltoniks, GmbH, Germany). In case no growth was obtained on blood agar despite visualization of seagull-shaped gram-negative bacilli on Gram stain, broth from blood culture bottle was directly processed for identification by MALDI-

TOF MS using our laboratory's protocol, as described previously. (16) Antimicrobial susceptibility testing was not done routinely for these isolates.

Statistical analysis: Categorical variables were expressed as percentages and continuous variables as mean ± standard deviation. Since the age of patients had a vast variation, it was expressed as median with interquartile range (IQR). To compare the demographical and clinical differences among the three species of Campylobacter, chi-square test was employed for categorical variables and one-way analysis of variance for continuous variables. A p value of less than 0.05 was considered statistically significant. All analysis was done using Microsoft Excel (Microsoft Corp., WA, USA) and Epitools (Epitools Epidemiological Calculators, Ausvet, Australia).

RESULTS

1. **Demographical characteristics:** 39 episodes from 38 patients of CBSI were reported during the study period of seven years. There was one patient with recurrence of CBSI as two episodes were reported five months apart. The maximum number of cases were reported in the year 2015 (n=9). As the total number of positive blood culture bottles processed during these 7 years was 26,068, the rate of CBSI was 0.15% of all BSI (ranging from 0.05% to 0.25% during different years). The distribution of cases was random throughout the year with no seasonal trend. There were 29 (76%) males and 9 (24%) females, the M: F being 3.2:1. The patients' age ranged from newborn to 95 years old with a median age of 10 years (IQR 3.25-39.5). 57.9% (22/38) were children and 42.1% (16/38) were adults.
2. **Clinical characteristics**: Clinical details could be collected from 33 out of 38 patients [22 children, 11 adults] and data of 5 adult patients could not be retrieved.

a. **Presenting symptoms** - The most common presenting symptom was fever present in 91% (30/33) patients. Gastrointestinal symptoms were present in 54.5% (18/33) patients, with most patients presenting with abdominal distention 24.2% (8/33), diarrhoea 24.2% (8/33), vomiting 6% (2/33) and abdominal pain 6% (2/33). 54.5% (18/33) had ascites, 51.2% (17/33) had icterus and 33.3% (11/33) had deranged liver enzymes suggesting hepatic dysfunction. Overall, only 4 patients (12.1%) had neither gastrointestinal symptoms nor signs of hepatic dysfunction.

b. **Predisposing conditions** – Overall, liver disease, nephrotic disease, solid organ malignancies and haematological malignancies were present in 9/33 (27.2%), 6/33 (18.2%), 3/33 (9.1%) and 2/33 (6.1%) patients, respectively. Among the 22 paediatric patients, 100% had some form of immunosuppression. 6/22 (27.3%) patients had steroid-dependent nephrotic syndrome (SDNS), 4/22 (18.2%) had severe protein-energy malnutrition and 4/22 (18.2%) were born with congenital malformations causing failure to thrive. Two children had haematological malignancies, one Thalassemia intermedia trait and one had Ewing's sarcoma with metastasis. There were two (9.1%) cases of primary immunodeficiencies namely X-linked agammaglobulinemia and Hirschsprung disease. One neonate had complicated delivery with preterm birth, birth asphyxia with early-onset neonatal sepsis. The patient with recurrence of CBSI also had early onset neonatal sepsis and failure to thrive. Among the adult patients, 9/11 (81.8%) had chronic liver disease (CLD) [decompensated cirrhosis (n=6), severe alcohol hepatitis (n=2) and primary biliary atresia with febrile neutropenia (n=1)]. The remaining two patients were undergoing chemotherapy for carcinomas of head of pancreas and gall bladder.

c. **Clinical management and outcome** – This data was available for all 38 patients of CBSI. 30/38 patients [19 children and 11 adults] were admitted in the general wards of the hospital requiring non-intensive care management. Among those children, 17/19 were discharged after successful treatment and two left against medical advice. Among those 11 adult patients,

seven were discharged after recovery, three left against medical advice and one died [record not available]. 6/38 patients [2 children, 4 adults] were admitted in the intensive care units; while all four adults and one child were discharged after successful management, one child with severe malnutrition developed septic shock and succumbed to multiorgan failure. 2/38 patients [1 child, 1 adult] visited the hospital only on out-patient basis. The adult was lost to follow up while the child died the same day. This child was a known case of Thalassemia intermedia, had undergone splenectomy in the preceding year and presented to us in altered sensorium and septic shock. Overall, 76.3% (29/38) patients were discharged, 13.2% (5/38) left against medical advice, 7.9% (3/38) died and 2.6% (1/38) were lost to follow-up. The average length of hospital stay was 9 days, ranging from 1 to 32 days.

3. Microbiological characteristics:

a. Species distribution: Out of the 39 episodes of CBSI, C. jejuni was the most prevalent species found in 23/39 (59%) episodes. C. coli was identified in 10/39 (25.6%) episodes and C. fetus in 6/39 (15.4%) episodes. C. jejuni, C. coli and C. fetus constituted 50%, 36.4% and 13.6% episodes, respectively among paediatric patients and 75%, 12.5% and 12.5% episodes, respectively among adult patients.

b. Inter-species differences: Table 1 compares the differences in clinic-demographical variables among the patients growing three different species of Campylobacter. While the mean age of the patients infected with different species was comparable, male preponderance was significant among patients infected with C. jejuni and C. coli (p=0.01). Among the predisposing factors, the use of steroid or immunosuppressive therapy was significantly associated with CBSI due to C. jejuni and C. coli while C. fetus occurred even among patients not taking any such therapy (p=0.01). Neonatal complications were more associated with C. jejuni and C. fetus than C. coli (p=0.04). Other pre-disposing conditions like liver disease, malignancy and malnutrition were comparable among the three species. Clinical signs of fever and jaundice were similar among the three species while gastrointestinal symptoms were least in C. fetus, though not significantly. The patients with C. fetus CBSI had significantly longer length of hospital stay than the other two species (17 vs 9; p=0.01). There was no significant difference in mortality among the three species.

Table 1. Comparison of clinical characteristics of bacteraemia by C. jejuni, C. coli and C. fetus among 39 episodes of Campylobacter bloodstream infections.

	Variable	C. jejuni (n=23)	C. coli (n=10)	C. fetus (n=6)	Total (n=39)	P value
1.	Mean age, yrs (range)	28.7 (0-95)	12 (0-46)	19.5 (0-62)	23 (0-95)	0.23
2.	Male n (%)	18 (78.3%)	9 (90%)	3 (50%)	30 (77%)	0.01
3.	Liver disease	6 (26%)	2 (10%)	1 (16.7%)	9 (23%)	0.55
4.	Immunosuppressant/ steroid use	4 (17.4%)	6 (60%)	0	10 (25.6%)	0.01
5.	Malignancy	3 (13%)	2 (20%)	1 (16.7%)	6 (15.4%)	0.87
6.	Neonatal complication	4 (17.4%)	0	3 (50%)	7 (17.9%)	0.04
7.	Severe malnutrition	3 (13%)	0	1 (16.7%)	4 (10.2%)	0.44
8.	Fever	19 (82.6%)	9 (90%)	5 (83.3%)	33 (84.6%)	0.86
9.	Jaundice	10 (43.4%)	4 (40%)	3 (50%)	17 (43.6%)	0.92
10.	Diarrhoea	5 (21.7%)	5 (50%)	0	10 (25.6%)	0.06
11.	Abdominal pain	2 (8.7%)	1 (10%)	0	3 (7.7%)	0.73
12.	Ascites	9 (39.1%)	7 (70%)	2 (33.3%)	18 (46.1%)	0.20
13.	Days of stay (n, range)	9 (0-26)	6 (0-11)	17 (7-32)	9 (0-32)	0.01
14.	Mortality	2 (8.7%)	1 (10%)	0	3 (7.7%)	0.73

DISCUSSION

In the present study, the overall incidence of CBSI over seven years was 0.15% of all BSI, lower than the reported incidence of 0.21% from London (10) and 0.24% from Madrid(7). The relatively lower incidence in the current study could be attributed to larger vegan population in north India than the European countries. The cases of CBSI were randomly distributed throughout the year in our study without any seasonal trend. Most previous studies have also reported similar observation, except two reports wherein rise in CBSI was noted in summer season in Finland (6) and Japan (17), coinciding with travel outside the country.

Table 2 summarizes the clinical characteristics of the published case series on CBSI from across the world. A male preponderance (3.2:1) was observed among cases of CBSI in the present study. This was in tune with previous studies where M:F ratio ranged from 1.3(6) to 3.5(7). The median age of patients with CBSI was 10 years in the present study ranging from 0 to 95 years. Previous studies have reported a higher median age of 31 years in Japan (12) and 64 years in France. (11) This difference in the age-group affection of CBSI between India and rest of the world possibly points towards the protection offered to the Indian adult population by their predominant vegan diet. Multiple risk factors like immature immune systems, hand-to-mouth behaviour, environmental contamination and cross-contamination in the kitchen could increase the vulnerability of Indian paediatric population, as noted earlier among Israeli children. (18) The observation that all our paediatric patients had some form of immunosuppression while only 19.2% adults were immunosuppressed, could have further contributed to such skewing of age. Previous studies with higher median age for CBSI have also reported some form of immunosuppression ranging from 50% (7) to 80% (11) among their adult patients.

Table 2. Summary of clinical characteristics of patients with Campylobacter bloodstream infection reported as case series from across the world and a comparison with the current study.

Author Year	Fica 2011 (14)	Feodoroff 2011 (7)	Fernandez 2010 (8)	Hussein 2016 (5)	Liao 2012 (10)	Nielsen 2010 (6)	O'Hara 2017 (11)	Pacanowski 2008 (12)	Tasaka 2016 (13)	Current study
Country	Chile	Finland	Spain	Israel	Taiwan	Denmark	London	France	Japan	India
Study duration (Study period)	24 years (1986-2010)	10 years (1998-2007)	23 years (1985-2007)	16 years (2000-2015)	10 years (1998-2008)	10 years (1995-2004)	44 years (1970-2013)	23 hospitals 5 years (2000-2004)	16 years (2000-2015)	7 years (2013-2020)
n	7	76	71 episodes in 63 patients	65	24	46	41	183 episodes in 178 patients	9	39 episodes in 38 patients; 33*
Incidence of CBSI	NM	0.3% of all Campylobacter infections	0.24% of all BSI	0.08/1000 admissions/yr	0.39-0.42/10,000 admissions	2.9/milli me person-years	0.21% of all BSI	NM	0.15% of patients with GE	#0.15% of all BSI
M:F (M/F)	4:3 (1.3)	56:20 (2.8)	52:30 (1.7)	36:29 (1.2)	16:8 (2)	NM	27:14 (1.9)	124:54 (2.3)	7:2 (3.5)	#29:9 (3.2)
Mean age	32.4	46	52	42	45	56	42	64	31	#10

Author Year	**Fica 2011 (14)**	**Feodoroff 2011 (7)**	**Fernandez 2010 (8)**	**Hussein 2016 (5)**	**Liao 2012 (10)**	**Nielsen 2010 (6)**	**O'Hara 2017 (11)**	**Pacanowski 2008 (12)**	**Tasaka 2016 (13)**	**Current study**
(range)	(19-63)	(1-95)	(31-72)	(0-91)	(7-83)	(0-94)	(30-63)	(6-97)	(2-64)	(0-95)
GI symptoms	4 (57.1%)	60 (78.9%)	23 (32.3%)	41 (63%)	NM	27 (59%)	16 (44%)	59 (33%)	3 (33%)	18 (54.5%)
Hepatic disease	1 (14.2%)	3 (3.9%)	21 (32.8%)	9 (13.8%)	9 (37.5%)	NM	3 (8%)	69 (39%)	4 (44%)	9 (27.2%)
Nephrotic/ kidney disease	0	NM	2 (3%)	7 (10.8%)	10 (42%)	NM	NM	NM	NM	6 (18.2%)
Cardiac disease	2 (28.5%)	NM	3 (4.7%)	9 (13.8%)	2 (13%)	11 (24%)	NM	NM	NM	NE
Haematological malignancy	1 (14.2%)	0	4 (6.3%)	28 (43%)	NM	NM	NM	21 (12%)	1 (11%)	2 (6.1%)
Solid organ CA	1 (14.2%)	5 (6.5%)	3 (4.7%)	NM	8 (33%)	7 (15%)	3 (8%)	46 (26%)	1 (11%)	3 (9.1%)
Immunocompromised	3 (42.8%)	NM	33 (51.6%)	36 (55.4%)	NM	NM	NM	141 (79%)	NM	24 (72.7)
No underlying disease	NM	53 (70%)	4 (5.8%)	10 (15%)	5 (21%)	NM	20 (50%)	NM	NM	0
Species distribution	C. fetus - 5(71.4); C.jejuni- 2(28.5%)	C. jejuni- 73(96%); C. coli - 3(3.9%)	C jejuni - 42(66%); C fetus- 13(19%); and C coli- 8(12%)	C. jejuni- 33(50.7%); C. coli - 7(10.7%); C. fetus -5(7.6%); C. upsaliensis - 1(1.5%); C. hyointestinalis- 1(1.5%). Campylobacter species 18 (28%)	C. coli -15 (62.5%) ; C. fetus - 6 (25%); C. jejuni - 3 (12.5%)	C. jejuni -37 (80.43); C. coli- 5(10.8%); C. fetus - 3(6.5%), C. lari- 1(2.1%)	C. jejuni- 20(48.8%); C. fetus -2(4.9%); C. coli -3(7.3%); C. hyointestinalis- 1(2.4%); C. upsaliensis -1 (2.4%); C. ureolyticus - 1(2.4%); no speciation- 13(31.7%)	C. fetus- 94(53%); C. jejuni- 54(30.3%); C. coli- 16(8.9%); C. lari- 2(1.1%)	C. jejuni - 8(88.8%); C. coli- 1(11.1)	#C. jejuni 23/39 (59%); C. coli 10/39 (25.6%); C. fetus 6/39 (15.4%)
Mean LOS (d)	NM	4	NM	7	NM	8	NM	NM	3	9#

Author Year	Fica 2011 (14)	Feodoroff 2011 (7)	Fernandez 2010 (8)	Hussein 2016 (5)	Liao 2012 (10)	Nielsen 2010 (6)	O'Hara 2017 (11)	Pacanowski 2008 (12)	Tasaka 2016 (13)	Current study
30-day mortality	2 (28.5 %)	2 (2.6%)	10 (16%)	3 (4.6%)	4 (17%)	2 (4.3%)	2 (4.8%)	27 (15.2%)	0	3# (7.8 %)
Resistance to FQ	NM	6.5%	50%	65%	60%	26%	50%	32%	NM	NE
Recurrence, rate	NM	NM	4 (5%)	NM	NM	0	NM	5 (2.8%)	NM	1 (3%)

*GI, gastrointestinal; CA, carcinoma; BSI, bloodstream infection; LOS, length of stay; NM, not mentioned; NE, not evaluated; FQ, fluoroquinolones; *Clinical details (symptoms and predisposing factors) available for 33 patients out of 38; #Evaluated using 39 as denominator.*

The most common predisposing conditions for CBSI were SDNS in children and CLD in adults, constituting 18.2% and 27.2% of the total patients, respectively. The literature also reports a similar contribution by SDNS (ranging from 3% in Spain (7) to 41% in Taiwan (9)), and CLD (ranging from 4% in Finland (6) to 40% in France (11) and Japan (12)). Severe protein-energy malnutrition and congenital malformations causing failure to thrive were identified as novel risk factors for CBSI among our paediatric patients. 6.1% children had haematological malignancy as predisposing condition in the present study. While Spain reported haematological malignancy at a similar rate (6.3%) (7), Israel observed presence of haematological malignancy in 43% of their CBSI patients (3).

One of the 33 patients (3%) had recurrence of CBSI in the current study. Previous researchers have also reported recurrence of CBSI ranging from 2%(7) to 6%(11) patients. Recurrence of CBSI had probed investigation for X-linked hypogammaglobulinemia in an 18-year old Korean boy, (19) however, in the current study, recurrence was observed in a patient with early-onset neonatal sepsis who left against medical advice before a detailed work-up for any defect in humoral immunity could be carried out. In contrast to Fernandez et al (7) wherein all episodes of recurrent CBSI were caused by C. jejuni, the infection in our patient was due to C. fetus.

C. jejuni (59%) was the predominant species isolated from patients of CBSI in the present study, followed by C. coli (25.4%) and C. fetus (15.6%). C. jejuni has been the most frequently reported species in most studies on CBSI with isolation ranging from 48% (10) to 96%(6), except two studies wherein C. fetus was most commonly isolated (53%(11) and 71%(13)) and one study where C. coli was the predominant species at 62.5%(9). Unlike the findings of Liao et al (9) wherein no clinical characteristics were comparable among the three species of Campylobacter, significant differences were observed in the current study. For instance, infection with C. fetus significantly occurred in non-immunocompromised and relatively healthy patients. This was in accordance with Kirk et al (20) who reported that unlike other species of Campylobacter that get rapidly cleared off the circulation owing to their inherent susceptibility to human serum, C. fetus is more resistant and can cause sustained bacteraemia even in a healthy host. Episodes of C. fetus CBSI, unlike other species, were not associated with gastrointestinal symptoms in the present study. This was concordant with Bel-Shimol et al(15) who documented that C. fetus is rarely reported as a cause of intestinal infection and is known to have a high predilection for human vascular endothelium. A complicated neonatal period, (in the form of congenital malformation, preterm birth and early-onset neonatal sepsis), was identified as a significant risk factor for C. fetus CBSI in the present study. Patients with C. fetus CBSI also had significantly longer duration of hospital stay than other two species, possibly due to more vulnerable neonatal population. These findings could be verified in future studies involving larger number of neonates with CBSI.

CBSI is amenable to treatment using fluoroquinolones, macrolides, aminoglycosides, chloramphenicol, tetracyclines and azithromycin.(21) Recently, fluoroquinolone resistance rates of 6%(6) to 70%(3) have paved way for amoxicillin/clavulanate and carbapenems.(15) In the current study, the patients responded well to treatment with aminoglycosides, ciprofloxacin, third generation cephalosporins like ceftriaxone and carbapenems as their subsequent blood cultures were sterile after three days of antibiotics.

The 30-day mortality in the current study was 7.9% (3/38), however the mortality attributable to CBSI was nil as the two deceased patients had several other co-morbid factors to which they succumbed within two days of hospital stay and the clinical details of the third patient were not known. Literature reports a 30-day attributable mortality ranging from 2%(3) to 17% (11). A single study reported higher mortality when patients of C. fetus CBSI were treated with fluoroquinolones and those with C. jejuni/ C. coli were treated with third-generation cephalosporins. (11) However, such treatment did not alter the course of the outcome in other studies. (22)(6) No such association was found in the present study.

An important limitation of the study is that antibiotic susceptibility data was not generated. This was due to the fact that during 2013-2016, there were no guidelines on how ABST should be performed for a fastidious organism like Campylobacter (21)(23) and different authors used non-uniform methods like agar dilution using Enterobacteriaceae criteria (9), disk diffusion using national society's criteria (11) or no mention of methodology (3). In 2016, the Clinical Laboratory Standards Institute CLSI M45 3rd edition (24) recommended using cation-adjusted Mueller Hinton agar with 5% lysed horse blood for disk diffusion wherein plates were to be incubated at 420C for 24 hours. Since, CBSI contributed merely 0.15% of all positive BSI at our centre, it wasn't practical to set up a special ABST process for a handful of isolates, that too when they are known to cause self-limiting infection. Another limitation was that cases of CBSI visiting the hospital only on an out-patient basis could not be included.

Conclusion

To conclude, constituting 0.15% of all BSI among north Indian patients, CBSI mainly occurred in paediatric patients having some form of immunosuppression and adult patients with chronic liver disease. Unlike rest of the world, CBSI in north India was found more among paediatric population, and severe malnutrition and congenital malformations were identified as novel risk factors. While C. jejuni was the most frequently isolated species, it was C. fetus that not only infected immunocompetent patients but also caused longer hospital stay. The overall outcome of CBSI was good.

Authors Contribution

All authors have contributed equally.

Financial Support and Sponsorship

Nil

Conflict of Interest

There are no conflicts of interest.

Declaration Of Generative AI And AI Assisted Technologies In The Writing Process

The authors haven't used any generative AI/AI assisted technologies in the writing process

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