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Antibiotic Resistance patterns of *Campylobacter jejuni* isolated from diarrheal patients in Gaza strip

Abdel Moati Kh. Al Jarousha

Faculty of Applied Medical Sciences
Al-Azhar University-Gaza, Palestine

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Abstract:

A case control study was conducted to determine the epidemiology risk factors and antimicrobial resistance of Campylobacter jejuni strains isolated from stools of children up to the age of 12 years admitted in pediatric Gaza strip hospitals. Stool samples were cultured in a Campylobacter blood-free medium that was incubated for 48h at 42 ˚C under microaerophilic conditions. The suspected Campylobacter jejuni isolates were tested for catalase ,oxidase production, urease enzyme, nitrate reduction, H_2S production, and API 20 E system. Sensitivity testing was carried out using the Modified Kirby Bauer disc diffusion technique. Thirty stool samples were positive for campylobacter jejuni (5%). 14 (47%) cases were male, 87% of stool samples consistency were watery and 13% mucoisymptoms recorded were abdominal pain (73%), fever (60%), 60% vomiting and 13% dehydration. The age group of 4-6 years in both female and male was affected with 44% and 36% respectively. Antibiotics resistance rate for Trimethoprim /sulphamethoxazole 93%, Cephalothin 86%, Tetracycline 86%, Ampicillin 50%, Erythromycin 27%, Ciprofloxacin 27%, Gentamicin 27%, Amikacin 17%, Azithromycin 15%, Ceftriaxone 13% and Meropenem 0%. The risk factors associated with developing C. jejuni infection was malnutrition (anemia) P-value 0.006, odds ratio 3.2, and low mother education P-value 0.002 odds ratio 3.6 ,

In conclusion:The study showed a significant number of C. jejuni isolated strains from children .The susceptibility pattern reflects variable susceptibility with high resistance to Trimethoprim/sulphamethoxazole, Teracycline and Cephalothin and low resistance to Meropenem, Azithromycin and Ceftriaxon. Risk factors should be applied in the control of this pathogen

Key words: Campylobacter jejuni, Antibiotic resistance, Risk factor, Diarrhea

Introduction:

The pathogenic strains of *C. jejuni* is considered one of the most frequent causes of diarrhea both in adults and in children in developed and developing areas [1]. The genus Campylobacter belong to a family called *Campylobacteraceae* and has 18 species but only two are considered importance for human health *C. jejuni* and *C. coli* [2].The prevalence of *C.jejuni* is high in different parts of the world and some estimate account for 400 million cases of *Campylobacter* associated diarrhea occur worldwide per year [3].There are various sources for acquiring *C.jejuni* mostly through the consumption of contaminated food and liquids [4-6] .The clinical signs and symptoms of *C.jejuni* infections range from mild, self limiting illness relapsing febrile diarrheal illness .The severity of illness has been shown to vary by age, residency region and immune status[1,7]The majority of *C.jejuni* infections are sporadic cases and few investigations were conducted to show up the risk factors for sporadic *Campylobacter* infections in human these studies differed in location, technique, and sample size, ultimately these indicated several dominant sources of infection, including contact with and consumption of poultry, transmission from pets and other animals, consumption of raw milk, and contaminated drinking water [8,9].Other sources recorded include digs cats ,environmental sources[10].Some of these case control studies showed that the handling or eating of raw or undercooked chicken represent high risk [11].The antibiotic susceptibility patterns among different strains of *C. jejuni* varied in different parts of the world ,but generally there are increasing rate of antimicrobial resistance, the strains of Antibiotic-resistant *C.jejuni* are more 'virulent' than antibiotic-susceptible isolates, in which there is the possibility of adverse clinical outcomes associated with inappropriate empiric therapy [12,13].The empirical treatment of the Campylobacteriosis can be by using (Fluoroquinolone ,Tetracycline and Erythromycin) in which can be used the invasive cases and to shorten for the duration of symptoms if given early in the illness [14]. In many cases of clinical isolates of *C. jejuni* it was reported to be resistant to Ciprofloxacin and Azithromycin [15]. Also increased resistance to other clinically important drugs used for campylobacter treatment (especially Macrolides and Fluoroquinolones) is increasingly reported .There is evidence that patients infected with antibiotic-resistant strains suffer worse outcomes (invasive illness or

death) than those infected with sensitive strains [16].Antibiotic susceptibility studies are necessary because variation occurs among different countries. Studies in Europe have shown *C. jejuni* to be sensitive *in-vitro* to antibiotics such as Tetracycline, Erythromycin, Gentamicin while many strains are resistant to Ampicillin, Penicillin and Metronidazole [17].

The objectives of the study were to better describe the burden of illness, to identify specific risk factors associated with sporadic *C. jejuni* infection in the Gaza strip and showing the antimicrobial susceptibility patterns of that pathogen

Materials and Methods

Clinical setting

The study population comprised children younger than 12 years who were admitted to the pediatric departments of Al Dorra Hospital (100 beds), Al Nasser Hospital (250 beds) and Shohada Al Aqsa Hospital (80 beds) or who presented to the outpatient clinics of these hospitals, seeking treatment for a gastroenteritis infection.

Case selection

A matched case–control study was performed by comparing each case *of C. jejuni* to uninfected controls. The selection of cases was carried out according to symptoms and signs of gastroenteritis. Suspected gastroenteritis was defined as a case of acute diarrhea (three or more stools a day) [18]. Outpatients were first examined by a physician and those requiring further care were admitted to the hospital wards. A physician performed physical examination and assessed the patient's level of dehydration according to clinical signs and symptoms.

Case definition

The Campylobacteriosis cases were those with acute diarrhea (three or more stools a day), from which *C. jejuni* isolates were identified by laboratory techniques.

Control

One hundred non-diarrheal cases were selected from the same age group; these children had a diagnosis other than gastroenteritis, such as chest infection, skin, or orthopedic problems, or were present at the clinic for vaccination. These controls were non-diarrheal controls with negative *C. jejuni* or other enteropathogens. Furthermore, for each diarrheal and control case, a complete blood count was done in the hematology laboratories; a low hemoglobin level (anemia) was considered as an indicator of malnutrition status. The non diarrheal

cases were considered as a control cases in the statistical analysis in order to investigate the specific risk factors dealing g with developing infection with *C. jejuni*

Demographic characteristics

Demographic data were subsequently collected through a structured questionnaire: the parents or guardians of the cases were questioned post explaining the objectives about house crowdedness (crowdedness index, per room), maternal education, family income, and other relevant information including disposal of sewage and water supply residency in rural or urban area and consumption of poultry and turkey meats. The poverty rate is based on a monthly household income of low, moderate and high according to the local standards of life. For maternal education level, low level of education was defined as primary or preparatory school and high level of education was defined as secondary school or university.

Isolation the pathogens

Stools were processed and analyzed for enteric bacteria on the day of sample collection. Standard culture and identification methods were used to identify *C. jejuni* [19,20]. Samples were collected in clean sterile polypropylene containers with screw caps. Briefly, each fecal transport swab was plated on a blood free charcoal based selectivemedia (CCDA) (BioMerieux, Paris, France) andBlood contained media selective for Campylobacter

(BioMerieux, Paris, France) and incubated for 48h at 42°C in a microaerophilic environment. The suspected colonies of *Campylobacter* were further evaluated by Gram's stain, oxidase and catalase activity to differentiate the *Campylobacter* isolates into *C. jejuni* and *C. coli* in addition to use API 20E system[21,22.23]Final identification of *C. jejuni* species by using specific antisera. (Denka Japan)

Antimicrobial susceptibility testing

The antibiotic susceptibilities of isolates were determined by the disk diffusion method on Mueller–Hinton agar plates (HIMedia laboratories Pvt. Limited, Mumbai,India). using calibrated inoculums of the isolates based on McFarland standard with the following Disc susceptibility tests (BioMerieux, Paris, France antibiotics) Ampicillin, Chloramphenicol, Tetracycline Cephalothin,Trimethoprim /sulphamethoxazole, Nalidixic acid, Erythromycin, Azithromycin,

Ceftriaxone, Gentamicin, Amikacin, Tetracycline, Ceftriaxone, Ciprofloxacin and Meropenem.)

Questionnaire.

Structured questionnaire was used to collect data for demographic, clinical symptoms, previous history of diarrhea, socioeconomic status of the diarrheal cases and control groups. The questionnaire was revised by experts in pediatrics, epidemiologists and public health specialist.

Statistical analysis

Statistical analysis was carried out using SPSS version 15 for determination of different proportions. Odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated to assess the magnitude of association between correlates. Variables found to be significant by univariate analysis at p-values of < 0.1 and Odds ratio >1.0.

Ethical considerations

The study was conducted in according with the rules and regulations of the Helsinki Committee and the Palestinian Ministry of Health. In compliance with the Helsinki declaration, a consent form for study participation was signed by parents of the children following an explanation of the objectives of the study.

Results

Geographical distribution of *Campylobacter* cases

Table 1 illustrates that the distribution of *C. jejuni* in different parts of Gaza strip that 40% of cases belonged to Gaza city, 33% were from north area, 17% were from southern area and 10% were from Mid zone of Gaza strip.

Table 1 Distribution of Campylobacter cases by residency

Resident Area	No of Cases N=30	percentage
North Gaza Strip	10	33
Gaza town	12	40
MID Zone Gaza Strip	3	10
South Gaza Strip	5	17

Distribution of *Campylobacter jejuni* cases by age and gender

Table 2 illustrates the distribution of *Campylobacter jejuni* cases by age and gender. Thirty (14 M and 16 F) *C. jejuni* (5%) were successfully isolated during the study period. The mean age of *C. jejuni* cases was 4.2 years while for the control cases was 4.8 years. The age distribution of the *C. jejuni* cases were 10 patients (33%) belonged to 1-3 years, 12 (40%) 4-6 years, 6 (20%) 7-9 years and 2 (6%) older than 9 years. No cases recorded in the age group of less than one year; the ratio of males to females was 0.87 of all specimens investigated.

Table 2: Distribution of *Campylobacter jejuni* cases by age and gender

Age	Male N=14		Female N=16	
	N	%	N	%
< 1.0 year	0	0	0	0
1-3 years	4	28	6	37
4-6 years	5	36	7	44
7-9 years	3	21	3	19
10-12 years	2	15	0	0

Antimicrobial Susceptibility Results

Table 3 illustrates the antibiotic susceptibility and resistance pattern of 30 *C. jejuni* isolated from different hospitals against fourteen chosen antimicrobial agents. Resistance rate was high with Trimethoprim /Sulfamethoxazole 93%, Cephalothin and tetracycline 86%, Ampicillin 80%, Nalidixic acid 50%, Ciprofloxacin– Gentamicin and Erythromycin 27%, Amikacin 17% , Azithromycin 15% ,Ceftriaxone 13% , and no strains was resistant was for meropenem .The overall resistance rates to cephalosporins (Cephalothin, Ceftriaxone) was (13-86%) while the resistance rate for Aminoglycosides (Gentamicin and Amikacin) was (20-27%) and the overall resistant rates Quinolones (Nalidixic and Ciprofloxacin) was (27-50%).

Table 3: The Antibiotic Susceptibility and Resistance patterns for the isolated strains of *Campylobacter jejuni*

Antibiotics	Number of Susceptible strains N=30	Percentage of susceptibility	Percentage of Resistant
Meropenem	30	100	0
Ceftriaxone	26	87	13
Azithromycin	25	85	15
Amikacin	24	83	17
Erythromycin	22	73	27
Gentamicin	22	73	27
Ciprofloxacin	22	73	27
Nalidixic acid	15	50	50
Ampicillin	6	20	80
Tetracycline	4	14	86
Cephalothin	4	14	86
Trimethoprim /Sulfamethoxazole	2	7	93

Risk factors of acquiring *C. jejuni* infection:

Table 4 illustrates the risk factors of acquiring *C. jejuni* infection included Malnutrition. 63% of the patients were anemic with P-value 0.006 Odds ratio of 3.21. Another significant risk factor was the level of mother education (Primary school) P-value 0.002 and odds ratio 3.6.

Table 4: Possible risk factors of acquiring *Campylobacter jejuni* infection

Parameters	Diarrhea (N=30)		Control (N=100)		P - value	OR	95% CI
	N	%	N	%			
Gender							
Male	14	47	53	53			
Female	16	53	47	47	0.974	1.93	0.447-2.296
Age group							
<1.0	0	0	12	12			
1-3	10	33	30	30			
4-6	12	40	25	25	0.110	2.0	0.847-4.723
7-9	6	20	18	18			
10-12	2	7	15	15			
Malnutrition							
Anemia	19	63	35	35	0.006	3.208	1.373-7.495
Normal	11	37	65	65			
Family income							
Low	16	53	48	48	0.608	1.238	0.547-2.804
Moderate /High	14	47	52	52			
Mother Education							
Primary	16	53	24	24	0.002	3.619	1.544-8.480
Secondary	9	30	46	46			
University	5	17	30	30			
Residency							
Rural	12	42	49	49			
Urban	18	58	51	51	0.386	1.441	0.629-3.302
Consumption of poultry / Turkey							
Yes	5	16	9	9	0.235	2.022	0.622-6.577
No	0	0					

OR= Odds ratio; CI= Confidence interval

Clinical Signs and Symptoms

Figure 1 illustrates the clinical signs and symptoms accompanied the infection with *C. jejuni*. About 73% of the patients complained of abdominal cramps, 60% were complained of vomiting and fever, 13% of the cases were complained of dehydration.

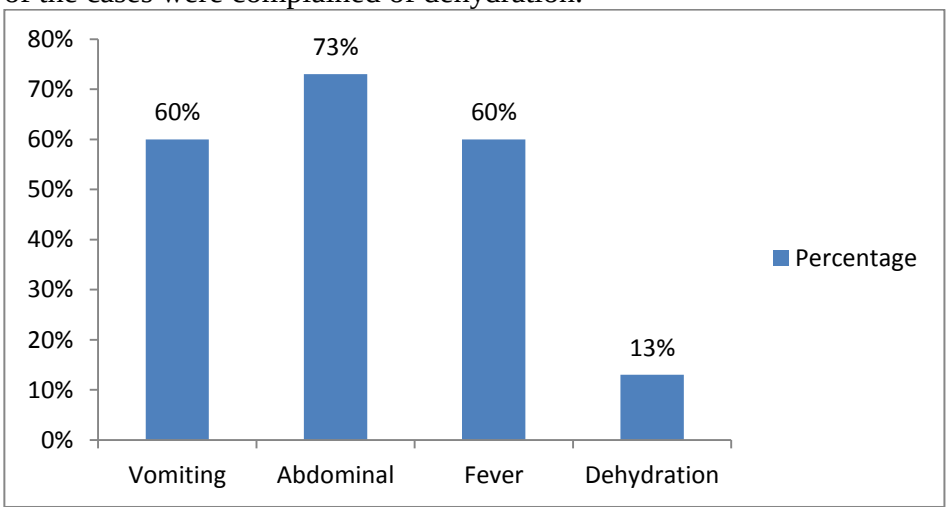

Fig 1: The clinical symptoms associated with *Campylobacter jejuni* infection

Consistency of stool

Figure 2 shows that 87% of diarrheal cases infected with *C. jejuni* had a watery consistency while 13% were mucoid.

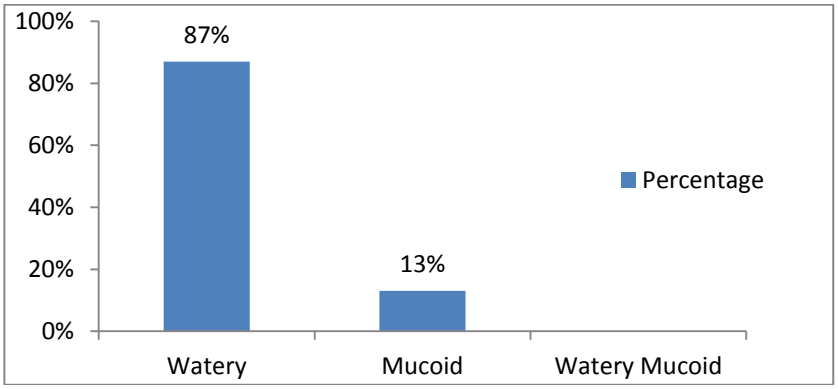

Fig 2: Consistency and physical characteristics of the stool of *Campylobacter jejuni* isolates.

Discussion

The current study collected epidemiological data from cases of campylobacter in Gaza strip over one year, in order to determine epidemiology, risk factors and antimicrobial resistance in *C. jejuni* strains isolated from the stools of children admitted with diarrhea/dysentery in pediatric hospitals. Among the diarrheal cases examined thirty cases of *C. jejuni* were identified (5%). As far as we know that there are no previous data describing the prevalence of *C. jejuni* infection in Gaza strip in hospitalized children with diarrhea.

Similar results were recorded in Croatia (4.2%) [24], India 4.5% [25and Taiwan 6.8% [26].Other results obtained from other parts of the world showed higher than our recorded results like in Argentina infection rate among patients was 15% [27], Malawi 21% [28,9% in Uganda[29] and Campylobacter infection occurred in 22% of all bacterial gastrointestinal diseases in the city of Sofia during the study period [30]. This variation in infection rate across different countries may reflect the technical difficulties of isolation of *Campylobacter* species in poor resource settings because of its fastidious growth requirements and/or the relative insensitivity of some culture techniques.

The age distribution of cases in this study was variable. The highest rate of infection was reported in the age group of 1-6 years with proportion of 73%. The highest rate of infection was found in group of 4-6 years old and this may be due this age group start to be outdoor of houses especillay in thr kindergarten or in the streat play and contaminate hands .The rate of infection in males of this age group was less than in females and in the 4-6 year-old age group, the proportion of males to that of females was (0.87). This age and sex distribution has been similarly described in England and Wales [31]. The incidence of *C. jejuni* infection in the United States is higher among males than females in all age groups [32]. Kapperud from Norway in their study have also shown that males are at increased risk for *C. jejuni* infection however the reason remains unclear [33].The risk factirs analysiswere dealing with the general health of the patients and the social economical conditions of the patients family which directly affect the deceloping of infections The Anemia was the major risk factor and the social factor like low mother education were the major risk factors detected in the study Other factors not found to be

significantly to be a risk factors but they may contribute to initiate infection such as low family inome due to no ,employment for the father which causes a poverty and other factors mnot mentioned poor hygiene and sanitation and proximity to animals which influence the general health conditions of the population but the low standard of in the Gaza strip districts was the major risk factor. In Australia, animal contact (owning a pet puppy or chicken) was described as the only significant risk factor for illness in infants under 3-years-old [34]

The antimicrobial resistance of *C. jejuni* isolates has revealed that a higher proportion of isolates were resistant to ,trimethoprim/sulphamethoxazole cephalothin tetracycline and ampicillin,and showed high sensitivity to Meropenem Ceftriaxone Azithroname and Amikacin .All of Ciprofloxacin ,Gentamicin ,Erythromycin has low resistant rate and no resistant strains were found for Meropenem . Fluoroquinolones are frequently prescribed empirically for diarrheal illness including travelers diarrhea because of their effectiveness against a wide range of enteric bacteria [35]. Fluoroquinolones also was found to shorten the diarrhea and severity of symptoms caused by *C. jejuni* [36]. Epidemiologic and since the late 1980s resistance in *campylobacter* isolates to Fluoroquinolones has been recorded data from several countries suggest that Fluoroquinolones use in poultry is a major contributor to the increase in human Fluoroquinolones-resistant *C. jejuni* infections and Poultry has been documented repeatedly as a major food reservoir for human *C. jejuni* infections [37]. Hou et al reported during the period 1994-1998, that 44.5% of *C. jejuni* strains were resistant to Fluoroquinolones, 0% to gentamicin, and 0% to cefuroxime; in 2005-2010, resistance increased significantly to 97.9%, 16.7%, and 93.0%, respectively ($p < 0.0001$) but the resistance to erythromycin did not change significantly (3% vs 6.4%, $p = 0.4$). [38]. Osterlund et al reported that *C jejuni*/*coli* strains acquired outside Sweden and 575 acquired in Sweden during 1990-2002. There was a clear gradual increase in ciprofloxacin and tetracycline resistance among *C. jejuni/coli* strains acquired outside Sweden during the 13 y period. This trend was not seen for erythromycin or in domestically acquired strains for any of the 3 antibiotics tested [39]. Epidemiological studies of macrolide resistance in *C. jejuni* demonstrated that infections with macrolide-resistant *C. jejuni* could be associated with an increased

risk of adverse events, development of invasive illness or death compared to macrolide-susceptible isolates[40]. Our results showed that resistant rate for Erythromycin 27% and for Azithromycin 15%, other different studies recorded resistant strains of *C. jejuni* for Macrolides [41,42]. The over-use of antibiotics in the human population and in animal husbandry has led to an increase in antibiotic-resistant infections, particularly with Fluoroquinolones. This is problematic because *C. jejuni* gastroenteritis is clinically indistinguishable from that caused by other bacterial pathogens, and such illnesses are usually treated empirically with Fluoroquinolones. Since *C. jejuni* is naturally transformable, acquisition of additional genes imparting antibiotic resistance is likely.

In conclusion, diagnosis of infection with *C. jejuni* is still important for children with diarrhea, the susceptibility pattern reflects variable susceptibility with maximum resistance to Teracycline ,Cephalothin and Trimethoprim/sulphamethoxazole and low resistance to Meropenem ,Azithromycin and Ceftriaxon . The risk factors obtained are important for the patients and public in order to be taken in consideration in the future control programme

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