Campylobacteriosis a single center experience - literature review and own research

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Abstract—**Campylobacteriosis is the most common acute bacterial diarrheal disease in our population. It is caused by bacteria of the genus Campylobacter species whose prevalence in the environment and ease of transmission make these infections a serious epidemiological problem. Although the disease usually has a picture of mild self-limiting diarrhea in some cases there is a more severe course with the need for hospital care. Colonization by Campylobacter spp. also plays on of the main role in the pathogenesis of other diseases. The study was conducted using data from the records of 67 patients aged 3 months to 10 years hospitalized for acute diarrheal illness caused by Campylobacter spp. Microbiological culture yielded growth of C. coli in 14 cases and C. jejuni in 52 patients. The isolated pathogens showed significant antibiotic resistance variable depending on the bacterial strain. The least susceptibility to the drugs occurred with erythromycin and was mainly related to C jejuni. In 42 children it was necessary to implement antibiotic therapy during which azithromycin, amoxicillin with clavulanic acid, or Biseptol were used.**

Keywords—**Campylobacter spp.; Campylobacteriosis; Children; Diarrhea**

I. Introduction

A. Characteristics of the pathogen

Campylobacter is a zoonotic cosmopolitan pathogen that is the most common cause of bacterial foodborne illness [1]. Campylobacter spp. can lead to infection in humans, which in its acute course is referred to as campylobacteriosis [2]. Its incidence has been gradually increasing in recent years, particularly in developing countries. However, this trend is also occurring within the European Union including, among others, Poland [3]. Campylobacter spp. are Gram-negative spiral bacteria 0.5-5 microns long and 0.2-0.9 microns in diameter. They are motile, mobile, thermophilic, do not form spores, produce

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oxidase and have high adherence abilities. Most species grow under microaerobic conditions. Among some varieties, growth in anaerobic environments is also observed [1]. Pathogenesis in Campylobacter spp. infections represents a several-stage process. The pathogen, after entering the gastrointestinal tract and overcoming the chemical barrier formed by gastric acid, begins to colonize the distal segment of the large intestine. Adhesion to the wall of the gastrointestinal tract occurs through a process of chemotaxis, in which numerous virulence factors are involved. Their type depends on the strain of a particular pathogen. Then the bacterium, set in rotary motion with the use of threads, overcomes the cell membrane and begins to multiply inside the intestinal epithelium. A toxin (cytolethal- distending toxin-CDT), leading to the destruction of enterocytes and triggering an inflammatory response, is most likely directly responsible for the symptoms seen in humans. [4], [5] Nowadays, the two main species (C. jejuni and C. coli) are the main pathogenic pathogens [6], [7]. Other less pathogenic species are capable of causing disease as well. However that consider mainly immunosuppressed patients. [1]

During 2018, the 28 member states of the European Union collectively documented 246,571 confirmed instances of campylobacteriosis in humans. This resulted in an EU notification rate of 64.1 cases for every 100,000 individuals. The countries with the highest number of infections in that year were in the former Czechoslovakia. There were reported 215.8 cases per 100,000 people in the Czech Republic and 153.2 cases in Slovakia. These courtiers were followed by Luxembourg with 103.8 cases, and the United Kingdom with 98.4 cases. On the opposite end of the spectrum, the nations reporting the lowest rates in 2018 included Cyprus, Greece, Bulgaria, Romania, Poland, Latvia and Portugal, where the rates were all less than 5.9 cases per 100,000 population. [3]

B. Transmission routes

Campylobacter bacteria are widespread in the environment. They are detected in animal products and drinking water, among others. They are part of the normal human bacterial flora in the digestive tract of many animals (both wild and domesticated). In this group, farmed birds deserve special mention. Campylobacter bacteria are extremely easily transmitted within farms, which are one of the main starting points of mass infections in highly developed countries [8].

Campylobacter spp. transmission in companion animals predominantly occurs through faecal-oral routes (direct or indirect). The primary sources of infection include undercooked or raw food items, unpasteurized milk, water, as well as direct exposure to fresh faeces of infected animals. Additionally, indirect transmission can take place through various carriers of infection, such as clothing, utensils, furniture, vectors, and the environment itself. The interplay of these factors complicates the understanding and management of Campylobacter spp. in companion animals, making it imperative to delve into various aspects of prevalence and transmission [9].

The prevalence of Campylobacter spp. in domestic animals (especially Canis familiaris and Felis catus) is subject to considerable variation, owing to numerous influencing factors. These factors include the age of the animals, the specific species under study, their housing conditions, the presence of concurrent diseases or infections with other enteropathogenic organisms, the sampling season, geographical location, and the study design employed. This multifaceted nature of prevalence underscores the need for comprehensive research and surveillance efforts to better comprehend the dynamics of Campylobacter infection in companion animals [10], [11].

Remarkably, the infected animals typically display no overt clinical symptoms, rendering detection challenging and heightening the risk of pathogen transmission to humans. An alarming statistic reveals that approximately 90% of campylobacteriosis cases in humans can be traced back to the consumption of animal products. Investigations have indicated that the highest risk of bacterial transmission arises from the consumption of meat (pork, beef, poultry, small ruminant meat), and dairy products, among others. This emphasizes the significance of rigorous food safety measures, particularly in the handling and preparation of these products [12], [13].

Furthermore, it is worth noting that Campylobacter bacteria have the potential to disseminate through food that has been contaminated, which may include produce such as vegetables and fruits. Contamination can occur at different stages, including primary production during harvesting and subsequent retailing. Moreover, there exists a notable risk of cross-contamination within kitchen environments, both in households and professional culinary settings. This underscores the importance of stringent hygiene practices in food preparation and handling [14].

Asymptomatic carriage of Campylobacter bacteria also occurs in humans. This creates the possibility of indirect (through contaminated food and water) and direct (through sexual contact) transmission of infection between humans.

The minimal quantity of bacteria required to trigger symptomatic infection can vary significantly among individuals and is often challenging to pinpoint precisely. Nonetheless, human experimental investigations conducted under carefully controlled conditions have demonstrated that some volunteers experienced diarrhoea when exposed to doses as low as 800 Colony-Forming Units [15]. A detailed analysis reveals that domestic instances have been prominently documented in several EU nations, including but not limited to the Czech Republic, Hungary, Latvia, Malta, Poland, Portugal, Romania, and Slovakia. Strikingly, these domestic cases collectively account for a staggering 96% of reported occurrences, highlighting a significant public health concern within these countries. In stark contrast, incidents associated with travel have exhibited distinct patterns, predominantly manifesting in Nordic countries. Finland, Denmark, Sweden, Iceland, and Norway have reported substantial cases related to travel, constituting 79.9%, 46.8%, 54.3%, 91.0%, and 60.1% of their respective reported cases. This intriguing disparity underscores the nuanced nature of Campylobacteriosis transmission, with travel acting as a substantial contributing factor in these Nordic regions. Further delving into the data, a comprehensive examination of 15,210 cases linked to identifiable countries of infection reveals compelling insights. Nearly half of these cases were directly correlated with travel within the European community, elucidating the substantial impact of intra-European travel on the prevalence of Campylobacteriosis. Beyond European borders, certain countries have emerged as key sources of infection. Thailand, Turkey, and Morocco have been frequently identified as the primary countries outside of Europe, contributing significantly to the spread of Campylobacteriosis, accounting for 9.9%, 5.8%, and 5.2% of cases, respectively. [3]

C. Disease symptoms

Campylobacteriosis usually occurs in the form of a self-limiting intestinal disease. Its incubation period lasts 2-5 days, and symptoms disappear after an average of 7 days. Typical symptoms are diarrhoea (mostly watery), spasmodic abdominal pain and fever. In some cases, blood can be observed in the stool. [16] Extraintestinal manifestations of the disease include meningitis, abscesses, myocarditis, hepatitis and cholecystitis. [1] Although gastroenteritis is the main effect of Campylobacter spp. infection. These organisms are associated as well with several other serious gastrointestinal conditions (for example inflammatory bowel disease, esophagealitis, periodontitis, functional gastrointestinal disorders (FGID), celiac disease, cholecystitis and gastrointestinal cancers). In addition, Campylobacteriosis caused by C. jejuni can be linked to autoimmune diseases like Guillain-Barré syndrome and Miller-Fisher syndrome.. [1]

1) Bacteremia: Bacteremia resulting from Campylobacter spp. infection is a rare occurrence, affecting fewer than 1% of individuals with intestinal infections, as reported in reference [1]. The majority of these cases, approximately 93%, are linked to predisposing factors like advanced age, chronic liver disease, HIV infection, cancer, and compromised humoral immune function. [17], [18]. Among the most commonly isolated etiological agents, we can distinguish C. jejuni, C. coli and C. fetus [19]. The disease is generally a complication of a single episode of gastroenteritis in children or recurrent episodes in immunocompromised children without gastrointestinal symptoms [20]. The mortality rate for bacteremia is 4% - 16%. This risk is significantly higher with C. fetus isolation compared to other species. This fact is most likely due to the higher proportion of immunosuppressed patients in this group [21].

2) Diseases of the esophagus: Esophageal disorders encompass conditions like gastroesophageal reflux disease, Barrett's esophagus, and esophageal neoplasm. Gastroesophageal reflux disease is a persistent ailment that significantly elevates the risk of esophageal dysplasia and adenocarcinoma. Research has indicated variations in the bacterial composition among individuals with a healthy esophagus, gastroesophageal reflux disease, and Barrett's esophagus, with four main bacterial types predominantly present: Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria. Furthermore, investigations have revealed the prevalence of Campylobacter species, particularly Campylobacter concisus, in patients suffering from gastroesophageal reflux disease and Barrett's esophagus. A study found that 57% of patients with Barrett's esophagus had Campylobacter species colonisation in their mucosal samples, with Campylobacter concisus being the most common type.

The presence of Campylobacter bacteria in individuals with Barrett's esophagus may imply their involvement in the initiation or exacerbation of processes leading to the development of adenocarcinoma. [22]. In another study, Blackett and colleagues determined differences in esophageal microflora disparities in various health conditions. Their research identified Campylobacter concisus as the primary colonizer in individuals suffering from reflux disease and Barrett's esophagus. Moreover, the study demonstrated a significant link between the presence of these bacteria and heightened expression of cytokines linked to cancer development, notably IL-18. Interestingly, this correlation was not observed in patients diagnosed with esophageal cancer [23].

3) Periodontal diseases: Gingivitis and periodontitis are disease entities in whose pathogenesis an important role is played by the bacterial biofilm that accumulates at the edges of the gums. In 2000, Macuch and Tanner conducted a study finding which Campylobacter species were associated with periodontal disease. They identified at least seven types of Campylobacter bacteria in subgingival sites. The species found in cases with primary and established periodontitis were compared with the composition of the biofilm found in healthy individuals. It was found that C. rectus was present more frequently and in higher concentrations in people with periodontal conditions [24].

4) Inflammatory bowel disease: IBD are chronic inflammatory conditions of the gastrointestinal tract that include Crohn's disease (CD) and ulcerative colitis (UC). Their pathogenesis and course depends on many factors, among which the intestinal bacterial flora plays an important role. In the realm of gastrointestinal research, a pivotal study conducted by Gradel and colleagues in 2009 illuminated a significant association between Campylobacter jejuni infection and the heightened risk of IBD. Their findings, derived from a meticulous population-based cohort study, provided compelling evidence linking individuals who had experienced a laboratory-confirmed episode of gastroenteritis attributed to Campylobacter to a subsequent increased susceptibility to developing IBD [25].

The association between Crohn's disease and various Campylobacter species, including C. ureolyticus, C. showae, C. hominis, C. gracilis, C. rectus, and C. concisus, was initially elucidated by the research team led by Mitchell and colleagues. In a pivotal study conducted in 2009 involving a pediatric population newly diagnosed with Crohn's disease, they observed a noteworthy connection. Specifically, the researchers found a significantly elevated presence of C. concisus as well as higher levels of antibodies directed against C. concisus in this group compared to a control cohort. This discovery shed light on a potential link between specific Campylobacter species and the onset of Crohn's disease, providing valuable insights for further exploration and understanding of the disease's etiology [26]. The prevalence of C. concisus was also described as higher in patients with inflammatory bowel disease in subsequent studies [27]. In 2009, Tnakovic and colleagues showed a higher presence of C. concisus in patients with inflammatory bowel disease than in controls [28].

In a study conducted by Man and colleagues in 2010, it was reported that 65% of fecal samples obtained from individuals diagnosed with Crohn's disease tested positive for C. concisus. This contrasted with the findings in healthy controls, where 33% of samples exhibited the presence of C. concisus, and non-IBD controls, where the rate was 37% [29].

A parallel correlation was observed among patients with ulcerative colitis (UC). Mahendran and colleagues identified a notably higher prevalence of C. concisus in colon biopsy specimens from adult UC patients compared to control subjects [30]. Additionally, two other studies demonstrated an increased prevalence of C. concisus DNA in both adult and pediatric patients diagnosed with UC. [31], [32]. In a further study, Mukhopadhya and colleagues also found a significantly higher presence of C. ureolyticus in patients with ulcerative colitis [32].

5) Functional diseases of the gastrointestinal tract: Studies of post-infectious irritable bowel syndrome associated with Campylobacter jejuni have shown rates ranging from 9.0 to 13.8% of cases [33]. Long-term observational studies have shown that post-infectious symptoms of irritable bowel syndrome associated with C. jejuni can persist up to 10 years after the original infection [34]. Correlations have also been observed between C. jejuni and other Campylobacter species and FGID (that starts after infection), IBS and functional dyspepsia [35].

D. Prevention

Certainly, preventing Campylobacter infections necessitates a multifaceted approach. Vaccinating poultry, implementing rigorous hygiene protocols in production, ensuring strict controls during slaughter, and educating the public about safe food practices are vital components of this strategy [1]. Moreover, advancements in detection techniques have significantly enhanced our ability to identify Campylobacter in contaminated food. Polymerase Chain Reaction (PCR) assays offer highly specific and sensitive methods for Campylobacter DNA detection. Additionally, sophisticated technologies such as Matrix-Assisted Laser Desorption/Ionization and Time-of-Flight Mass Spectrometry (MALDI-TOF MS) enable rapid and precise identification of pathogens by analyzing their unique protein profiles. By integrating these preventive measures and

advanced detection methods, we not only bolster food safety but also empower healthcare professionals with accurate tools for timely interventions, ultimately safeguarding public health against infections [36].

E. Diagnosis and treatment

The confirmation of human infection diagnosis is commonly achieved by means of culture methods and polymerase chain reaction (PCR) testing of fecal samples. [37]. Treatment of most Campylobacter infections is only symptomatic. The self-limiting course of the disease does not require any therapeutic intervention other than supportive treatment (including fluid therapy). The need for antibiotic therapy is present in immuno-compromised patients with severe or persistent symptoms and extraintestinal infections [38]. Antimicrobial susceptibility is set by the Kirby-Bauer disc diffusion method or E test [1]. A high rate of resistance to ciprofloxacin is observed among Campylobacter spp. This is a direct result of the excessive use of antimicrobial drugs in industrial animal husbandry (especially poultry) and the large amounts of pharmacological agents released into the ecosystem [39], [40]. For this reason, macrolides are the first-line antibiotic [14], [36]. Insufficient or delayed administration of appropriate antimicrobial therapy does not seem to be linked to higher mortality rates, as indicated by reference [41].

Among the cases with a documented status, approximately 30.6% necessitated hospitalization. Notably, the countries with the highest hospitalization rates included certain Central European countries (Poland, Latvia, Romania) and the United Kingdom. In these nations, a significant proportion of infected patients received inpatient care concurrently. This phenomenon can be attributed to the structure of epidemiological surveillance, which primarily focuses on identifying severe cases, thereby potentially distorting the overall picture of infection prevalence within the population. [3]

II. METHODS AND MATERIALS

The study received approval from the Institutional Review Board (or Ethics Committee) of Wroclaw Medical University on March 15, 2021. The study was undertaken using a data extracted from the records of patients treated at the 9th Pediatric Ward at J. Gromkowski WSS in Wroclaw in 2018. The analysis included cases with microbiologically confirmed Campylobacter spp. infection. Antibiotic resistance was determined in cultures of bacteria isolated from culture of fecal samples. Above that, all children underwent a complete pediatric examination and basic laboratory tests (blood count, blood gas, basic blood biochemistry and urinalysis).

III. STATISTICAL ANALYSIS

The data was processed using MS Excel 2016 and Statictica, a software developed by TIBCO. To analyze the data, Paerson's Chi-square test of concordance with Yeates' correction for nonparametric data and Mann-Whitney U test for parametric data were performed. The statistical significance level was set at p0.05.

IV. RESULTS

A. Study group

The study included 67 patients (35 male and 32 female) aged between 3 months and 10 years. The average age was 3.1 years old. The children's hospital stay lasted an average of 4.32 days. In the case of 6 patients, repeat hospitalization was necessary, the average duration was 5.83 days.

B. Disease symptoms

Among the symptoms observed in children, the most common were diarrhea in 59 cases (88%), features of dehydration in 49 cases (73%) and fever in 45 cases (67%). Abdominal pain was the least frequently reported, occurring in 8 patients (12%). The frequency of disease symptoms in the study group of children is shown in Table I.

TABLE I
NUMBER OF PATIENTS WITH SELECTED SYMPTOMS

Symptoms	Number of patients	Percentage of patients
Fever	45	67%
Abdominal pain	8	12%
Diarrhea	59	88%
Blood in stools	36	54%
Vomits	20	30%
Dehydration	49	73%
Abdomen tense/bloated	9	13%
Abdominal tenderness	12	18%
Increased peristalsis	28	42%
Perineal chafing	11	16%

C. Deviations in additional examinations

In the red blood cell system morphology performed on admission, a reduction in MCV (29 patients) and MCH (12 patients) was observed in some patients. However, they constituted a minority of cases. In terms of the protein-cell system, 17 cases had neutrophilia. In the vast majority of patients, elevated monocyte levels were determined (52 patients). Reduced platelet levels were observed in 12 children. Other abnormalities in morphology were present only in single cases. As for blood biochemical tests, significant changes occurred only in CRP. Its elevated level was shown in 56 patients. Selected parameters from blood count and biochemical tests are shown in Table II.

D. Microbiological culture results and antibiotic resistance

Stool samples from patients most often yielded Campylobacter jejuni growth in 52 (79%) cases, while Campylobacter coli was detected in 15 (7%) cases. In all microbiological samples, susceptibility was determined against three antibiotics: ciprofloxacin, erythromycin and tetracycline. In the case of ciprofloxacin, antibiotic resistance was significantly more common in C. jejuni compared to C.coli (p<0.0005), and was detected in 51 samples. Sensitivity to tetracycline was demonstrated in more than half of the samples. In the case

TABLE II
SELECTED PARAMETERS FROM BLOOD COUNT AND BIOCHEMICAL TESTS

Parameter	Below the norm		Within the norm		Over the norm	
WBC	7,46%	5	74,63%	50	17,91%	12
RBC	2,99%	2	94,03%	63	2,99%	2
HGB	8,96%	6	89,55%	60	1,49%	1
MCV	43,28%	29	56,72%	38	0,00%	0
MCH	17,91%	12	82,09%	55	0,00%	0
HCT	19,40%	13	80,60%	54	0,00%	0
MCHC	2,99%	2	97,01%	65	0,00%	0
PLT	17,91%	12	82,09%	55	0,00%	0
NEU	0,00%	0	71,64%	48	28,36%	19
EOS	40,30%	27	50,75%	34	8,96%	6
BAS	8,96%	6	91,04%	61	0,00%	0
LYM	4,48%	3	95,52%	64	0,00%	0
MON	0,00%	0	22,39%	15	77,61%	52
AlAT	0,00%	0	100,00%	67	0,00%	0
AspAT	0,00%	0	89,55%	60	10,45%	7
CRP	—	—	16,42%	11	83,58%	56

of erythromycin, the vast majority of bacteria showed no resistance to the drug.

The type of bacterial species isolated from the patients had no statistically significant effect on the course of the disease, the clinical symptoms presented or the abnormalities in laboratory tests.

TABLE III
NUMBER OF CASES OF ANTIBIOTIC RESISTANCE

	Ciprofloxacin		
	Sensitive	Resistance	P
Campylobacter jejuni	1	51	<0,0005
Campylobacter coli	11	4	
	Erythromycin		
	Sensitive	Resistance	P
Campylobacter jejuni	50	2	0,92831
Campylobacter coli	9	5	
	Tetracycline		
	Sensitive	Resistance	P
Campylobacter jejuni	29	23	0,22085
Campylobacter coli	9	5	

E. Antibiotic therapy

During hospitalization, 48 children required antibiotic therapy. The most commonly used drug was azithromycin (in 32 children). Less frequently, treatment was implemented with amoxicillin with clavulanic acid (in 10 cases) and Biseptol (in 5 cases). The duration of hospitalization for children taking the antibiotic averaged 4.6 days. It was significantly longer than in the other group of patients, whose hospitalization lasted an average of 3.6 days. Regarding the type of antibiotic used, there was no analogous correlation in the length of hospitalization.

F. Conclusion

The study identified that the most prevalent symptoms observed in children were diarrhoea, dehydration, and fever.

TABLE IV
NUMBER AND EFFECTS OF ANTIBIOTIC THERAPY

	Number of cases		Average hospitalization [days]	P
Treatment with an antibiotics	48	72%	4,6	0,028
Treatment without an antibiotics	19	28%	3,59	
Azithromycin	32	48%	4,3	0,059
Amoxicillin with clavulanic acid	10	15%	4,89	
Biseptol	3	4%	4,8	
Other	8	12%	5,25	

Abdominal pain was found to be a less common symptom. The stool samples collected from the children predominantly showed growth of Campylobacter jejuni, with varying antibiotic susceptibilities. The antibiotics prescribed to the children were evaluated and it was found that azithromycin was the most frequently prescribed antibiotic. Interestingly, the study found that children who were treated with antibiotics had a longer average hospitalization duration of 4.6 days compared to those who did not receive antibiotics, whose average hospitalization duration was 3.6 days. This was most likely influenced by the condition of the patients. However, it was found that the specific antibiotic used did not have any significant correlation with the duration of hospital stay.

V. DISCUSSION

The high prevalence of Campylobacter in the environment and its ease of transmission pose significant challenges from an epidemiological perspective. As per a 2018 report jointly published by the European Food Safety Authority and the European Center for Disease Prevention and Control, Campylobacter infections represent a major public health concern. Among the 36 European countries examined in the report (comprising 28 member states and 8 non-member states), campylobacteriosis emerged as the most commonly reported zoonotic disease in humans. In fact, it accounted for approximately 70% of all reported zoonotic cases, underscoring its prominent status as a public health issue [3]. The two main strains detected in our patients were Campylobacter jejuni (c.84%) and Campylobacter coli(c.10%). This corresponds to the picture presented in a nationwide report on infections where, in confirmed cases of campylobacteriosis. The other were much rarer - l 0.1% Campylobacter lari, 0.1% Campylobacter fetus and 0.1% Campylobacter upsaliensis. [42] These infections, although extremely common, require time-consuming microbiological diagnosis due to the lack of characteristic symptoms and changes in laboratory tests for confirmation. This hinders the timely implementation of appropriate treatment, which plays a major role in groups particularly vulnerable to serious sequelae of the disease, including children [16]. The selection of appropriate treatment is further hindered by the high resistance to antibiotics caused, among other things, by their excessive use in the food industry. As our study showed, antibiotic resistance to

at least one drug was present in all cases. This picture is not an isolated situation. Due to the overuse of antimicrobial drugs in many sectors of the economy, mainly in the food industry, a decreasing sensitivity of bacteria to the most commonly used antibiotics has been observed for years [14]. According to our observations, patients in whom antibiotic therapy was implemented required significantly longer hospitalization than other patients. However, this phenomenon may be due to differences in the severity of symptoms in these patients compared to patients not requiring antibiotic therapy. Another likely reason is the low susceptibility of pathogens to the treatment used, related to bacterial resistance to antibiotics [36]. A separate problem is the group of patients in whom the infection is sparsely symptomatic. Despite the existence of mandatory reporting of campylobacteriosis in most European countries, including Poland, the disease is still insufficiently often properly diagnosed and reported. Due to inadequate sanitary and epidemiological control, the etiological agent in many cases is not established, which increases the risk of transmission of the disease to others and the formation of epidemic outbreaks. Thus, when analyzing statistical data, it should be borne in mind that recorded cases represent only a small percentage of true infections [42]. An additional consequence of the lack of accurate statistical data is that it is difficult to determine the long-term effects of infection and colonization by Campylobacter spp. [43]. Between 2009 and 2018, there has been a significant upward trend in the number of reported cases of infection across the EU and individual member states. The rise observed in certain countries may not solely be attributable to shifts in exposure. It could also be due to enhancements in monitoring systems, broader implementation of regular diagnostic procedures nationwide, and heightened physician awareness. [3] This gives hope for improvement of the situation and improvement of treatment standards.

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