REVIEW ARTICLE

MIXED INTESTINAL INFECTIONS IN PATIENTS RETURNING FROM TROPICAL DESTINATIONS – DIAGNOSTIC CHALLENGES

Mieszane zakażenia jelitowe u pacjentów powracających z tropikalnych destynacji – wyzwania diagnostyczne

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Abstract

The increasing popularity of travel to tropical regions has led to a rise in mixed intestinal infections among returning travelers. These infections, caused by a combination of bacterial, viral, and parasitic pathogens, present complex diagnostic and treatment challenges. Travel patterns are evolving, with a growing number of individuals venturing into tropical regions. This trend is likely to continue, highlighting the need for a greater understanding of mixed intestinal infections in this population. A diverse range of pathogens can cause mixed intestinal infections, with Enteroadherent *E. coli*, Enteropathogenic *E. coli*, the protozoan *Giardia intestinalis*, noroviruses, and the stramenopile *Blastocystis hominis* being particularly prevalent. The interplay between these organisms can lead to a broad spectrum of clinical manifestations. Co-infections with multiple pathogens are common in mixed intestinal infections and can significantly worsen the severity of symptoms. Understanding the mechanisms and interactions of co-infections is crucial for effective management. Diagnosing mixed intestinal infections requires a multifaceted approach, combining clinical presentation, stool analysis, and advanced tests such as polymerase chain reaction. Early and accurate diagnosis is essential for prompt and appropriate treatment.

Streszczenie

Rosnąca popularność podróży do regionów tropikalnych doprowadziła do wzrostu przypadków mieszanych zakażeń jelitowych wśród powracających podróżnych. Zakażenia te, spowodowane kombinacją patogenów bakteryjnych, wirusowych i pasożytniczych, stanowią złożone wyzwanie diagnostyczne i terapeutyczne. Wzorce podróżowania zmieniają się i coraz więcej osób odwiedza regiony tropikalne. Trend ten prawdopodobnie się utrzyma, co wymaga lepszego zrozumienia mieszanych zakażeń jelitowych w tej grupie pacjentów. Szeroka gama patogenów może powodować mieszane zakażenia jelitowe, przy czym szczególnie rozpowszechnione są enteroadherentne *E. coli*, enteropatogenne *E. coli*, pierowtniaki *Giardia intestinalis*, norowirusy oraz stramenopile *Blastocystis hominis*. Wzajemne oddziaływanie tych organizmów może prowadzić do różnorodnych objawów klinicznych. Koinfekcje wieloma patogenami są częste w przypadku mieszanych zakażeń jelitowych i mogą znacznie zaostrzyć nasilenie objawów. Zrozumienie mechanizmów i interakcji w przebiegu koinfekcji jest kluczowe dla skutecznego postępowania. Diagnostyka mieszanych zakażeń jelitowych wymaga podejścia wieloaspektowego, łączącego ocenę kliniczną, analizę kału oraz zaawansowane testy, takie jak łańcuchowa reakcja polimerazy. Wczesna i dokładna diagnoza jest niezbędna dla szybkiego i właściwego leczenia.

Keywords: mixed intestinal infections (MIIs); co-infections; tropical destinations

Słowa kluczowe: mieszane zakażenia jelitowe (MZJ); koinfekcje; tropikalne destynacje

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Introduction

The field of tropical medicine is continuously evolving, with new challenges emerging that require innovative solutions. Among these challenges, the diagnosis and treatment of mixed intestinal infections (MII) in patients returning from tropical destinations stand out as particularly complex. These infections, which may involve a combination of bacterial, viral, and parasitic pathogens, present a convoluted puzzle for clinicians. The pathogens responsible for these infections are as diverse as the regions from which they originate. Bacterial culprits such as *Salmonella*, *Escherichia coli*, and *Campylobacter jejuni* are frequently implicated in MII, alongside viral agents like norovirus and sapovirus, and parasites such as *Giardia intestinalis* and *Cryptosporidium parvum*. The interplay between these organisms can lead to a wide spectrum of clinical manifestations, ranging from mild discomfort to severe, debilitating illness [1]. Travel patterns play a significant role in the epidemiology of these infections. The globalization of travel has increased the number of individuals venturing into tropical regions, often for leisure or work-related purposes. This has, in turn, has led to a rise in the incidence of MIIs among returning travelers. The risk factors associated with acquiring these infections are multifaceted, encompassing the duration of travel, the purpose of the visit, and the level of exposure to local pathogens [2]. The diagnostic process for MIIs is intricate, requiring a multifaceted approach. Clinicians must rely on a combination of patient history, physical examination, and a suite of diagnostic tests, including stool analysis, culture, and molecular techniques, to identify the responsible pathogens [3]. The symptomatic overlap between different pathogens can make this process particularly challenging, as it involves the differentiation between multiple potential causes of the patient's symptoms. Treatment strategies for MIIs are similarly nuanced. The presence of multiple pathogens often necessitates a combination of therapeutic agents, each targeting a specific organism. This approach must be balanced with the need to minimize antimicrobial resistance and consider potential drug interactions. Furthermore, treatment must be tailored to the individual patient's clinical presentation and the pathogens identified, requiring a personalized approach to care [1]. In conclusion, MIIs in patients returning from tropical destinations represent a significant challenge in tropical medicine. The complexity of diagnosing and treating these infections requires a comprehensive understanding of the pathogens involved, the travel patterns that contribute to their spread, and the nuanced approach needed for effective management. As global travel continues to expand, the importance of addressing these challenges becomes ever more critical, underscoring the need for continued research and development in this field.

Travel characteristics

In recent years, there has been a steady increase in the number of people traveling abroad. It is estimated that by 2030, the number of individuals traveling outside their country of residence could exceed 1.8 billion [4]. In addition to the increasing number of travelers, travel patterns are also changing. In 2019, the number of people visiting tropical regions significantly increased. Despite the decline in air traffic caused by the SARS-CoV-2 pandemic, there is still an increase in the number of people traveling to tropical countries [5]. Also in Poland, in recent years, the habits of travelers seem to align with global trends. In 2022, the number of people traveling abroad reached 18% of the society. Of these, over a million travelers chose tropical destinations, especially the UAE, Thailand, Zimbabwe, Namibia, and Tanzania [6]. The destinations of patients seem to mirror this global trend (Fig. 1).

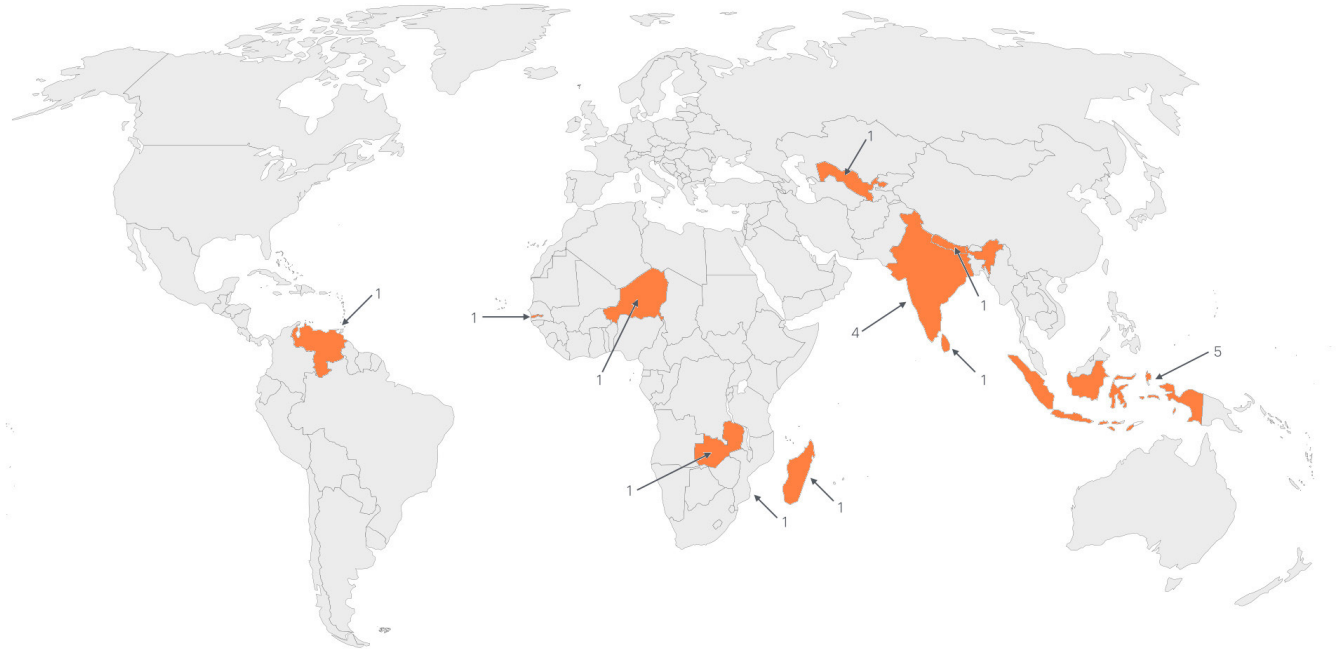

Figure 1. Patients travel destinations

Pathogens

Among the surveyed returnees from Nepal, Indonesia, Venezuela, Gambia, Zambia, Uzbekistan, India, Sri Lanka, Madagascar, Central African Republic, and Tanzania, the most common gastrointestinal infections are caused by Enteroadherent *E. coli* (EAEC) (10 cases) and Enteropathogenic *E. coli* (EPEC) (9 cases) (Tab. 1). The third most prevalent pathogens include the protozoa *Giardia intestinalis*, norovirus, and the stramenopile *Blastocystis hominis*. Enteroadherent *E. coli* colonizes the small intestine, with infection transmitted via the fecal-oral route [7]. Manifestations of infection include gastrointestinal disorders. EAEC adheres to small intestinal epithelial cells to form a biofilm and secrete enterotoxins, including thermostable enterotoxin (EAST-1) or toxin (Pet), a type V serine protease auto-transporter. The exact mechanism by which EAEC causes diarrhea remains unclear [8]. Enteropathogenic *E. coli* ranks as the second most common cause of diarrhea in hospitalized patients after rotavirus in developing countries. Infection also occurs via the fecal-oral route [7]. EPEC induces gastroenteritis, anorexia, rapid cachexia, and even death, especially in children under two years of age (constituting 10–40% of cases). EPEC virulence factors (pEAF, BFP, LEE, and Nle effectors) lead to the obliteration of microvilli, tightly adhering to intestinal epithelial cells [8]. *Giardia intestinalis* is mainly found in developing countries, with children being more commonly affected. Infection occurs through the ingestion of water or food containing cysts. The parasite inhabits the duodenum and jejunum, causing giardiasis, characterized by acute, subacute, or chronic diarrhea, nutritional deficiencies, weight loss, nausea, or vomiting. Asymptomatic cases have also been described [9]. Norovirus occurs in various geographical areas and causes seasonal epidemics, primarily affecting children. It spreads via the fecal-oral route and often causes asymptomatic infections. It is detected in fecal samples, but there have been cases of symptomatic infections where norovirus was isolated from plasma. Symptoms of infection include diarrhea, nausea, vomiting, and abdominal pain. In most patients, symptoms resolve within 1–3 days. However, in patients with co-morbidities, immunocompromised individuals, or children under two years of age, the infection may persist longer and be more severe. Necrotizing enterocolitis associated with norovirus infection has been observed in infants [10]. *Blastocystis hominis* is one of the most common zoonotic parasites, mainly found in developing, tropical, and subtropical regions. The disease predominantly affects adults aged 31–50 years [11] and children aged 10–14 years. Individuals at higher risk of infection include those in contact with animals (exposed to manure and human feces in soil), rural residents, and inhabitants of mountainous regions [12]. Infection occurs via the fecal-oral route. *Blastocystis hominis* infection can range from asymptomatic to manifesting gastrointestinal symptoms such as abdominal pain, nausea, vomiting, diarrhea, flatulence, and enteritis. In summary, the symptoms of infection by each pathogen are non-specific and similar. To identify the specific agent, it is necessary to take a comprehensive patient history and conduct appropriate stool tests. It is crucial for travelers to tropical

Table 1. Pathogens identified in patients returning from tropical destinations

Country/ Pathogens	Nepal	Indonesia	Venezuela	Gambia	Zambia	Uzbekistan	India	Sri Lanka	Madagascar	Central African Republic	Tanzania
Sapovirus	●						●				
Norovirus	●							●	●		●
Giardia intestinalis					●		●●●				
Entamoeba histolytica						●	●				
Shigella spp.			●				●				
Enteroadherent *E. coli*		●●●●		●			●	●	●	*	●
Enteropathogenic *E. coli*		●●●●			●			●	●	*	●
Enteroinvasive *E. coli*							●				
Enterotoxigenic *E. coli*		●									
Enterohemorrhagic *E. coli*		●	●								
Clostridioides difficile		●●		●							
Salmonella enterica							●				
Blastocystis hominis						●	●●●				
Rotavirus									●		
Campylobacter jejuni		●●					●				
Trichomonas hominis							●				
Yersinia enterocolitica			●								

● Patient not prepared by tropical medicine specialist
* Patient prepared by tropical medicine specialist

countries and medical practitioners to be aware of the risk of infection by each pathogen and take adequate preventive measures.

Co-infections

Travelers returning from tropical destinations often experience intestinal infections caused by not just one, but multiple pathogens (co-infections). Therefore, there is a need to analyze the specific interactions between pathogens to acquire a broader understanding of the diseases. Gastrointestinal infections can stem from various pathogens, including sapoviruses, noroviruses, *Shigella*, *E. coli*, and *Salmonella*, etc. [13]. While numerous studies have focused on the mechanisms of single infections, there is a need to concentrate on the interactions between co-infections [14]. In clinical settings, co-infections are frequent occurrences, with one pathogen potentially influencing another, either directly or indirectly. Understanding the mechanism of co-infections could significantly contribute to disease control and patient treatment. Co-infections are primarily manifested by alterations in the microbial flora: a decrease in bacterial numbers, reduced diversity, and general disturbances [15]. Studies commonly report an intra-host preference effect, suggesting that the effects of infections depend on the sequence pathogen arrival [16]. However, some argue that the severity of infection is primarily determined by the number of pathogens present, although the regulatory mechanism behind this remains unclear. The influence of co-infections on the intestinal epithelium is under investigation, with studies still in their preliminary phases, yet given the number of patients affected, this topic warrants discussion [17]. Travelers returning from tropical destinations are frequently infected by multiple types of *E. coli*, EPEC, EAEC, and others. This trend is particularly common among tourists returning from Indonesia. Co-infections involving Enteroadherent *E. coli*, Enteropathogenic *E. coli*, and norovirus are often observed in patients arriving from Sri Lanka, Madagascar, Tanzania, and the Central African Republic (Tab. 1). The interaction between selected strains of *E. coli* may be a protective feature that facilitates survival in unfavorable environments. It is believed that two strains of *E. coli* can coexist in a form of cross-protection mutualism, protecting each other and surviving in antibiotic concentrations that would inhibit the growth of either type alone [18]. Additionally, the most significant co-infections are suggested to occur between bacteria and viruses. Firstly, direct interactions between pathogens can enhance thermal stability by binding bacterial surface polysaccharides to viral particles [19]. Moreover, the infected intestinal tract becomes more susceptible to infections caused by other pathogens due to disruptions in microbial flora, damage to the intestinal barrier, and increased expression of cell surface receptors [20]. However, there is also potential for unfavorable competition. Certain types of bacteria secrete substances that inhibit the synthesis of important viral proteins. In some cases, the immune response triggered by the first pathogen makes subsequent infections difficult or even impossible [21]. Studies have shown that compared to rotavirus and norovirus infections alone, co-infections with EPEC and EAEC are frequently associated with diarrhea and vomiting [22]. The rate of co-infections linked to norovirus is considered high. Studies showed that the rate of multiple pathogen detection is approximately 30% [23]. Notably, the most common co-infections among patients with norovirus involve *C. difficile* and *E. coli* [24]. This is an important fact because the latest studies focus on the risk of occurrence of diarrhea in patients suffering from multiple pathogens. The main mechanism driving the severity of symptoms is the synergy between pathogens [25]. In patients returning from Nepal, co-infections especially between sapoviruses and noroviruses were observed. Additionally, among patients coming from India, sapovirus was detected alongside other enteric pathogens. This is notable, as previous research has primarily focused on the occurrence of sapoviruses in pediatric populations or elderly individuals (over 60 years old) [26]. Co-infections are common in patients suffering from intestinal infections, and pathogens can influence each other's cell infection processes in certain ways. Viruses that naturally inhabit the intestines may modulate the infection pathways for other pathogens. As a result, the presence of multiple pathogens may herald a more severe course of the disease [27].

Diagnostics

Among the patients described with MII, non-specific symptoms predominated, including fever, abdominal pain, vomiting, nausea, diarrhea with traces of blood, mucus, and water, headaches, and dysuria. Basic laboratory tests revealed an increase in inflammation markers, hyperbilirubinemia, shifts in proteinogram, elevated pancreatic enzyme levels, hypertransaminasemia, and erythrocyturia with leukocyturia. However, to identify specific pathogens and implement patient-tailored therapy, more advanced tests are necessary.

In the cases described above, pathogens were diagnosed using the ELISA method, which tested antibodies in the IgG or IgM classes against *Yersinia enterocolitica* and *Entamoeba histolytica*. The nested PCR method was used to determine the presence of genetic material for Enteroadherent *E. coli*, Enteropathogenic *E. coli*, norovirus, *Salmonella enterica*, *Yersinia enterocolitica*, *Campylobacter jejuni*, Enteroinvasive *E. coli*, Enterotoxigenic *E. coli*, Enterohaemorrhagic *E. coli*, *Shigella* spp., *Clostridioides difficile*, *Giardia intestinalis*, *Entamoeba histolytica*, norovirus GI/GII, rotavirus, and sapovirus. Coproscopic examination was also conducted for *Entamoeba histolytica/dispar*, *Giardia intestinalis*, *Trichomonas hominis*, and *Blastocystis* spp. Assessing risk factors in patients can also aid in diagnosing MII [28]. In this context, one can distinguish between non-modifiable and modifiable risk factors [29]. Recent studies identify age, gender, and country of birth as some of the most significant non-modifiable factors for MII. As for gender, it is suggested that a higher risk may be expected in women [30]. Another study indicates that being born in non-Western regions (Asia, South America, Africa, etc.) may be a protective factor, possibly due to exposure to native gastrointestinal pathogens during childhood, leading to the development of basic immunity [31]. Moreover, it has been postulated that the risk of MII decreases with increasing age in adult patients. This may be related to the increase in living standards and travel patterns, which may occur at different stages of life [32]. As for modifiable risk factors, travel for the purpose of visiting friends (VFT) has recently been considered.

However, due to the complex nature of MII, VFT can be a positive or negative factor depending on the travel destination [33]. In addition, an elevated risk may be associated with the length of travel, with longer travel durations increasing the risk, and with the choice of travel direction, as medium- and low-income countries are linked to an increased risk of disease [34]. Another significant factor that may contribute to the occurrence of MII is the low rate of specialist consultations before traveling to tropical regions. Among the patients observed, only one had consulted a tropical medicine specialist before the planned trip.

Conclusion and future prospect

In light of the growing popularity of trips to tropical regions, the analysis of factors responsible for MIIs seems crucial. A broader understanding of risk factors, alongside a thorough analysis of individual pathogens causing MIIs, could facilitate quicker patient diagnosis and enable more personalized treatment in the future. Currently, in most cases, the initial diagnosis, upon first contact with health services, is based on the assessment of symptoms reported by the patient and the clinical evaluation conducted by the medical facility staff. Travelers unprepared by a specialist in tropical diseases showed a higher incidence of mixed gastrointestinal infections. The situation is worsened by the limited experience in diagnosing and treating MIIs in hospitals and primary healthcare settings, where nonspecific symptoms resulting from a multitude of overlapping pathogenic factors may be improperly managed. To improve the situation, as the number of travelers to regions where exposure to MIIs is prevalent continues to rise, it would be beneficial for patients to have professional preparation for travel, including methods for preventing infections and guidance on actions to take if symptoms arise. To raise awareness, information should be conveyed by qualified medical personnel, travel agencies, and relevant government bodies. Thanks to these actions, it will be possible to significantly reduce the costs borne by hospitals in the future and improve the health outcomes of an increasingly mobile population.

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