Article received on December 15, 2019 and accepted for publishing on March 23, 2020.

ORIGINAL ARTICLES

Diagnostic challenges in gastrointestinal infections

Nicoleta Negrut[1], Shamim A. Khan[2], Simona Bungau[3], Dana C. Zaha[4], Corb A.R. Anca[4], Ovidiu Bratu[5], Camelia C. Diaconu[6], Florentina Ionita-Radu[7]

Abstract: *Gastrointestinal infections are among the most common infectious diseases found all over the world, varying depending on the etiological agent. Symptoms usually include diarrhea, vomiting, and abdominal pain. Water and electrolyte imbalance is the main consequence of gastrointestinal infections. Most of them are cured or self-limited in few days, but at the same time, for a specific population such as immunocompromised, elderly patients or new-borns, these infections are potentially severe. In this context, it is very important to identify the etiological agents of acute diarrhea for the appropriate treatment and infection control measures. While routine laboratory diagnosis of parasitic diarrhea still depends largely on microscopic examination of fecal samples, immunological and molecular methods are becoming increasingly commercially available and, in well-resourced settings, will ultimately displace traditional methods. The present paper presents some of the most common and well-known pathologies of this type, being a brief presentation of the variety of gastrointestinal diseases, each with characteristic clinical manifestations and diagnosis.*

Keywords: *gastrointestinal infections, Rotavirus, Salmonella, Shigella, Helicobacter pylori*

INTRODUCTION

Worldwide, acute gastrointestinal infections are the second most common infectious diseases after respiratory tract infections and a major cause of morbidity and mortality among infants and children [1]. Gastrointestinal infections can be caused by a large number of microorganisms present in the water, food, or hospital environment, that cause inflammation of different segments of the gastrointestinal tract. The prevalence of the different microorganisms causing gastroenteritis depends on several factors, such as age (children, adults), community or nosocomial acquisition, country (developing or developed), patients who have traveled abroad and immune status [2].

The common clinical picture usually looks like acute gastroenteritis, with a sudden or insidious onset, immediately after or after a while from returning to the country of origin. At the first presentation, it is important to identify the patient's journey, with detailed information on particular aspects of the trip. Failure in identification of the epidemiological link may lead to delayed diagnosis and treatment, with increased risks of complications. Empirical intervention is often important when there is a strong possibility of a certain condition and confirmatory lab tests

Corresponding author Simona Bungau
simonabungau@gmail.com

[1] Department of Psycho-Neuroscience and Recovery, Faculty of Medicine and Pharmacy, University of Oradea, Oradea
[2] Faculty of Medicine and Pharmacy, University of Oradea, Oradea
[3] Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Oradea
[4] Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea
[5] Clinical Department 3, University of Medicine and Pharmacy "Carol Davila", Bucharest 050474, Romania
[6] Department 5, "Carol Davila" University of Medicine and Pharmacy, Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest,Bucharest, Romania
[7] Department of Gastroenterology, University Emergency Central Military Hospital, Bucharest, Romania

are delayed or unavailable, especially for infections that are rapidly progressive or with prolonged testing duration [3].

Traveling for business and pleasure is a small proportion of the total movement of people. Modern transport ways allow more goods and people to travel around the world at a faster pace; they also open up the airways to the transcontinental movement of vectors for infectious diseases. While traveling, people carry their genetic profile, immunological sequelae from previous illnesses, cultural preferences, traditions, and patterns of behavior. They are also accompanied by microbes, animals and other biological lives [4]. The range of infectious diseases present at a certain time and in a certain region has increased, with the increasing travel possibilities from one country to another and between continents. Transiting through different geographical areas, in a short time (as with long-distance flights), may increase the risk of contamination with foreign etiological agents. Cities are becoming important centers for the transmission of infectious diseases due to international travel and migration, as shown by recent pandemics. Several factors contribute to infectious disease emergence. Others commonly listed include microbial adaptation and change, demographics and behaviour, changes in the environment, technology and economic development, deterioration of public health and surveillance programs, and international travel and trade [5].

Many tropical diseases havea polymorphic clinical feature, making the diagnosis difficult, especially for clinicians from countries outside tropical areas. In developing and developed countries, doctors in urban settings need to be aware of developments in infectious diseases. Upon travel, an ill traveler's history must analyze exposure specifics, including visited destinations, activities, ingestion of infected food or drink, contact with insects, livestock, freshwater or blood and body fluids and other possible exposures. Information on the geographic dissemination of infectious disease is significant in creating the differential diagnosis and testing [6].

The purpose of this paper is to make a brief review of the most common gastrointestinal infections, with their relevant clinical features and diagnosis.

GASTROINTESTINAL INFECTIONS

In the geographical area of Romania, southeastern Europe, Rotavirus, Salmonella species, Shigella species, Clostridium difficile, Escherichia coli and Giardia lamblia are the most common etiological agents of gastrointestinal infections [7-9]. Infections with Helicobacter pylori, Campylobacter spp., and other viruses are also frequent. Several tropical infectious diseases, such as amebiasis, malaria, leishmaniasis, dracunculiasis, schistosomiasis, brucellosis, leptospirosis, dengue fever, yellow fever and viral haemorrhagic fever, can have a digestive onset, requiring increased attention from the clinician. Experimental animal studies and clinical research have shown that the virulence of infectious microbial agents can have variable severity, sometimes being involved even in deaths because of sepsis [10, 11].

Viral gastrointestinal infections

The most important etiological viral agents of diarrhea are rotavirus, norovirus, adenovirus, astrovirus, sapovirus and enterovirus. Gastroenteritis caused by norovirus, asingle-stranded RNA (ssRNA) viruses belonging to the family of Caliciviridae, may manifest with severe nausea, vomiting and diarrhea. The genogroup I (GI), II (GII) and IV (GIV) of Rotaviruses (double stranded RNA) are the main cause of diarrhea in children under 5 yo and responsible for the death of around 200,000 children/year. Rotaviruses belong to the Reoviridae family [12]. Major symptoms are usually abdominal pain, vomiting and waterydiarrhea (AWD). Rotaviruses serogroups A, B, and C are responsible for human infections.

Adenoviruses cause respiratory diseases, bladder infections, conjunctivitis. Adenoviruses belong to Adenoviriadae family of double-stranded (dsDNA) viruses. Taking into consideration 51 serotypes of human adenoviruses (classified into six groups, from A to F), gastroenteritis is mainly caused by Adenoviruses serotype 40 and 41.

Astroviruses discovered in 1975 are single-stranded (ssDNA) viruses and belong to the family of Astroviridae; the incidence of these infections is constantly increasing [13]. Clinical signs include vomiting and severe diarrhea, with moderate dehydration. In developed countries, the Astrovirus infection incidence is between 2-9%, affecting mainly children [14]. To date, serotypes 1 - 5 are the most relevant. Serological studies indicate that most children infected with Astroviruses develop antibodies to the virus early in life, which provide protection against future infections.

Sapoviruses are part of the family of Caliciviridae and are major causative agents of gastroenteritis worldwide, causing disease in humans of all ages. The highest incidence was described for children under 5 year-old, but infections are diagnosed in adults as well, with diarrhea, vomiting, and fever (similar clinical symptoms to those of norovirus infections). However, self-limited sapovirus infections lead to less severe gastroenteritis compared to norovirus-induced gastroenteritis [15].

There is a variety of different subtypes of human enteroviruses, such as human enterovirus 70/71, poliovirus, Coxsackie virus A and B, echovirus, with different degrees of tissue tropism and virulence, although retaining a basic antigenic identity. Infections are usually asymptomatic or present with mild cold-like symptoms. Severe enterovirus infections are poliomyelitis, meningitis and myocarditis. Coxsackie viruses are present worldwide and can cause the so-called “summer diarrhoea”. Other severe infections with Coxsackie virus or human enterovirus 70/71 can lead to conjunctivitis and myocarditis, whereas echovirus infections can result in aseptic meningitis, with echovirus 30 being the most common meningitis-causing serotype in Europe, America and Asia [16, 17].

Viral hemorrhagic fever (VHF) is characterized by severe multiple organ dysfunction syndrome. Etiologically, four particular RNA viral families (Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae) lead to VHF. The viruses that cause VHFs are spread across most of the globe. Haemorrhagic viruses are considered as potential biological warfare agents. Initially, clinical symptoms include fever, cephalgia, myalgia, arthralgia and chills, which can lead to massive haemorrhages, shock or even acute multiple organ dysfunction. Paraclinical parameters show an increase in liver enzymes and a decrease in albumin levels. The coagulation panel shows an increase in prothrombin time and a decrease in fibrinogen. These results of the paraclinical tests may be similar to diseases like disseminated intravascular coagulation, malaria, haemolytic uremic syndrome. Although the confirmation of the diagnosis requires detection of viral RNA, viral antigens, or specific antibodies, the clinician must raise the suspicion quickly, before laboratory results, because these diseases require strict isolation measures and biosafety level 4 laboratory facilities [18].

Dengue fever is a global arboviral infection spread by the mosquito genus Aedes (A) (primarily A. aegypti, but also A. albopictus, and A. polynesiensis), a mosquito found in the tropical and subtropical regions of the world, also involved in spreading Zika virus disease, yellow fever, and Chikungunya. About 40% of the world population, almost 3 billion people live in regions with a dengue threat [19]. In more than 100 countries, people are affected by dengue fever resulting in up to 22,000 deaths per annum globally [20]. In 2018, Romania reported 4 cases of dengue fever, all travel-associated [21]. With incubation of 3-14 days, 50-80% of patients are asymptomatic during the period of illness [22]. Classic dengue fever (break-bone fever) is distinguished by high fever, severe cephalgia, myalgia, arthralgia, retro-orbital pain, abdominal pain or tenderness with persistent vomiting, and hepatomegaly. The diagnosis is supported by the combination of thrombocytopenia, leukopenia, modifications of the liver function tests and serological tests for dengue virus.

Yellow fever virus etiologically belongs to Flaviviridae family, which causes acute viral disease transmitted by A. aegypti, and Haemagogus mosquitoes. The name's "yellow" refers to jaundice that affects most patients. In tropical regions of Africa and Central and South America, the virus is endemic. In 2018, one case of yellow fever was reported by Romania [21]. Severe cases can have a mortality rate of up to 50% [23, 24]. With an incubation period of 3-6 days, clinical manifestations in the second phase, which generally affect liver and kidney, consist in fever, vomiting, abdominal pain, jaundice, dark urine, hemorrhage, and even shock. Yellow fever, especially during early stages, is difficult to diagnose, it can be mistaken for diseases like leptospirosis, fulminant forms of viral hepatitis, or even severe malaria. Confirmation of the diagnosis requires the detection of the virus by identifying viral ribonucleic acid (RNA), specific antigen or immunoglobulins M.

Digestive infections caused by protozoans and parasites

Parasitic infections causing diarrhea are particularly important in young children, immunocompromised patients, and those living in conditions of poor sanitation and hygiene, with unsafe food and water supplies. Travelers from developed countries are another group at risk, particularly susceptible to parasitic pathogens, because they lack protective immunity acquired from previous exposure. Several of these organisms are of zoonotic origin, and there may be occupational or recreational exposure risks [25].

Giardia lamblia, Cryptosporidium spp., Entamoeba histolytica and Dientamoeba fragilis are the most important diarrhoea-causing protozoans. Helminths are less important as agents of diarrhea, but they may produce loose or even dysenteric stools in acute or heavy infections (for example, intestinal schistosomiases). One important exception is the nematode Strongyloides stercoralis, which has the unusual capacity to maintain subclinical infections for years or decades, being discovered only when the patient is immunosuppressed for various reasons, when severe or potentially fatal disseminated infection may occur [26].

Giardia lamblia infections (synonym G. Intestinalis, G. duodenales) in developed countries occur in 6-8% of children and 2% of adults, and around 33% of the population is infected with protozoans [27, 28]. In the US for example, CDC estimated 77,000 cases/year of Giardiasis [29].

One of the several species of the genus Cryptosporidium is

Cryptosporidium parvum, which, together with C. hominis, are the most common cause's ofcryptosporidiosis in humans [29]. Similar clinical symptoms could reveal infections by other Cryptosporidium spp. such as C. felis, C. meleagridis, C. canis, and C. Muris.Around 748,000 cryptosporidiosis cases/year occurred in the US [30, 31].

The causative agent of amoebiasis is Entamoeba histolytica - the only human pathogenic species of the genus Entamoeba. Amebiasis has a worldwide distribution, prevalent in Central and South America, Africa, and Asia, being produced by trophozoites of Entamoeba histolytica.

Clinical manifestations can appear up to 4 months from the contact with contaminated food or objects. In about 90% of cases, the disease may evolve asymptomatic, self-limiting, with recurrences. The rest of the patients may have different severity clinical forms, such as acute colitis (bloody diarrhea, fever, abdominal pain), severe colitis (fulminant, abscesses), and chronic form (ameboma, and inflammatory bowel disease). The etiological diagnosis is based on the microscopic identification of cysts and trophozoites in the stool of the patients, specific antibodies and antigens detection. Around 50 million people worldwide suffer from amoebiasis each year, resulting in 100,000 deaths each year [32].

One of the most underestimated diarrhea-causing protozoansis Dientamoeba fragilis and recent studies demonstrated the direct implication as a common cause of gastrointestinal disease and, in the meantime, his pathogenic potential.The prevalence of Dientamoeba fragilis varies from 0.3% to 52% and often exceeds that of Giardia lamblia [33].

Malaria is produced by infection with Plasmodium species, by the bite of Anopheles mosquito, being recognized as the second cause of death by infections in Africa. According to the European Centre for Disease Prevention and Control (ECDC), Romania confirmed and reported 18 cases of malariain 2018 [21]. The disease is endemic in sub-Saharan Africa and South Asia and has an incubation period between 8-25 days, with a clinical picture dominated by cyclical fever. The following manifestations: insomnia, weakness, arthralgias, myalgias, diarrhoea, abdominal pain, headache, and hepatosplenomegaly can be associated with the fever in case of acute malaria. Classical clinical triad present in malaria consists of fever, splenomegaly, and anaemia. The microscopic examination of thin or thick blood smears, the detection of the parasite nucleic acid by real-time polymerase chain reaction assay, the identification of the plasmodium antigen by immunochromatography are specific tests used to confirm the diagnosis of malaria [34].

Leishmaniasis is a neglected tropical disease, protozoan vector-borne infection, whose transmission is through the bite of an infected female sand fly (Phlebotominespecies). It is present in environments ranging from tropical forests in South and Central America to desert areas in West Asia, including North of Africa with cutaneous leishmaniasis, which is the most common form, mucocutaneous, and visceral leishmaniasis, the last one being the most severe form of the disease. The period of incubation varies widely, from a few weeks to several months after the initial bite, depending on the species. The wide spectrum of clinical manifestations in visceral leishmaniasis includes fever, anorexia, abdominal pain, emesis, diarrhea, hepato-splenomegaly. Diagnostic findings are based on skin biopsy, tissue culture, and presence of antibodies [35].

Dracunculiasis, also known as Guinea worm disease, can be found in rural areas of South Sudan, Chad, Ethiopia, and Mali, which relies on contaminated water supplies. Clinical symptoms can take up to a year to appear, and may include painful blister centered on the worm, usually localized in the lower extremity, fever, nausea, vomiting, and local lymphadenopathy [36].

Schistosomiasis is a disease caused by parasitic worms (Genus Schistosoma), also known as bilharzia, which is endemic in tropical and subtropical areas and considered as one of the neglected tropical diseases. With an incubation period of about 2-8 weeks, the acute clinical picture presents a flu-like syndrome, nausea, vomiting, abdominal pain, bloody diarrhoea, hepatosplenomegaly, and lymph-adenopathy. Laboratory findings include the direct detection of eggs by the microscopic examination or of the parasite's nucleic acid in patients'stool and urine, and serological tests for identifying the specific antibodies in patients returned from endemic areas, but without eggs demonstrated in faecal or urine samples [37].

Digestive infections caused by bacteria

One of the most common bacterial causes of gastroenteritis worldwide is Campylobacter spp. frequent especially in children under 2 year-old, causing diarrhoea, abdominal cramps, vomiting, fever and even bleeding. It is usually generated by the consumption of raw or undercooked meat (frequent/especially poultry) or contaminated milk.

Up to 25% of cases of antibiotic-associated diarrhea in healthcare institutions and hospitals are generated by Clostridium difficile. Elderly and immunocompromised patients have a higher risk. The most recent emergence of highly toxigenic and resistant C. difficile strains has led to more severe outbreaks, increasing mortality and morbidity [38].

In the developing countries, especially among children, Escherichia coli is a major cause of diarrheal disease and the leading cause of travellers'diarrhoea. The infections are produced by drinking water contaminated with human or animal feces. A special strain of this genus is Escherichia coli O157:H7, a Shiga toxin producing. These bacteria generate gastrointestinal infections with symptoms including vomiting and sometimes even bloody diarrhoea. Although it is usually cured after a few days, a percentage of 5-10% of infections lead to haemolytic uremic syndrome and its consequences (destruction of blood platelets, anaemia, kidney failure) [39].

Helicobacter pyloriis the main cause of gastritis and is associated with the development of gastric and duodenal ulcers or even stomach cancers. H. Pylori is the strongest etiological factor in both of these conditions, with the World Health Organization classifying it as a class I carcinogen. According to the CDC, approximately two-thirds of the population is infected with H. pylori, but less than 20% have a risk of developing ulcers or stomach cancer [40]. On the other hand, infection with H. pylori may protect against some cancers, such as oesophageal adenocarcinoma and gastroesophageal reflux disease [41]. It can cause stomach pain or nausea, but in many cases, there are no symptoms.

Salmonella and Shigella are food-borne GI illnesses. Salmonella is common and is found in raw meats, poultry, seafood and eggs, as well as milk and dairy products. Acute symptoms include nausea, vomiting, abdominal cramps, diarrhea, fever, and headache. Shigella is frequently found in water polluted with human feces. Symptoms of shigellosis or bacillary dysentery include abdominal pain, cramps, diarrhoea, fever, vomiting, and blood, pus, or mucus in stool.

Yersinia enterocolitica is a cause of diarrhea and abdominal pain relatively frequent after eating contaminated food, especially raw or undercooked pork products, milk or ice cream. Common symptoms are fever, abdominal pain and diarrhea, which is often bloody.

The most common cause of food intoxication, characterized by violent onset, severe nausea, cramps, vomiting, and diarrhea is Staphylococcus aureus. It is also associated with a large range of food, and could be found on humans (infected cuts, skin, throats and noses).

Brucellosis is a zoonosis caused by four different species of Brucella. It is considered as a major infectious disease in the Caribbean, the Middle East, Eastern Europe, Asia, and Africa. According to ECDC, one case of brucellosis was reported by Romania, in 2018 [21].The incubation period is between 2 weeks to 5 months. General brucellosis signs are usually vague and flu-like, with gastrointestinal symptoms such as dyspepsia, diarrhoea, constipation, vomiting, abdominal pain, hepatic abscesses. However, the clinical picture is dominated by fever, with undetected aetiology through routine laboratory investigations. The diagnosis of brucellosis, although easy to confirm based on serological tests, often requires a period of up to one year, due to the presence of a polymorphic, sometimes oligo-symptomatic clinical picture.

Leptospirosis is a global zoonotic infection with a high prevalence in Caribbean and Pacific islands, Central and South America, Southeast Asia, predominantly during the rainy period, caused by pathogenic spirochetes of genus Leptospira. In 2018, 51 cases of leptospirosis were confirmed in Romania [21]. Usually the incubation period is 1-2 weeks. It presents with a wide range of clinical symptoms, which could be easily mistaken for other diseases, including flu-like syndrome, nausea, vomiting, diarrhoea, rash, dry cough, jaundice, hepatomegaly and splenomegaly, oliguria/anuria, haemorrhages, with the involvement of multiple organs. Suspicion occurs in the case of association between digestive, liver, kidney manifestations with fever, and myalgia. Confirmation requires the determination of specific antibodies.

DIAGNOSIS

In the presence of symptoms of a possible gastrointestinal infection, the diagnosis could be confirmed by different old and modern laboratory tests using stool specimens first and others such as serum for specific antibodies (serological tests). The standard culture to isolate bacteria remains the gold standard for bacterial pathogens, even if it has a relatively low sensitivity and it is time-consuming (more than 24 h), but it may be followed by antibiotic susceptibility testing. In this way, the therapeutic options may be evaluated, but also the assessment of microbial resistance to antibiotic therapy [42]. Ova or parasite examination are ordered in case of suspicion of parasites. For this purpose, a direct examination by microscopy or a concentration method is used, but it has a low sensitivity and it is, once again, time consuming and requiring specific training of the laboratory staff. In addition, there are antigen tests used to detect Clostridium difficile (GDH, toxins), Giardia lamblia, Cryptosporidium spp., Helicobacter pylori, or Entamoeba histolytica. However, antigen tests can only detect a few specific parasites and therefore cannot replace ova and parasite examination. Antigen tests are useful to rapidly detect viruses causing gastroenteritis, such as rotavirus and adenovirus; however, these tests are not available for all entero-pathogens and show a variable sensitivity.

Taking into account the wide range of pathogens that can

cause diarrhea and the similarity of the clinical manifestations produced by different pathogens; the molecular techniques seem to be the best tools for a rapid diagnosis. In the last years, some tools based on polymerase chain reaction (PCR) techniques have been developed to detect specific microorganisms or a panel of different entero-pathogens directly from stool samples [43-45]. Real-time PCR allows the simultaneous detection and differentiation of viral, bacterial and parasitic gastrointestinal pathogens. This assay also showed a high sensitivity for most pathogens included in the panel and efficient detection of coinfections. The main advantages of the molecular tools for the diagnosis of gastroenteritis are: high sensitivity, increased diagnostic spectrum, improved workflow (processing and diagnosis time is between 1 and 5 h), favorable impact on infection control and costs. Some disadvantages of molecular methods are the inability to distinguish between viable and nonviable microorganisms; they do not offer antibacterial susceptibility or epidemiological data; high cost; detection of the asymptomatic carriage could be difficult to distinguish from symptomatic/asymptomatic infections. Therefore, the application of these tools should be performed in patients selected based on clinical condition and/or the severity of gastroenteritis. Particularly in hospital settings, the rapid diagnosis provides important information for implementing infection control measures [46-48].

The clinical symptoms of all these diseases are nearly identical. Thus, it is difficult and almost impossible to determine the pathogenic cause based on clinical features alone. Rapid diagnosis, appropriate treatment, and infection control are important measures in these contexts. The early medical challenge is to include the possibility of tropical infectious diseases that are not common in the area, in the differential diagnosis. Not only the characterization of the symptoms but also the detection of infectious diseases based on a detailed history of the patient and a quick assessment can enormously help the clinicians in establishing a correct diagnosis and treatment.

Emerging evidence suggests that many gastrointestinal diseases are associated/caused by alterations in the gut microbiome. Specific microbiome signatures have been reported for irritable bowel syndrome and inflammatory bowel disease, and these have been associated with pro and anti-inflammatory effects, contributing to disruption or maintenance of gut homeostasis. Colorectal cancer is the third most common malignancy diagnosed worldwide, one of the leading causes for cancer-related mortality in both men and women. Different hereditary, environmental and inflammatory factors have been shown to increase the risk of colorectal tumorigenesis, but recently, bacteria and viruses have been described to be involved in colorectal carcinogenesis through direct modulation of epithelial cells, leading to genomic or chromosomal instability. Observational studies have found positive associations between gastric ulcers, periodontal disease, bacterial infections, and the risk of pancreatic cancer, the most rapid lethal cancer, with over 70% of patients dying within one year after diagnosis.

CONCLUSIONS

Concerning human mobility, several specific aspects must be considered, such as undiagnosed, atypical and subclinical types of diseases. These diseases are mistakenly treated as intercurrent diseases, and serious latent infections may develop. In the last few years, molecular methods have become readily available for many clinical laboratories and their utilization has resulted in a more rapid diagnosis and increased pathogens detection. As travel around the world continues, microbes will continue to evolve, adapting to new environmental conditions. The emergence of new infections will continue, and the distribution, severity and frequency of the identified infections will change, considering the new conditions. Travel or migration of people will continue to be an important factor in the occurrence and development of diseases. The analysis and monitoring of pathogens will focus the specialized actions and researches on the global movement and evolution of microbes. Integration of medical knowledge and multidisciplinary skills – social, biological and physical sciences – are therefore required.

References:

1. World Health Organization (WHO). Diarrhoeal disease. Fact Sheet no 330. Geneva: WHO; 2013 Apr. Available from: http://www.who. int/mediacentre/factsheets/fs330/en

2. Fletcher SM, McLaws ML, Ellis JT. Prevalence of gastrointestinal pathogens in developed and developing countries: systematic review and meta-analysis. J Public Health Res. 2013;2(1):42-53. doi:10.4081/jphr.2013.e9

3. Owen RL.Infections of the gastrointestinal tract. Gastroenterol. 2003; 125(5):1550-1551. doi https://doi.org/10.1016/ j.gastro.2003.05.007

4. Taylor, LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. Philos Trans Royal Soc Lond, Ser. B: Biol Sci. 2001; 29:983-989.

5. Tatem AJ, Rogers DJ, Hay SI. Global transport networks and

infectious disease spread. Adv Parasitol. 2006;62:293-343. doi:10.1016/S0065-308X(05)62009-X

6. WHO. Globalization and infectious diseases: A review of the linkages. Available from: https://www.who.int/tdr/publications/documents/seb_topic3.pdf

7. Codrean A, Dumitrascu DL, Codrean V, Tit DM, Bungau S, Aleya S, Rus M, Fratila O, Nistor Cseppento DC, Aleya L, Negrut N. Epidemiology of human giardiasis in Romania: a 14 years survey. Sci Total Environ. 2019; ID 135784. https://doi.org/10.1016/j.scitotenv.2019.135784

8. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier 2019.

9. Chiotan M. Boli infecțioase. 3th ed. Național; 2011.

10. Judea-Pusta CT, Bungau S, Buhas CL, Popa AR, Vesa CM, Buhas BA, Bardaca (Urducea) C, Tit DM, Abdel-Daim M, Judea, AS. Experimental study upon the virulence of infectious microbial agents involved in violent deaths presenting septic state. Rev Chim - Bucharest 2019; 70(8):2720-2726.

11. Abdel-Daim MM, El-Tawil OS, Bungau SG, Atanasaov AG. Applications of Antioxidants in Metabolic Disorders and Degenerative Diseases: Mechanistic Approach. Oxid Med Cell Longev. 2019; 2019: ID 4179676. https://doi.org/10.1155/2019/4179676

12. Clark A, Black R, Tate J, et al. Estimating global, regional and national rotavirus deaths in children aged <5 years: current approaches, new analyses and proposed improvements. PLoS One 2017; 12. doi: 10.1371/journal.pone.0183392.

13. Medici MC, Tummolo F, Calderaro A, Elia G, Banyai K. MLB1 astrovirus in children with gastroenteritis, Italy. Emerg Infect Dis. 2014; 20:169-170. doi.10.3201/eid2001.131259.

14. Bosch A, Pinto RM, Guix S. Human astroviruses. Clin Microbiol Rev. 2014; 27:1048-1074.doi: 10.1128/CMR.00013-14.

15. Oka T, Wang Q, Katayama K, Saifb LJ. Comprehensive Review of Human Sapoviruses. Clin Microbiol Rev. 2015; 28(1):32-53. doi.org/10.1371/journal.pone.0178157

16. Nougairede A, Bessaud M, Thiberville SD, Piorkowski G, Ninove L, Zandotti C, et al. Widespread circulation of a new echovirus 30 variant causing aseptic meningitis and non-specific viral illness, South-East France, 2013. J Clin Virol. 2014; 61(1):118-24. doi: 10.1016/j.jcv.2014.05.022.

17. McWilliam Leitch EC, Cabrerizo M, Cardosa J, Harvala H, Ivanova OE, Kroes AC, et al. Evolutionary dynamics and temporal/geographical correlates of recombination in the human enterovirus echovirus types 9, 11, and 30. J Virol. 2010; 84(18):9292-300.doi: 10.1128/JVI.00783-10.

18. WHO. Laboratory diagnosis and diagnostic tests, in Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition. Geneva, 2009. Available from: https://www.ncbi.nlm.nih.gov/books/NBK143156/

19. Smith SD, Mariano DJ, Trautwein ML. What is the global incidence of dengue? Emedicine.medscape.com. 2019. Available at: https://www.medscape.com/answers/215840-43482/what-is-the-global-incidence-of-dengue. Accessed 23.12.2019

20. Smith SD, Mariano DJ, Trautwein ML. Dengue. Emedicine.medscape.com. 2019. Available at: https://emedicine.medscape.com/article/215840-overview#a5 Accessed 23.12.2019.

21. European Centre for Disease Prevention and Control. Surveillance Atlas of Infectious Diseases. 2019. Available at: http://atlas.ecdc.europa.eu/public/index.aspx, accessed 23.12.2019

22. Kyle JL, Harris E. Global spread and persistence of dengue. Annu Rev Microbiol. 2008; 62:71-92. doi:10.1146/annurev.micro.62.081307.163005

23. Blyth DM. Yellow fever. Emedicine.medscape.com. 2019. Available from: https://emedicine.medscape.com/article/232244-overview Accessed 29.12.2019.

24. CDC – Yellow fever. Cdc.gov. 2017. Available from: https://www.cdc.gov/globalhealth/newsroom/topics/yellowfever/index.html Accessed 30.12. 2019.

25. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infect Dis. 2017;65(12):e45–e80. doi:10.1093/cid/cix669

26. Keiser PB, Nutman TB. Strongyloides stercoralis in the Immunocompromised Population. Clin Microbiol Rev. 2004;17(1):208-217. doi:10.1128/cmr.17.1.208-217.2004

27. Centers for Disease Control and Prevention 2011. Giardia Epidemiology & Risk Factors, http://www.cdc.gov/parasites/giardia/epi.html. Aufgerufen am 10.07.2012.

28. Sorokman TV, Sokolnyk SV, Popelyuk AMV, Bezruk TO, Bezruk VV, Popelyuk NO. Giardiasis in children: molecular genotyping, growth and calprotectin levels. Arch Balk Med Union. 2019;54(3):522-531

29. Food and Drug Administration (FDA) 2011. Bad Bug Book 2nd Edition. http://www.fda.gov/food/foodsafety/foodborneillness/foodborneillnessfoodbornepathogensnaturaltoxins/badbugbook/default.html.

30. Centers for Disease Control and Prevention. http://www.cdc.gov/parasites/crypto/biology.html. Accessed 07.03.2019.

31. Leitch GJ and Qing He. Cryptosporidosis - an overview. J Biomed Res. 2012, 25(1):1-16.doi: 10.1016/S1674-8301(11)60001-8

32. Fotedar R, Stark D, Beebe N, Marriott D, Ellis J, Harkness J. Laboratory diagnostic techniques for Entamoeba species. Clin Microbiol Rev. 2007, 20(3):511-532.

33. Stark D, Barratt J, Roberts T, Marriott D, Harkness J, Ellis J. A review of the clinical presentation of dientamoebiasis. Am J Trop Med Hyg.2010, 82(4):614-619. doi: 10.4269/ajtmh.2010.09-0478.

34. Nayyar GM, Breman JG, Newton PN, Herrington J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. Lancet Infect Dis. 2012 Jun;12(6):488-96. doi: 10.1016/S1473-3099(12)70064-6

35. Torres-Guerrero E, Quintanilla-Cedillo MR, Ruiz-Esmenjaud J, Arenas R. Leishmaniasis: a review. F1000Res.2017;6:750. doi:10.12688/f1000research.11120.1

36. Beyene HB, Bekele A, Shifara A, et al. Elimination of Guinea

Worm Disease in Ethiopia; Current Status of the Disease's, Eradication Strategies and Challenges to the End Game. Ethiop Med J. 2017;55(Suppl 1):15-31.

37. Nelwan ML. Schistosomiasis: Life Cycle, Diagnosis, and Control. Curr Ther Res Clin Exp. 2019;91:5-9. doi:10.1016/j.curtheres.2019.06.001

38. Bintsis T. Foodborne pathogens. AIMS Microbiol. 2017;3(3):529-563. doi:10.3934/microbiol.2017.3.529

39. Croxen MA, Law RJ, Scholz R, Keeney KM, Wlodarska M, Finlay BB. Recent advances in understanding enteric pathogenic Escherichia coli. Clin Microbiol Rev. 2013;26(4):822-880. doi:10.1128/CMR.00022-13

40. Centers for Disease Control and Prevention. "Helicobacter pylori: Fact Sheet for Health Care Providers." Updated July 1998. http://www.cdc.gov/ulcer/files/hpfacts.pdf. Accessed 30.12. 2019.

41. Blaser MJ. Disappearing Microbiota: Helicobacter pylori Protection against Esophageal Adenocarcinoma. Cancer Prev Res. 2008; 1(5):308-311.doi: 10.1158/1940-6207.CAPR-08-0170

42. Zaha DC, Bungau S, Aleya S, Tit DM, Vesa CM, Popa AR, Carmen P, Maghiar OA, Bratu OG, Furau C. Moleriu RD, Petre I, Aleya L. What antibiotics for what pathogens? The sensitivity spectrum of isolated strains in an intensive care unit. Sci Total Environ. 2019; 687:118-127. https://doi.org/10.1016/j.scitotenv.2019.06.076

43. Zhang H, Morrison S, Tang Y-W. Multiplex polymerase chain reaction tests for detection of pathogens associated with gastroenteritis. Clin Lab Med. 2015; 35(2):461-486.doi: 10.1016/j.cll.2015.02.006.

44. Spinu D, Bratu O, Marcu D, Mischianu D, et al. The use of ELISA and PCR in identifying correlations between viral infections and benign prostatic hypertrophy. Rev Chim. 2018; 69(3):645-649.

45. Spinu D, Bratu O, Popescu R, Marcu D, Radulescu A, Mischianu D. Clostridium difficile-an emerging plague. Rom J Mil Med, 2015, 118(3): 12-15.

46. Crisu GC. Ionita-Radu F, Costache RS, et al. Efficacy and safety of Ombitasvir/Paritaprevir/Ritonavir+ Dasabuvir and Ribavirin in patients with compensated HCV cirrhosis. Rom J Mil Med, 2019, 122(1): 22-26.

47. Popescu AL, Ionita-Radu F, Jinga M, et al. Laparoscopic sleeve gastrectomy and gastroesophageal reflux Rom J Int Med, 2018, 56(4): 227-232.

48. Foster GR, Coppola C, Derbala M, et al. Impact of Safety-Related Dose Reductions or Discontinuations on Sustained Virologic Response in HCV-Infected Patients: Results from the GUARD-C Cohort. PLOS ONE, 2016, 11(3), Article Number: e0151703.