Revista Argentina de Microbiología 57 (2025) 98–104

asociación argentina de microbiología

REVISTA ARGENTINA DE MICROBIOLOGÍA

www.elsevier.es/ram

ORIGINAL ARTICLE

Use of stool molecular panel in hospitalized patients with diarrhea. Experience in a tertiary care center

Nicolás Cimmino [a,*], **Maria Josefina Etchevers** [a], **Astrid Smud** [b], **Patricia Yolleth Andrade Pino** [b], **Marisa del Lujan Sanchez** [b], **Maria Laura Gonzalez** [a], **Maria Victoria Acosta** [c], **Gissel Zuñiga** [c], **Karina Alejandra Perez** [c], **Juana Freggiaro** [c], **Valeria Rosa Alexander** [c], **Maria Florencia Veiga** [c], **Mariangeles Visus** [c], **Mariano Martin Marcolongo** [a]

[a] *Servicio de Gastroenterologia del Hospital Italiano de Buenos Aires, Argentina*
[b] *Servicio de Infectologia del Hospital Italiano de Buenos Aires, Argentina*
[c] *Servicio de Bioquimica del Hospital Italiano de Buenos Aires, Argentina*

Received 3 December 2023; accepted 18 October 2024
Available online 5 December 2024

KEYWORDS
PCR multiplex;
FilmArray;
Diarrhea;
Immunosuppressed

Abstract Infectious diarrhea is a common health issue that affects a large number of individuals each year. It causes significant morbidity and mortality, greatly impacting healthcare system costs. Rapid detection of the causative organism and timely treatment alters the management and outcome of the condition. Molecular panels in stool allow to analyze a wide range of pathogens quickly and easily. For this study, a cross-sectional cohort analysis with a retrospective analysis of adult patients hospitalized with diarrhea and negative conventional stool bacteriological studies was conducted. Data obtained from the use of molecular panels in stool and the role of endoscopy in the diagnostic pathway were analyzed. A positivity rate of 52% (n = 41) out of a total of 79 samples was reported. The test contributed to a change in therapeutic approach in 58% (n = 46) of the patients. Among the patients with a negative molecular panel, 39.5% underwent further evaluation with colonoscopy involving biopsies, resulting in a diagnostic yield of 87%. Based on these results, we can conclude that molecular techniques contribute to the diagnosis and change in therapeutic approach in hospitalized patients with diarrhea.

* Corresponding author.
E-mail address: nicolas.cimmino@hospitalitaliano.org.ar (N. Cimmino).

https://doi.org/10.1016/j.ram.2024.10.005

PALABRAS CLAVE
PCR multiplex;
Filmarray;
Diarrea;
Inmunosuprimidos

Uso del panel molecular fecal en pacientes internados con diarrea. Experiencia en un centro de tercer nivel

Resumen La diarrea infecciosa es una problemática de salud frecuente que afecta a una gran cantidad de personas al año. Esta ocasiona una importante morbimortalidad, con un impacto significativo en los costos de los sistemas de salud. Es por esto que una rápida detección del organismo causal y un tratamiento oportuno pueden cambiar el manejo y la evolución del cuadro. Los paneles moleculares para muestras de materia fecal nos permiten analizar una amplia gama de patógenos en forma rápida y sencilla. En este estudio se evaluó una cohorte transversal mediante un análisis retrospectivo de pacientes adultos internados con diarrea y resultados bacteriológicos fecales negativos por estudios convencionales. Se analizaron los datos obtenidos con el uso de paneles moleculares en materia fecal y el rol de la endoscopía en el proceso diagnóstico. Con el panel molecular, se reportó una tasa de positividad del 52% (n = 41) sobre 79 muestras. La prueba contribuyó a un cambio de conducta terapéutica en el 58% (n = 46) de los pacientes. De los pacientes con panel molecular negativo, en un 39,5% se continuó su estudio con colonoscopia con biopsias; el rédito diagnóstico de esta última fue del 87%. A partir de estos resultados, podemos concluir que la técnica molecular contribuye al diagnóstico y el cambio de conducta terapéutica en pacientes internados con diarrea.

Introduction

Diarrhea is the eighth leading cause of death globally across all age groups, thus becoming a public health concern.

The morbidity and mortality from this cause vary widely, depending on the comorbidities present in the individual suffering from this condition, the most vulnerable being the immunosuppressed[9,10,14,16] who commonly need hospitalization due to the impact on their overall health.

The advance in molecular technologies has led to the development of diagnostic techniques by PCR in stool samples which over time evolve into multiplex PCR panels. These have allowed to analyze a wide range of pathogens in stool with a rapid result (within hours). At the moment there are no cost-effectiveness studies to recommend their use at the beginning of the study in a diarrheal episode[4,8,17].

In this sense, various guidelines have been created on the best way to study infectious diarrhea[11]. However, none of them establishes an optimal timing for the use of multiplex PCR techniques in the algorithm. Some guidelines recommend their use in immunosuppressed patients with diarrhea or immunocompetent patients with severe, inflammatory or persistent diarrhea[19].

Regarding the endoscopic role in the management of diarrhea, there is still no consensus, its main indication being in immunosuppressed patients with persistent diarrhea and multiple negative tests for the detection of microorganisms[18,20,22].

Considering the aforementioned, in this study, we aimed to analyze the results and implications of using multiplex PCR techniques (FilmArray GI® by bioMerieux in stool samples) in hospitalized patients in a high-complexity center, a reference in solid organ transplant and bone marrow transplant.

We will focus on demonstrating whether the use of this technique in hospitalized patients shows a benefit or leads to a change in the employed therapy approach compared to the use of traditional technologies as well as describing the endoscopic role in this scenario.

Aims

Primary, to describe the results obtained with the use of multiplex PCR in hospitalized patients with diarrhea in a high-complexity health center and its impact on medical management. Secondary, to describe the microorganisms detected by the different diagnostic techniques in the various studied populations, to evaluate the diagnostic yield of the technique in immunocompetent and immunosuppressed populations, to analyze the impact on the patient's therapy following the multiplex PCR result, to describe the usefulness of colonoscopy in patients with multiplex PCR analysis, and to determine the frequency of co-infections.

Materials and methods

A descriptive observational study was conducted on a cross-sectional cohort with a retrospective approach, which included a period from January 2020 to May 2023.

Of the total samples processed using molecular techniques, those belonging to hospitalized patients with diarrhea over 18 years old, as per hospital protocol, were included.

Eighty multiplex PCR samples were obtained, one of which was excluded due to an invalid result. The 79 PCR samples obtained belonged to a total of 73 patients. The difference is due to some patients having more than one

hospitalization during the study period, requiring more than one PCR technique.

The population was subanalyzed based on their immunological status.

Hospital protocol for the study of diarrhea in immunocompetent individuals

The study begins with a stool culture, the analysis of *Clostridium difficile* toxins A and B, GHD (glutamate dehydrogenase), and stool parasitology (routine techniques). Treatment is determined based on positivity in any of these techniques.

If routine techniques yield negative results and symptoms persist, they are repeated.

If diarrhea persists (more than 72 h) or has an impact on the patient's overall condition (dehydration, hypotension, or alteration of internal environment), a decision is made with the infectious diseases service to perform multiplex PCR on stool.

If molecular techniques yield negative results, a colonoscopy is performed if clinical conditions allow, to rule out non-infectious causes.

Hospital protocol for the study of diarrhea in immunosuppressed individuals

At the onset of diarrhea, if the patient is clinically stable, the study begins with routine techniques and proceeds in a similar manner to that used for immunocompetent patients.

If the patient shows a decline in his/her general condition, the study is carried out jointly with the infectious diseases service using multiplex PCR at the onset.

If stool molecular techniques yield negative results, a colonoscopy is performed if clinical conditions allow, to rule out the presence of graft-versus-host disease, cytomegalovirus, or other non-infectious causes.

Therapeutic management change

A therapeutic strategy change was defined as the rotation of antibiotic regimen, discontinuation of antibiotics initiated prior to the analysis of stool using molecular techniques, and modification of immunosuppressive strategy.

Multiplex PCR panel

A FilmArray GI® (bioMerieux) multiplex PCR panel was used, which analyzes 22 microorganisms including bacteria, viruses and parasites.

The analyzed microorganisms are the following: *Campylobacter* (*C. jejuni*, *C. coli* and *C. upsaliensis*), *C. difficile* A/B toxin, enteroaggregative *Escherichia coli* (EAEC), Shiga toxin-producing *E. coli* (STEC) stx1/stx2, *E. coli* O157, *Shigella*/enteroinvasive *E. coli* (EIEC), enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC) lt/st, *Plesiomonas shigelloides*, *Salmonella*, *Vibrio* (*V. parahaemolyticus*, *V. vulnificus* and *V. cholerae*), *Yersinia enterocolitica*, *Cryptosporidium*, *Cyclospora cayetanensis*, *Entomoeba histolytica*, *Giardia lamblia*, Adenovirus 40/41, Astrovirus, Norovirus GI/GII, Rotavirus A, Sapovirus (I, II, IV and V).

Study procedure/data collection

Patient data was obtained from the laboratory stool molecular panels. The medical records of hospitalized patients who underwent multiplex PCR testing on stool samples were reviewed to collect the following information: demographic data, immunosuppression status, type of diarrhea, associated symptoms, molecular panel results and analyses performed to study their diarrhea, including endoscopies.

Statistical analysis

Data was cleaned by searching for errors and missing information. All variables were checked for extreme values, ranges, and possible inconsistencies. A statistical analysis was performed using descriptive statistics. Continuous variables were analyzed using appropriate measures of centrality (mean or median) and dispersion (standard deviation or interquartile range) based on their distribution.

Ethical considerations

Access to personal information was restricted to the study coordinator and authorized personnel when necessary to verify the study data and procedures, but always maintaining its confidentiality in accordance with the current legislation.

The study was carried out following the principles established in the Declaration of Helsinki and good clinical practice standards. The supplementary examinations performed in this study were procedures usually performed by the patients' attending physicians. No new tests or treatments were requested; therefore, no additional expenses were generated for the care of each patient.

Results

Basic characteristics of the population

Eighty (80) multiplex PCR samples were included. One sample was excluded due to an invalid result. The 79 selected samples correspond to a total of 73 patients. Forty-three percent (43%) were women and the median age was 53 years (IQR 32–65). The diarrhea presented at the time of the study was primarily acute diarrhea 64.6%, with the main concomitant symptoms being abdominal pain 36.9% (n = 41), fever 30% (n = 33) and vomiting 19% (n = 21), respectively; 74.7% of the patients were immunosuppressed (n = 59) and their main causes of immunosuppression were solid organ transplant and bone marrow transplant. The most frequently associated immunosuppressants were tacrolimus, corticosteroids and mycophenolate. The remaining basic characteristics are shown in Table 1.

It was observed that in 69.62% (n = 55) of the cases, the reason for hospitalization was diarrhea, while the remaining group consisted of patients who developed diarrhea during hospitalization and were subsequently studied for it. Of

Table 1 Basic characteristics of the patients studied with multiplex PCR.

	Overall (n = 79)
Women	43.03% (34)
Age, years (median)	53 (IQR 32–65)
Types of diarrhea	
Acute	64.55% (51)
Subacute	15.18% (12)
Chronicle	20.25% (16)
Associated symptoms	(n = 111)
Vomiting	21 (18.92%)
Dysentery	9 (8.11%)
Fever	33 (29.73%)
Abdominal pain	41 (36.94%)
Hypotension	1 (0.90%)
Dehydration	6 (5.41%)
Immunosuppressed	74.68% (n = 59)
Reason for immunosuppression	(n = 59)
Solid organ transplant	24 (40.68%)
Bone marrow transplant	14 (23.73%)
Oncological	9 (15.25%)
Inflammatory bowel disease	6 (10.17%)
HIV	3 (5.08%)
Other autoimmune diseases	2 (3.39%)
Severe malnutrition	1 (1.69%)
Immunosuppressants	
Tacrolimus	34
Corticosteroids	33
Mycophenolate	16
Cyclophosphamide	3
Methotrexate	3
Azathioprine	3
Everolimus	2

the total number of patients hospitalized due to diarrhea, 74.55% were immunosuppressed.

We also observed that the median length of hospital stay for patients whose reason for admission was diarrhea was 8 days (IQR 4–13), and that for these same patients, the median time to request PCR testing according to the hospital protocol was 1 day (IQR 1–2).

Multiplex PCR results

In 51.9% (n = 41) of the total population samples, pathogens were detected in stool samples. The most frequent ones were: *C. difficile* (n = 13), enteropathogenic *E. coli* (EPEC) (n = 11), and Norovirus (n = 11). The remaining results are listed in Table 2.

In the immunosuppressed population the detection rate was 47.45% (n = 28). The most frequent detected microorganisms were: enteropathogenic *E. coli* EPEC (n = 10), Norovirus GI/GII (n = 10) and *C. difficile* (n = 7). The remaining results are listed in Table 3. On the other hand, in the immunocompetent population, the detection rate was 65% (n = 13). The most frequent detected microorganisms were: *C. difficile* (n = 6), *Campylobacter* (n = 2) and enteroinvasive *E. coli* (n = 2). The remaining results are listed in Table 3.

Table 2 Microorganisms detected by multiplex PCR technique.

Overall	n = 60	%
C. difficile	13	21.67%
Enteropathogenic *E. coli* EPEC	11	18.33%
Norovirus GI/GII	11	18.33%
Campylobacter	8	13.33%
Enteroaggregative *E. coli* EAEC	3	5.00%
Enteroinvasive *E. coli* EIEC	3	5.00%
Salmonella	3	5.00%
Shiga toxin-producing *E. coli* (STEC)	2	3.33%
Adenovirus 40/41	1	1.67%
Cryptosporidium	1	1.67%
Enterotoxigenic *E. coli*	1	1.67%
Giardia lamblia	1	1.67%
Sapovirus	1	1.67%
Shigella	1	1.67%

Undetected microorganisms: Astrovirus, *Cyclospora cayetanensis*, *E. coli* O157, *Entamoeba histolytica*, *Plesiomonas shigelloides*, Rotavirus A, *Vibrio*, *Vibrio cholerae*, *Yersina enterocolitica*.

In the total samples, it was observed that the majority detected only one microorganism (n = 27). However, regarding co-infections of more than one pathogen, they were mainly of two (n = 24.4). In this particular group, the most frequent association was bacteria/bacteria (*Campylobacter*/EPEC) with 60% (n = 6/10), while the remaining cases involved bacteria/virus.

Change in medical management

Following the results of the multiplex PCR, the medical management was evaluated, revealing a change in therapy in 58.2% (n = 46) of cases. Of the total therapeutic changes made, 60.9% (n = 28) required an alteration in antibiotic regimen, 15.2% (n = 7) required a change in immunosuppression, and 4.35% (n = 2) discontinued antibiotic treatment. A total of 19.6% (n = 9) continued with the same treatment. The remaining 41.8% (n = 33) did not require any of the aforementioned changes.

Endoscopic role in diarrhea

A total of 16 colonoscopies was performed, 15 of which were conducted on patients with negative PCR results for microorganism detection. Out of all the studies performed, a diagnosis was reached via endoscopy involving biopsies in 87.5% (n = 14/16) of cases: graft-versus-host disease (n = 5), inflammatory bowel disease (n = 4), microscopic colitis (n = 3), and cyytomegalovirus (n = 2).

It is noteworthy that endoscopically normal mucosa was observed in 60% of patients (9/15), and among them, diagnosis was obtained through the microscopic analysis of biopsies taken randomly from sectors in 77.8% (7/9) of cases.

Table 3 Comparative multiplex PCR results between immunosuppressed and immunocompetent individuals.

	Immunosuppressed	%	Immunocompetent	%
Negative	31	40.79%	7	31.82%
Enteropathogenic *E. coli* EPEC	10	13.16%	1	4.55%
Norovirus GI/GII	10	13.16%	1	4.55%
C. difficile	7	9.21%	6	27.27%
Campylobacter	6	7.89%	2	9.09%
Enteroaggregative *E. coli* EAEC	2	2.63%	1	4.55%
Salmonella	2	2.63%	1	4.55%
Shiga toxin-producing *E. coli* (STEC)	2	2.63%	0	0.00%
Enteroinvasive *E. coli* EIEC	1	1.32%	2	9.09%
Enterotoxigenic E. coli ETEC	1	1.32%	0	0.00%
Cryptosporidium	1	1.32%	0	0.00%
Giardia lamblia	1	1.32%	0	0.00%
Adenovirus 40/41	1	1.32%	0	0.00%
Sapovirus	1	1.32%	0	0.00%
Shigella	0	0.00%	1	4.55%

Undetected microorganisms: *Plesiomonas shigelloides*, *E. coli* O157, *Vibrio*, *Vibrio cholerae*, *Yersinia enterocolitica*, *Cyclospora cayetanensis*, *Entamoeba histolytica*, Astrovirus, Rotavirus A.

Discussion

Diarrhea is a common health issue and is the main manifestation associated with immune-related complications in patients[21]. It is not uncommon for it to be severe, persistent, or refractory to treatment, causing dehydration, malabsorption, and malnutrition, necessitating a correct and early diagnostic approach. Despite its high incidence, there is limited data on its epidemiology, prevalent etiological agents, and appropriate management[9,10,14,16].

The role of gastrointestinal molecular panels in the study of this condition is not well established. A retrospective analysis[7] examining the indications for Filmarray in stool and subsequent clinical management showed that microorganisms were isolated in only 20.2% (n = 629) of outpatient cases, with a clinical management change indication of 2.9% for antibiotic therapy and 5.2% for overall clinical management change. In our selected patient series with negative routine fecal studies, the yield was much higher, leading us to believe that if appropriately determined which patients would benefit, it could be of greater utility. Our report predominantly included patients with severe immunocompromise and, to a lesser extent, immunocompetent patients with severe, inflammatory, or persistent diarrhea.

The prevalence of diarrhea with an infectious etiology varies between 30% and 76.7%, differences that could be attributed to the number of microbiological studies and invasive procedures performed to reach a diagnosis[2,5,15]. The reported etiological agents differ in most cases, primarily being opportunistic pathogens or bacteria. Local data obtained from a study[6] conducted on 52 transplanted patients (renal and renopancreatic) showed a diagnosis of infectious etiology in only 36% of cases after a long series of studies. Another relevant point is that almost all patients had received empirical antibiotic treatment, and in approximately one-third, the immunosuppressive treatment was modified. In our series, the positivity of the gastrointestinal panel exceeded this value, reaching almost 52%. Furthermore, obtaining an infectious etiology diagnosis allowed for the suspension or adjustment of empirical treatment, improving the rational use of antibiotics in this population[1,13].

Regarding the detection of *C. difficile* in our sample, we can observe that although the previous search for toxin A and B was negative as part of the study according to the hospital protocol, positive results were obtained using the DNA detection technique for the microorganism. These results, similar to those with other microorganisms, do not necessarily imply causality of the symptoms; therefore, PCR techniques must be evaluated alongside the clinical context of each patient[12].

Another important advantage of the method lies in the improved management of institutional isolations. Upon admitting a patient with diarrhea to a hospital, given the suspicion or confirmation of certain pathogens (e.g., *C. difficile*, *Salmonella* or Norovirus), the patient must remain in isolation to avoid an outbreak within the hospital. Having an early report of the causative agent of diarrhea, especially in health centers without individual rooms, allows for a rapid de-isolation of patients who do not harbor pathogens with the potential to spread, thereby reducing associated costs. A study[3] showed that the amount of time spent in a single room was 1.8 days (95% CI: 1.5–2.2) in the group in which molecular techniques were used compared to 2.6 days in the control group (2.2–3.0), $p = 0.0017$. And the indication for time spent in isolation was 0.6 days (0.3–1.8) in the PCR group compared to 2.2 days (1.2–3.2) in the control group ($p < 0.0001$)[3].

It should be noted that in cases of persistent diarrhea with negative microbiological studies, colonoscopy plays a significant role in the management of these patients. Even in the absence of macroscopic involvement, random biopsies taken during the procedure can help determine the diagnosis[18,20,22].

Regarding the role of endoscopy in hospitalized patients with diarrhea, it is noteworthy that in our study, the use of a fecal molecular panel allowed us to select which patients benefit from this invasive study. Of the endo-

scopies performed, over 85% led to a diagnosis. As previously described, biopsy sampling is important regardless of endoscopic macroscopic findings when performed for a diarrhea study. In our cohort, over half of the studies were endoscopically normal with a high microscopic diagnosis rate close to 80%. These data reinforce the importance of taking sectoral biopsies in this selected group of patients with diarrhea, even if no macroscopic pathological findings are observed.

This series of patients has its limitations. It is a single-center study with a retrospective and observational design, which is why it presents biases and does not allow us to evaluate the true dimension of the problem. However, it provides relevant information on the real-life usefulness of multiplex PCR techniques for the management of hospitalized patients with diarrhea, providing data on the distribution of different etiologies. Despite the sample size, it submits valuable information for our center and other healthcare facilities that treat patients with similar characteristics.

Conclusion

Molecular techniques in stool samples significantly contribute to the diagnosis and change in medical conduct, regardless of the immunological status in patients hospitalized with diarrhea. They also allow a quick and accurate diagnosis. The data provided in this study could serve as a starting point for new studies that develop and evaluate diagnostic and therapeutic algorithms, in order to reduce the use of empirical antibiotic treatments and optimize diagnostic resources and decision-making timelines.

Funding

This research has not received any specific grants from agencies in the public, commercial, or non-profit sectors.

Conflict of interest

None declared.

References

1. Arslan H, Inci EK, Azap OK, Karakayali H, Torgay A, Haberal M. Etiologic agents of diarrhea in solid organ recipients. Transpl Infect Dis. 2007;9:270–5, http://dx.doi.org/10.1111/j.1399-3062.2007.00237.x.
2. Bauer TM. Derivation and validation of guidelines for stool cultures for enteropathogenic bacteria other than *Clostridium difficile* in hospitalized adults. J Am Med Assoc. 2001;285:313, http://dx.doi.org/10.1001/jama.285.3.313.
3. Brendish NJ, Beard KR, Malachira AK, Tanner AR, Sanga-Nyirongo L, Gwiggner M, Cummings JRF, Moyses HE, Clark TW. Clinical impact of syndromic molecular point-of-care testing for gastrointestinal pathogens in adults hospitalised with suspected gastroenteritis. Lancet Infect Dis. 2023;23:945–55, http://dx.doi.org/10.1016/s1473-3099(23)00066-x.
4. Buss SN, Leber A, Chapin K, Fey PD, Bankowski MJ, Jones MK, Rogatcheva M, Kanack KJ, Bourzac KM. Multicenter evaluation of the BioFire FilmArray gastrointestinal panel for etiologic diagnosis of infectious gastroenteritis. J Clin Microbiol. 2015;53:915–25, http://dx.doi.org/10.1128/jcm.02674-14.
5. Valencia-Shelton F, Anderson N, Palavecino EL, Navas ME, Larkin PMK, She R, Filkins LM. Approaches to developing and implementing a molecular diagnostics stewardship program for infectious diseases: an ASM Laboratory Practices Subcommittee report. J Clin Microbiol. 2024;62:e0094124, http://dx.doi.org/10.1128/jcm.00941-24.
6. Carena AA, Boughen S, Gagliardi MI, Galante M. Diarrea aguda en trasplantes renales y reno-pancreáticos [Acute diarrhea after kidney or kidney-pancreas transplantation]. Medicina (B Aires). 2015;75:29–36 [in Spanish; PMID: 25637897].
7. Clark SD, Sidlak M, Mathers AJ, Poulter M, Platts-Mills JA. Clinical yield of a molecular diagnostic panel for enteric pathogens in adult outpatients with diarrhea and validation of guidelines-based criteria for testing. Open Forum Infect Dis. 2019;6:ofz162, http://dx.doi.org/10.1093/ofid/ofz162.
8. Cybulski RJ Jr, Bateman AC, Bourassa L, Bryan A, Beail B, Matsumoto J, Cookson BT, Fang FC. Clinical impact of a multiplex gastrointestinal polymerase chain reaction panel in patients with acute gastroenteritis. Clin Infect Dis. 2018;67:1688–96, http://dx.doi.org/10.1093/cid/ciy357.
9. Dionne JC, Mbuagbaw L. Diarrhea in the critically ill: definitions, epidemiology, risk factors and outcomes. Curr Opin Crit Care. 2023;29:138–44, http://dx.doi.org/10.1097/mcc.0000000000001024.
10. Gioco R, Corona D, Ekser B, Puzzo L, Inserra G, Pinto F, Schipa C, Privitera F, Veroux P, Veroux M. Gastrointestinal complications after kidney transplantation. World J Gastroenterol. 2020;26:5797–811, http://dx.doi.org/10.3748/wjg.v26.i38.5797.
11. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, Hennessy T, Griffin PM, DuPont H, Bradley Sack R, Tarr P, Neill M, Nachamkin I, Reller LB, Osterholm MT, Bennish ML, Pickering LK. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis. 2001;32:331–51, http://dx.doi.org/10.1086/318514.
12. Levine MM, Robins-Browne RM. Factors that explain excretion of enteric pathogens by persons without diarrhea. Clin Infect Dis. 2012;55 suppl_4:S303–11, http://dx.doi.org/10.1093/cid/cis789.
13. Maes B, Hadaya K, de Moor B, Cambier P, Peeters P, de Meester J, Donck J, Sennesael J, Squifflet JP. Severe diarrhea in renal transplant patients: results of the DIDACT study. Am J Transplant. 2006;6:1466–72, http://dx.doi.org/10.1111/j.1600-6143.2006.01320.x.
14. Naymagon S, Naymagon L, Wong S-Y, Ko HM, Renteria A, Levine J, Colombel J-F, Ferrara J. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. Nat Rev Gastroenterol Hepatol. 2017;14:711–26, http://dx.doi.org/10.1038/nrgastro.2017.126.
15. Nikolic D, Richter SS, Asamoto K, Wyllie R, Tuttle R, Procop GW. Implementation of a clinical decision support tool for stool cultures and parasitological studies in hospitalized patients. J Clin Microbiol. 2017;55:3350–4, http://dx.doi.org/10.1128/jcm.01052-17.
16. Pant C, Deshpande A, Larson A, O'Connor J, Rolston DDK, Sferra TJ. Diarrhea in solid-organ transplant recipients: a review of the evidence. Curr Med Res Opin. 2013;29:1315–28, http://dx.doi.org/10.1185/03007995.2013.816278.
17. Rand KH, Tremblay EE, Hoidal M, Fisher LB, Grau KR, Karst SM. Multiplex gastrointestinal pathogen panels: implications for infection control. Diagn Microbiol Infect Dis. 2015;82:154–7, http://dx.doi.org/10.1016/j.diagmicrobio.2015.01.007.
18. Rice JP, Spier BJ, Cornett DD, Walker AJ, Richie K, Pfau PR. Utility of colonoscopy in the evaluation of diarrhea in solid organ transplant recipients. Transplantation. 2009;88:374–9, http://dx.doi.org/10.1097/tp.0b013e3181ae98ab.
19. Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, Langley JM, Wanke C, Warren CA, Cheng AC, Cantey

J, Pickering LK. 2017 Infectious diseases society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65:e45–80, http://dx.doi.org/10.1093/cid/cix669.

20. Shen B, Khan K, Ikenberry SO, Anderson MA, Banerjee S, Baron T, Ben-Menachem T, Cash BD, Fanelli RD, Fisher L, Fukami N, Gan SI, Harrison ME, Jagannath S, Lee Krinsky M, Levy M, Maple JT, Lichtenstein D, Stewart L, Strohmeyer L, Dominitz JA. The role of endoscopy in the management of patients with diarrhea. Gastrointest Endosc. 2010;71:887–92, http://dx.doi.org/10.1016/j.gie.2009.11.025 [Epub 25.03.10; PMID: 20346452].
21. Troeger C, Blacker BF, Khalil IA, Rao PC, Cao S, Zimsen SRM, Albertson SB, Stanaway JD, Deshpande A, Abebe Z, Alvis-Guzman N, Amare AT, Asgedom SW, Anteneh ZA, Antonio CAT, Aremu O, Asfaw ET, Atey TM, Atique S, Reiner RC Jr. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18:1211–28, http://dx.doi.org/10.1016/s1473-3099(18)30362-1.
22. Wahnschaffe U, Ignatius R, Loddenkemper C, Liesenfeld O, Muehlen M, Jelinek T, Burchard GD, Weinke T, Harms G, Stein H, Zeitz M, Ullrich R, Schneider T. Diagnostic value of endoscopy for the diagnosis of giardiasis and other intestinal diseases in patients with persistent diarrhea from tropical or subtropical areas. Scand J Gastroenterol. 2007;42:391–6, http://dx.doi.org/10.1080/00365520600881193.