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Review

Acute infectious gastroenteritis in childhood: the role of rapid multiplex molecular syndromic panels in diagnosis and clinical management

Gastroenteritis infecciosa aguda en la infancia: el papel de los paneles moleculares sindrómicos múltiples rápidos en el diagnóstico y manejo clínico

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Abstract

Acute infectious diarrhea is a major global health issue, especially in children, as gastrointestinal infections are the second most common infectious disease after respiratory infections. The implementation of rapid multiplex molecular syndromic panels (RMMSP) for the comprehensive detection and identification of enteric pathogens in stool samples has enhanced diagnostic precision, supplementing—or, in some cases, replacing—traditional methodologies. This narrative, non-systematic review synthesized the available evidence on the clinical performance of gastrointestinal RMMSP up to December 31, 2024. On May 27, 2024, specialists in Pediatrics and Microbiology met to assess the use of RMMSP in pediatric gastrointestinal infection diagnosis.

This review focused on RMMSP applicable to urgent management of infectious acute gastroenteritis (AGE), excluding those panels unsuitable for immediate diagnosis. RMMSP facilitated rapid pathogen detection in pediatric infectious AGE and have shown potential advantages over traditional microbiological methods, including a reduction in time to appropriate treatment. Their use appeared particularly useful in emergency and inpatient settings for inflammatory AGE, prolonged traveler's diarrhea, or cases at risk for complications. They were also considered for outpatient diagnosis in moderate/severe cases, chronic diarrhea, or immunocompromised patients.

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Within a diagnostic stewardship framework, current evidence suggests that RMMSP can contribute to minimizing unnecessary testing and hospitalizations, improving outbreak control, and optimizing antimicrobial use. However, further research is necessary to refine diagnostic workflows and ensure timely result delivery. This document evaluated key aspects regarding the application of RMMSP in pediatric infectious AGE, aiming to establish standardized protocols, support clinical decision-making, and facilitate optimal patient management.

Key words: Gastrointestinal infection. Diarrhea. Acute gastroenteritis. Rapid multiplex molecular syndromic panels. Multiplex PCR panel. Culture-independent diagnostic test.

Resumen

La diarrea infecciosa aguda es un importante problema de salud global, especialmente en niños, ya que las infecciones gastrointestinales son la segunda enfermedad infecciosa más frecuente después de las infecciones respiratorias. La implementación de paneles sindrómicos moleculares rápidos (PSMR) para la detección e identificación integral de patógenos entéricos en muestras de heces ha mejorado la precisión diagnóstica, complementando o, en algunos casos, sustituyendo las metodologías tradicionales.

Esta revisión narrativa no sistemática sintetizó la evidencia disponible sobre el rendimiento clínico de los PSMR gastrointestinales hasta el 31 de diciembre de 2024. El 27 de mayo de 2024, especialistas en Pediatría y Microbiología se reunieron para evaluar el uso de PSMR en el diagnóstico de infecciones gastrointestinales pediátricas. Esta revisión se centró en aquellos PSMR aplicables al manejo urgente de la gastroenteritis aguda infecciosa (GEA), excluyendo aquellos paneles inadecuados para el diagnóstico inmediato. Los PSMR facilitaron la detección rápida de patógenos en la GEA infecciosa pediátrica y mostraron ventajas potenciales sobre los métodos microbiológicos tradicionales, incluyendo la reducción del tiempo hasta el tratamiento adecuado. Su uso pareció particularmente útil en entornos de urgencias y hospitalización, especialmente en casos de GEA inflamatoria, diarrea del viajero prolongada o pacientes con riesgo de complicaciones. También se consideraron para el diagnóstico ambulatorio en casos moderados o graves, diarrea crónica o en pacientes inmunodeprimidos.

En el marco de una estrategia de uso racional del diagnóstico, la evidencia actual sugiere que los PSMR pueden contribuir a reducir las pruebas y hospitalizaciones innecesarias, mejorar el control de brotes y optimizar el uso de antimicrobianos. Sin embargo, se requiere más investigación para perfeccionar los flujos de trabajo diagnósticos y asegurar la entrega oportuna de los resultados. Este documento evalúa aspectos clave sobre la aplicación de los RMMSP en la GEA infecciosa pediátrica, con el objetivo de establecer protocolos estandarizados, apoyar la toma de decisiones clínicas y facilitar una gestión óptima del paciente.

Palabras clave: Infección gastrointestinal. Diarrea. Gastroenteritis aguda. Paneles sindrómicos moleculares multiplex rápidos. Panel PCR multiplex. Prueba diagnóstica independiente del cultivo.

Introduction

Acute gastrointestinal infections represent the second most prevalent category of infectious diseases worldwide, following respiratory tract infections, especially in pediatric populations [1-3]. According to World Health Organization (WHO) data, there are over 1.7 billion cases of diarrheal disease worldwide every year. Despite the reduction in mortality from this cause due to the introduction of the rotavirus vaccine and the implementation of oral rehydration solutions, diarrheal diseases rank as the third leading cause of global mortality in children under five years of age, especially in Africa, South America, and Southeast Asia [1,3,4].

In developed countries, these diseases continue to cause significant morbidity, representing a high health care burden in the pediatric population [5-7].

Moreover, the greater accessibility and frequency of travel have led to an unprecedented global dissemination of infectious diseases, with gastrointestinal illnesses being among the most prevalent health issues affecting returning travelers and immigrants [8-11].

Viruses, bacteria, and parasites are the predominant pathogens responsible for infectious acute gastroenteritis (AGE) in pediatric populations. These pathogens are transmitted to the host through diverse routes, including feco-oral, person-to-person, and via fomites [12-18].

An etiological diagnosis is not always necessary and should be pursued only when it influences patient management or has public health implications, such as in outbreaks or the need for isolation [19-22]. In these scenarios, in which etiological diagnosis is necessary, early identification is essential to optimize clinical and epidemiological management [19-22].

Traditional etiological diagnosis of gastrointestinal infections includes culture and antibiotic susceptibility testing, microscopic examination for parasites, and antigen detection via immunoassays [20,21]. Despite conventional culture remaining the gold standard for the diagnosis of bacterial enteropathogens, classical

techniques have limitations [20,21], such as low sensitivity of immunoassays and culture, and the long turnaround time (TAT) of the latter [20-24].

In recent years, rapid multiplex molecular syndromic panels (RMMSP) for the detection and identification of causative gastrointestinal agents in stool samples from patients with acute diarrhea have emerged as valuable tools, complementing and, in some cases, replacing, conventional diagnostic methods for gastrointestinal infections [19-24]. The primary benefits of molecular diagnostics include higher sensitivity, specificity, and shorter time-to-results compared with conventional techniques [19-28]. RMMSP can concurrently identify viral, bacterial, and parasitic pathogens within a single sample, including co-infections, thereby aiding clinicians in making more informed treatment choices, enhancing patient outcomes, avoiding inappropriate or contraindicated antibiotic treatments, and establishing proper isolation protocols in cohorts settings [19-31].

However, there is currently a need to establish clinical guidelines to facilitate the identification of patients who are the best candidates to benefit from the use of these molecular syndromic panels. The integration of these tools, in a rational and efficient manner, into the patient roadmap could optimize clinical and resource management.

Thus, the aim of this publication is to provide an overview of the current state of the art regarding RMMSP currently available in Europe and USA for diagnosing gastrointestinal infections and their clinical indications, focusing on the pediatric population requiring urgent management, supported by robust scientific evidence.

Methods

On May 27, 2024, a meeting was convened to deliberate on the feasibility of initiating a comprehensive review concerning the application of RMMSP in the diagnosis of gastrointestinal infectious diseases in pediatric patients. A multidisciplinary panel, comprising experts in Pediatrics and Microbiology, was assembled based on their expertise and experience in the field.

Search strategy

We conducted a comprehensive, albeit non-systematic, literature review using PubMed database up to December 31, 2024. The search strategy included keywords [“Molecular syndromic platforms” OR “Molecular syndromic panels” OR “molecular syndromic testing” OR “Syndromic panels” OR “Rapid multiplex molecular syndromic panels”] AND [“Pediatric” OR “Children”] AND “Gastrointestinal infection” OR “Diarrhea” OR “Traveler-Diarrhea” OR “Acute gastroenteritis”]. This study included articles involving human subjects and published in English, French, Italian, Portuguese, or Spanish languages.

Included in this review were those multiple panels available at the time of writing the document that were applicable to the urgent management of infectious AGE. There are other multiplex molecular syndromic panels intended to test multiple samples in a batch mode, which do not allow immediate processing and are therefore not useful for the management of acute patients. However, these panels also have high sensitivity and specificity and, in some centers, the “molecular stool culture” strategy is being used, even replacing the classic systematic stool culture, cultivating only PCR-positive samples for susceptibility studies [32,33]. Despite their potential usefulness in the microbiology laboratory, they are not an effective tool for the diagnosis of the acute patients, which is the reason they were not included in this review.

Results

Causative Agents of Infectious

Significant etiological agents of infectious AGE are summarized in **Table 1** according to inflammatory status. Bacterial infectious AGE and diarrhea include *Campylobacter*, *Salmonella*, *Shigella*, *Aeromonas*, *Plesiomonas*, *Vibrio*, *Yersinia enterocolitica*, and diarrheagenic strains of *Escherichia coli* [12-15]. In addition, *C. difficile* is another common cause of infectious diarrhea, mainly watery and of varying severity (sometimes it can produce severe symptoms) mediated by a toxin- mechanism. It mainly affects hospitalized children either with underlying conditions, and/or previous antibiotic treatment, especially if prolonged or broad-spectrum, although it has also been detected in patients without prior antibiotics [34].

However, it can commonly be an asymptomatic colonizer in children (described in up to 40-70% of infants, even more in hospitalized patients) [35,36]. In patients under 2 years old, it is extremely rare that it produces pathology, so a positive result in that age group should be interpreted with caution and other causes of diarrhea should be investigated [37]. Key viral agents responsible for infectious AGE are Rotavirus, Norovirus, Astrovirus, Adenovirus, and Sapovirus [12,13,16]. Parasitic infections mainly arise from various protozoa (*Giardia intestinalis*, *Entamoeba histolytica*, *Cyclospora cayetanensis*, and *Cryptosporidium* species) [17,18].

Table 1. Main etiological agents, other clinical manifestations, and other complications of acute infectious gastroenteritis in pediatric patients. Adapted from Hasan et al [2] and Menasalvas-Ruiz et al [15].

	Most frequent etiology	Other clinical presentations and possible complications
Non-inflammatory (secretory) diarrhea	Viruses: Rotavirus, Norovirus, Adenovirus, Astrovirus, Sapovirus	Exanthems, Respiratory symptoms, Seizures, Other neurological disturbances (encephalitis, cerebellar involvement, *Reye-like* syndrome)
	Bacteria: ETEC, EPEC, *Clostridium perfringens*, *Clostridioides difficile*, *Vibrio cholerae*, *Bacillus cereus*, *Staphylococcus aureus*	
	Parasites: *Giardia lamblia*, *Cryptosporidium parvum*	Anemia, Malabsorption, Weight loss/ Malnutrition
Inflammatory diarrhea (enteroinvasive)	*Campylobacter* spp.	Erythema nodosum, IgA nephropathy, Guillain-Barré syndrome, Hemolytic anemia, Reactive arthritis
	Salmonella spp.	Erythema nodosum, Reactive arthritis
	Yersinia enterocolitica	Erythema nodosum, GNF, Hemolytic anemia, Reactive arthritis
	Shigella spp.	Erythema nodosum, GNF, Reactive arthritis, Toxic encephalopathy (Ekiri syndrome)
	Escherichia coli (EHEC, EIEC, EAEC)	Primarily with Shiga-toxin producing *EHEC*, most commonly serotype 0157

ETEC: Enterotoxigenic *Escherichia coli*; EPEC: Enteropathogenic *Escherichia coli*; GNF: Glomerulonephritis; EHEC: Enterohemorrhagic *Escherichia coli*; EIEC: Enteroinvasive *Escherichia coli*; EAEC: Enteroaggregative *Escherichia coli*; HUS: Hemolytic uremic syndrome.

Treatment

Empirical antibiotic therapy with agents such as azithromycin or third-generation cephalosporins may be warranted in specific clinical scenarios associated with an increased risk of severe infection. These scenarios include suspected bacterial infectious AGE in patients presenting with risk factors such as age under three months, systemic manifestations, suspicion of invasive disease, immunosuppression, or significant systemic impairment [15].

In infections caused by *Salmonella*, antibiotics can favor the carrier state. Notably, antibiotics administration is contraindicated in suspected cases of gastrointestinal infection due to Shiga-toxin-producing *E. coli* (STEC), as it heightens the risk of Hemolytic Uremic Syndrome (HUS).

Upon microbiological confirmation, antibiotic therapy should adhere to specific guidelines as shown in **Table 2**.

Panel opinion: Empirical antibiotic therapy is not routinely indicated in the general pediatric population. However, its judicious use is warranted in selected high-risk patients. In clinical scenarios characterized by the presence of specific risk factors (such as those previously described) the initiation of empirical antibiotic treatment with agents including azithromycin or third-generation cephalosporins may be clinically justified.

Traditional diagnostic methods in Infectious AGE

Culture methods in specific media allow the isolation and identification of bacteria, enabling their susceptibility to antibiotics to be tested [38]. Although it is the gold standard for bacterial pathogens (it does not detect viruses or parasites), it has limited sensitivity and requires several days to obtain results. Micros-

Table 2. Overview of the recommended antibiotic therapy according to the multiplex syndromic gastrointestinal panel results. Adapted from Menasalvas et al [15].

Etiology	Indication for Treatment	First Choice	Second Choice
***Campylobacter* spp.**	Severe gastroenteritis or > 7 days, Infants < 3 months, Immunosuppression, Invasive disease	Azithromycin	Ciprofloxacin
Salmonella enteritidis **		3rd-generation cephalosporins	Ciprofloxacin/Trimethoprim-sulfamethoxazole
Yersinia enterocolitica		3rd-generation cephalosporins	Cefixime/Ciprofloxacin/Trimethoprim-sulfamethoxazole
***Shigella* spp.**	Always	Azithromycin	Ceftriaxone/Cefixime/Ciprofloxacin
Salmonella typhi		Ceftriaxone	Azithromycin/Ciprofloxacin/Trimethoprim-sulfamethoxazole
Vibrio cholerae		Azithromycin	Ciprofloxacin
***Escherichia coli* ETEC/EIEC**		Azithromycin	Ciprofloxacin
***Escherichia coli* EHEC**	Contraindicated due to increased risk of HUS		
Clostridioides difficile***	See special situations	Metronidazole or oral vancomycin	Fidaxomicin*
Giardia lamblia	Always	Tinidazole/metronidazole	Albendazole/Nitazoxanide/Quinacrine
Cryptosporidium parvum	Immunosuppression	Nitazoxanide	Paromomycin + azithromycin

*If there is a high risk of recurrence or relapse of a previous infection treated with vancomycin

***Salmonella spp.*: Systematic antibiotic treatment of *Salmonella spp.* may favor the carrier state. After *Salmonella spp.* infection, detection in feces is common for prolonged periods of time. Collection of control stool cultures is not recommended in immunocompetent children.

***Only treat symptomatic patients in whom other etiologies have been ruled out

AGEA: acute gastroenteritis; ETEC: enterotoxigenic *Escherichia coli;* EHEC: enterohemorrhagic *Escherichia coli*; EIEC: enteroinvasive *Escherichia coli*; HUS: hemolytic uremic syndrome.

copy allows the visualization of parasites or their eggs in stool samples [39]. Both techniques require trained personnel and require a long processing time. Antigen detection assays techniques detect specific proteins or antigens produced by pathogens [20,21]. They have low sensitivity and are only available for some viral or parasitic antigens (sometimes in kits for simultaneous identification of 2-3 pathogens).

Panel opinion: Although antigen detection assays exhibit limited sensitivity and are restricted to certain viral or parasitic targets, they remain valuable diagnostic tools due to their ease of use and rapid TAT. These assays require minimal staff training and provide results within minutes, advantages that are particularly significant in resource-limited settings where access to specialized personnel and prolonged processing times for culture or microscopy may be impractical.

Rapid multiplex molecular syndromic panels for diagnosing infectious AGE

RMMSP have gained increasing interest in the field of infectious disease diagnostics, mainly due to numerous advantages compared to traditional methodologies, such as smaller sample volume requirements, broader coverage without the need to order specific tests, improved capability to identify coinfections, faster TAT, and in some cases, heightened sensitivity and greater diagnostic throughput [19-28].

Integrating traditional methods with modern molecular techniques can enhance diagnostic accuracy and inform appropriate treatment strategies for pediatric gastrointestinal infections [20-23].

Different RMMSP are currently available worldwide for the detection of common pathogens, either in an open system requiring separate nucleic acid extraction or in closed systems performing nucleic acid extraction, amplification, and analysis. These assays can identify either prevalent or non-prevalent pathogens, with consideration of local epidemiology and institutional requirements before adoption. Some assays offer separate panels for bacteria, viruses, and parasites, allowing flexibility when specific testing is needed [19-28,31]. Others allow broader etiological diagnosis, simultaneously detecting viral, parasitic, and bacterial microorganisms in a single panel [24-28].

The BioFire® FilmArray® Gastrointestinal Panel (BF-GIP) (BioFire, Salt Lake City, UT, USA/ bioMérieux, Marcy-l'Étoile, France) is an advanced diagnostic platform designed for the concurrent identification of a wide array of pathogens, including 13 bacterial, 5 viral, and 4 parasitic species, surpassing the capabilities of conventional assays [40] (**Table 3**). The primary advantage of the BioFire® FilmArray® system lies in its extensive microorganism detection range, minimal hands-on time, and rapid TAT [19-28, 46,47]. A multicenter evaluation comparing the BF-GIP with conventional stool culture and molecular methods demonstrated a sensitivity of 100% for 12 out of the 22 targeted microorganisms, and greater than 94.5% for an additional 7 of the 22-microorganisms tested [41].

The BD Max™ system (Becton Dickinson, Sparks, MD, USA) is an integrated diagnostic platform with 4 panels intended to diagnose enteric infections: Enteric Viral Panel, Enteric Bacterial Panel, Extended Enteric Bacterial Panel, and Enteric Parasites Panel. It also has a separate determination of *Clostridioides difficile* (BD Max™ CDIFF). Depending on the clinical context, a decision on which panel to perform should be made, while all 4 panels can be performed simultaneously [44].

Comparative studies have demonstrated that the BD Max Enteric Panel exhibits enhanced sensitivity and specificity in detecting *Campylobacter*, *Salmonella*, *Shigella*, and STEC compared to conventional culture methods [48,49].

The QIAstat-Dx® Gastrointestinal Panel (GIP) (Qiagen, Hilden, Germany) is a multiplex PCR assay capable of concurrently identifying 24 enteric pathogens from stool samples (**Table 3**). The manufacturer has reported an overall assay sensitivity and specificity of 97.9% and 97.8%, respectively [42].

A multicenter comparative study involving the QIAstat GIP, BF-GIP, and Seegene Allplex GIP aimed to evaluate the performance of the QIAstat Gastrointestinal Panel (GIP) in detecting 24 gastroenteric pathogens from stool samples in Cary-Blair transport medium [50]. Prospective (n=163) and retrospective (n=222) stool samples were analyzed using the QIAstat GIP and compared to the FDA-approved BF-GIP, with Seegene Allplex GIP employed for discrepancy resolution. Following discrepancy analysis, the QIAstat GIP identified 447 out of 455 pathogens, achieving a sensitivity of 98.2% (95%CI: 96.6–99.1%). Eight instances of false-positive results were observed. Coinfections involving multiple pathogens were present in 32.5% of positive cases [50].

Huang et al. assessed the diagnostic accuracy of three multiplex molecular assays, namely Verigene Enteric

Table 3. Overview of the main advantages and limitations of the different multiplex gastrointestinal syndromic panels available in the US and EU for urgent diagnosis.

Multiplex Syndromic Panel	Manufacturer	Region (USA/EU)	Pathogens Detected	Time to Results	Advantages	Limitations	Sensitivity/ PPV	Specificity/ NPV	Performance
BioFire® FilmArray® Gastrointestinal Panel	BioFire Diagnostics bioMérieux	USA, EU	**Bacteria:** *Campylobacter (C. jejuni, C. coli, C. upsaliensis); Clostridioides (Clostridium)* difficile (toxin A/B); *Plesiomonas shigelloides; Salmonella; Vibrio (V. cholerae, V. parahaemolyticus, V. vulnificus); Yersinia enterocolitica;* Diarrheagenic *Escherichia coli/Shigella* (EAEC; EPEC; ETEC lt/st; STEC stx1/stx2*; Shigella/* EIEC). **Viruses:** Adenovirus F40/41; Astrovirus; Norovirus GI/GII; Rotavirus; Sapovirus (I, II, IV, and V). **Parasites:** Cryptosporidium; Cyclospora cayetanensis; *Entamoeba histolytica*; *Giardia lamblia*	~1 hour	Wide coverage, fast, easy to use High Sen and Spe	Greater cost than classical techniques	98.5% [41] 94-100% [41]	99.2% [41] 97-100% [41]	1 sample per assay
QIAstat-Dx Gastrointestinal Panel	QIAGEN	EU	**Bacteria:** *Campylobacter (C. jejuni, C. coli, C. upsaliensis); Shigella/*EIEC; EPEC*; ETEC lt/st; STEC stx1/stx2 (including specific identification of *E. coli O157* serogroup within STEC)*; *Salmonella; Plesiomonas shigelloides; Yersinia enterocolitica.* **Viruses:** Adenovirus F40/41; Astrovirus; Norovirus GI, GII; Rotavirus A. **Parasites:** Cryptosporidium; Cyclospora cayetanensis; Entamoeba histolytica; *Giardia lamblia***	~1 hour	Wide coverage, intuitive interface High Sen and Spe	Only CE marked. Higher cost than classic techniques	96-94% [42] 95-99% [42]	99.8% [42] 99-100% [42]	1 sample per assay

...continuation of table 3.

Multiplex Syndromic Panel	Manufacturer	Region (USA/EU)	Pathogens Detected	Time to Results	AdvantAges	Limitations	Sensitivity/ PPV	Specificity/ NPV	Performance
BD MAX Enteric Panels (Enteric panel, Extended Enteric Bacterial Panel, Viral Panel and Enteric Parasite Panel)	BD	USA, EU	**Bacteria:** *Campylobacter* spp*; Salmonella* spp*; Yersinia enterocolitica; Vibrio* spp *(V. cholera, V.* STEC *stx1/stx2; Shigella spp, Plesiomonas shigelloides*. **Viruses:** Adenovirus (F40/41); Astrovirus; Norovirus; Rotavirus (A); Sapovirus. **Parasites:** *Cryptosporidium* spp (*C. parvum, C. hominis*); *Entamoeba histolytica*; *Giardia lamblia*	3,5 hours	Easy to use It can combine different tests during the same run. High Sen and Spe	Greater cost than classical techniques	97.3-99.7% [43]	97.5-100% [43]	1 sample per test can be performed, although a maximum of 24 samples are allowed in one run
VERIGENE® Enteric Pathogens (EP)	Diasorin	USA, EU	**Bacteria:** *Campylobacter* spp; *Salmonella spp; Shigella* spp; *Yersinia enterocolitica*; *Vibrio* spp; **Toxins:** *Shiga Toxin 1 (stx1)*; *Shiga Toxin 2 (stx2*) **Viruses:** Norovirus; Rotavirus A	2 hours	89.8% to 99.7%. High Sen and Spe	Greater cost than classical techniques	89.8-99.7% [44,45]	91.4-99.8% [44,45]	One sample per test; maximum of one run at a time

This review includes only those panels that can be performed on a single sample in an urgent manner. Panels requiring the aggregation of multiple samples have been excluded, as they are not relevant to the urgent management context addressed in this study, though they may be useful in other settings, such as molecular stool culture.

* Results for STEC, *E. coli* O157 and EPEC are not reported for stool specimens preserved in FecalSwab transport media.

**Also Known as *Giardia intestinalis* and *Giardia duodenalis*.

EAEC: Enteroaggregative *E. coli* ; EPEC: Enteropathogenic *E. coli*; ETEC: Enterotoxigenic *E. coli*; STEC: Shiga-like toxin-producing *E. coli ;* EIEC: Enteroinvasive *E. coli;* Sen: Sensitivity; Spe: Specificity; PPV: Positive predictive value; NPV: Negative predictive value

Pathogens Test (Verigene®), BF-GIP, and Luminex xTAG® Gastrointestinal Pathogen Panel (Luminex®) by using 152 fecal samples to detect six common enteric pathogens: *Campylobacter*, *Salmonella*, *Shigella*, STEC, norovirus, and rotavirus [45]. The performance of detection varied across platforms: BF-GIP (sensitivity: 94.7%-100.0%; specificity:98.6%-100.0%); Verigene® (sensitivity: 71.4%-95.4%; specificity: 99.3%-100.0%); and Luminex® (sensitivity: 79.2%-100.0%; specificity: 100.0%-100.0%). Based on the results of this study, BF-GIP demonstrated the highest sensitivity across most pathogens, while Verigene® showed lower sensitivity, particularly for rotavirus [45].

Beckman and Ferrieri compared traditional culture methods with the Verigene® EP assay (PCR/microarray) for stool pathogen detection. Among 3,795 samples, 99.3% produced valid results, with 13.2% testing positive for at least one pathogen [51]. Bacterial PCR/microarray findings agreed with culture-based methods in 85.3% of cases. Compared to culture, Verigene® EP assay showed a sensitivity of 95.2% and specificity of 99.8% for *Salmonella*; and a sensitivity of 87.5% - specificity of 99.8% for *Shigella* [51]. In summary, Verigene® EP assay provided interpretable results for most samples and showed strong concordance with culture-based testing.

Advantages and limitations of rapid multiplex molecular syndromic panels

Table 4 presents a comprehensive summary of the main advantages and limitations of gastrointestinal RMMSP.

Main advantages

The use of RMMSP panels significantly increases the diagnostic yield over classical methods, given their ability to identify multiple pathogens simultaneously [13,19-28,46,47,52-55]. In addition, according to current evidence, they have superior sensitivity and specificity compared to classical techniques [41-45,48-56]. The greater sensitivity and specificity are consistent for each microorganism detected; however, diagnostic performance varies for certain pathogens [41-45,48-57].

Multiple studies have demonstrated greater diagnostic performance compared to traditional microbiological techniques, both in pediatric and adult populations, and in different clinical contexts (emergency department [ED], intensive care unit [ICU] for critically ill patients, travelers, etc.) [58-63]. Even in comparison to standard PCR methods, the BF-GIP achieved

Table 4. Main strengths and weaknesses of multiplex gastrointestinal syndromic panels in pediatric patients with acute infectious AGE

Advantages	Limitations

• ***Time to results***
  ○ Reducing time to diagnosis
  ○ Reducing time to optimal treatment
• ***Clinical performance***
  ○ Simultaneous diagnostics of multiples pathogens
  ○ High sensitivity and specificity
  ○ Ability to detect coinfections.
  ○ Need for little staff training.
• ***Impact on therapeutic decisions***
  ○ Improving proper use of antibiotics
  ○ Reducing time on empirical antibiotic treatment
  ○ Reducing time on antibiotics
• ***Infection control***
  ○ Indicate / Reduce / Remove isolation
• ***Cost effective***
  ○ Potential reduction of length of hospital stays
  ○ Potential reduction complementary tests
  ○ Potential medical costs reduction in some scenarios
	• ***Limited coverage***
	  ○ Panels may not detect all potential pathogens
	  ○ Lack of information on antibiotic sensitivity
	• ***Costs and Resources***
	  ○ Initial costs and ongoing maintenance
	• ***Interpretation challenges***
	  ○ Difficulty interpreting co-detections
	  ○ Difficulty in differentiating colonization from infection in some pathogens (lack of clinical correlation).
	  ○ Not useful for follow-up.

a higher diagnostic yield [59,64,65]. In one infection control study, multiplex gastrointestinal pathogen detection proved particularly useful: in 22.2% of patients, including mainly adults but also children, with negative conventional tests for *C. difficile* and/or rotavirus, while other pathogens were identified [66].

Another main advantage over other techniques is the ability to detect co-infections [41,50]. This is especially important because it is well known that a patient with a gastrointestinal pathogen identified is at greater risk of having other pathogens likely exposed to the same route of transmission (generally fecal-oral) [4-6,53,67-69]. Meyer et al. [21] in a systematic review and meta-analysis involving 17,585 patients, reported that the aggregate prevalence of co-detection using the BF-GIP was 18.1% (95% confidence interval: 13.4–24%).

Panel opinion: A precise etiological identification substantially enhances the clinical management of infectious AGE, enabling more targeted therapeutic interventions.

An accurate etiology greatly optimizes clinical management of infectious AGE. Although empirical antibiotic treatment is not generally indicated in most bacterial gastrointestinal infections, since viruses are the most frequent etiological agents, and that even in some bacterial infections, antibiotics are not recommended, rapid diagnosis is still valuable. In severe cases or vulnerable patients, empirical antibiotic treatment may be indicated if a rapid identification test is not available [25,70,71], which should be targeted to the pathogen as soon as possible. Furthermore, for *E. coli* producing Shiga toxin, the antibiotic treatment can negatively affect outcomes, increasing the risk of progression to HUS [72-76]; or for *Salmonella,* it could favor persistence and the development of a carrier state [77,78].

Panel opinion: Timely access to rapid and accurate diagnostic modalities is essential for optimizing empiric antimicrobial therapy, minimizing the use of unnecessary or potentially contraindicated treatments.

In a quality improvement study, including 305 children presenting to the emergency department with bloody diarrhea at risk of HUS, the introduction of both the BF-GIP and a clinical pathway was associated with decreased hospitalizations and overall costs without adverse clinical outcomes [75]. Furthermore, in a cohort of 172 children, prior to receiving stool culture outcomes, decisions regarding medical management were altered for 40 patients (23%) based on findings from the RMMSP BF-GIP. This included initiating treatment in 28 cases, modifying antibiotics in 2 cases, discontinuing antibiotics in 1 case, hospitalizing 1 patient, isolating 2 patients in specific rooms due to *C. difficile* infections, prescribing 4 additional tests, and canceling 2 tests [79].

Appropriate use of antibiotics is especially important to avoid the rise in antibiotic resistance, which is becoming a major public health problem (for example, pathogens such as *Campylobacter* or *Salmonella* have very high resistance rates to critically important antimicrobials, such as ciprofloxacin in some geographical areas) [80].

The implementation of the BF-GIP has been shown to reduce the time to first report from 47 hours to 18 hours. It also reduced the proportion of patients, both children and adults, receiving empirical antimicrobial therapy from 40% to 23.5% and shortened the time to initiation of antimicrobial therapy from 72 hours to 26 hours [59]. As a result, there was a shift in clinical practice over time, from empirical to targeted antimicrobial therapy, through use of the BF-GIP [59]. In another study, the use of the BF-GIP significantly decreased the duration of antibiotic use from 2.12 to 1.73 days [65].

Rapid etiological diagnosis also allows clinicians to avoid unnecessary additional tests and hospitalization time. The use of the BF-GIP significantly decreased the mean number of additional infectious stool tests from 3.02 to 0.58 per patient and the frequency of abdominal and/or pelvic imaging studies from 0.39 to 0.18 per patient [65]. The interval from sample collection to patient discharge was significantly shortened from 3.9 to 3.4 days [65].

Although there is still little evidence, some studies have shown significant cost-effectiveness [65,75,79,81-86], reducing overall economic costs, in relation to less antibiotic use and shorter courses, fewer complementary tests and hospitalization time. For example, considering all these factors, including the cost of testing, one report estimated a saving of $293.61 per patient tested with the BF-GIP [65]. The results of a prospective, multicenter, and pragmatic study showed that among children with gastroenteritis, who attended the emergency department, the use of BF-GIP was associated with a 21% reduction in the probability of subsequent healthcare consultations compared to the use of clinician-selected diagnostic testing [61]. This approach not only improves patient outcomes but also optimizes resource utilization in pediatric healthcare settings.

Panel opinion: Implementation of these diagnostic panels requires efficient information workflows and round-the-clock availability to facilitate prompt result delivery and support immediate clinical decision-making.

From a public health and infection control perspective, rapid pathogen detection facilitates effective infection control measures, including cohorting patients in isolation [24,67,87,88] and helps prevent the spread of infectious diseases [78,89], especially in managing possible outbreaks (intra- or extra-hospital), which might have a substantial impact on the safety of the rest of the patients, and allow better management of health resources and hospital capacity. This might be particularly relevant for hospitalized patients, especially in the case of highly transmissible pathogens such as rotavirus and norovirus [66]. Additionally, young children should be kept out of kindergarten or school during the symptomatic phase, even if hospitalization is not required, to mitigate the risk of infection transmission [90,91].

Main limitations

While gastrointestinal RMMSP offer substantial benefits in pediatric populations, they also present several limitations [19-28,46,47,92-95]. Therefore, careful consideration of these limitations is essential for optimizing their use in pediatric patient care and interpreting results in different clinical settings.

Although the false positive rate is low [52-55], they cannot differentiate between dead and viable organisms, potentially obtaining a positive result in cases of low microorganism load (which could be related to a previous infection and may not necessarily be causing clinical symptoms), which can typically occur in regions where these microorganisms exhibit high prevalence, complicating interpretation [30].

Elevated detection rates of some enteric pathogens have been documented in asymptomatic pediatric populations [96]. Globally, the prevalence of asymptomatic carriers of enteropathogenic *Escherichia coli* (EPEC) is estimated to be 8.8% in the overall population. This prevalence increases to 9.1% among outpatients and 15.6% in hospitalized patients [97]. Therefore, the diagnostic results need to be interpreted carefully depending on the patient's condition [95].

This is even more relevant for co-detections, which might complicate clinical decision-making [19-28,46,47,92-95]. The clinical significance of co-detections in gastrointestinal RMMSP among pediatric populations is an area of increasing interest [21,41,97-101].

The detection of non-viable microorganisms also makes these panels unsuitable for the follow-up of the infection. For *C. difficile*, positivity by PCR requires confirmation of the presence of the toxin by a specific test (i.e., enzyme immunoassay for toxin). In any case, in the event of any positive result, the possibility that *C. difficile* is an incidental finding must be considered, and a decision regarding treatment on an individual basis is needed [102].

In immunocompromised patients, some common etiologic agents are not detected by the RMMSP, such as cytomegalovirus (CMV) [25,103], which is frequently associated with flares in patients with inflammatory bowel disease (IBD) and in other severely immunocompromised patients. In these patients, it would be necessary to add a specific PCR for the microorganisms not included.

Nevertheless, in individuals with IBD, the vast array of potential pathogens detected may be very useful as many agents may be involved in relapses, as it has been increasingly reported with *C. difficile* infection. In these individuals, BF-GIP has been shown to yield a higher pathogen detection rate and lead to lower rate of IBD treatment modifications [104]. Nevertheless, a positive result should be interpreted cautiously since it may be a true pathogen or may represent over-diagnosis with misattribution of symptoms to infections, inappropriate use of antibiotics, and delay in IBD-directed therapy [104].

The implementation of molecular diagnostic panels and their associated instrumentation poses a significant financial challenge for certain healthcare settings. Although these panels offer numerous advantages, molecular biology techniques generally entail a substantially higher direct cost per test compared to conventional methodologies. This elevated cost represents a potential barrier to adoption, particularly in facilities or laboratories with constrained financial resources.

Nevertheless, when indirect costs are considered (such as those related to personnel, duration of hospital stay, the need for supplementary diagnostic procedures, and pharmacological interventions) the total cost per diagnostic process may, in some cases, be offset by overall savings. Despite this possibility, there is currently a lack of rigorously designed cost-effectiveness studies that conclusively substantiate this hypothesis.

On the other hand, while RMMSP streamline testing, they may not completely replace traditional methods

Table 5. Comprehensive examination of the variables to be considered during the interpretation of outcomes from multiplex syndromic gastrointestinal panels. The information presented in this table has been obtained from references [24,29-31,60,61,106,107**].**

Clinical correlation	• Symptomatology:
	  ○ To assess the clinical symptoms (such as diarrhea, vomiting, fever, abdominal pain, and dehydration) and correlate these symptoms with the pathogens detected.
	• Medical History:
	  ○ To consider the patient's recent medical history, including travel, contact with infected individuals, attendance at daycare, and recent antibiotic use. This context can help identify potential sources of infection.

Pathogen Significance	• Pathogenic versus (vs) Commensal:
	  ○ To differentiate between pathogenic organisms and commensal or benign organisms that may not require treatment. Some detected organisms might be part of the normal gut flora or transiently present without causing disease.
	• Single vs. Multiple Pathogens:
	  ○ To determine whether the detected pathogens can cause the observed symptoms independently or if they suggest a mixed infection. Co-infections might require more complex management.

Results Interpretation	• Asymptomatic Carriage:
	  ○ To recognize that some children may carry enteric pathogens asymptomatically. Positive results should be interpreted in the context of clinical symptoms.
	• Subclinical and Resolved Infections:
	  ○ To understand that positive results may indicate a subclinical or past infection, especially if the child shows mild or no symptoms.
	• Non-viable microorganisms:
	  ○ To consider the possibility of detecting nonpathogenic nucleic acids, which may lead to false positives if not clinically correlated.

Decision-Making for Treatment	• Antimicrobial Therapy:
	  ○ To decide about the need of antimicrobial therapy based on the identified pathogen, its known pathogenicity, and the clinical presentation.
	• Avoiding Unnecessary Treatment:
	  ○ To avoid unnecessary antibiotics for non-bacterial or self-limiting infections to prevent potential harm and antibiotic resistance.

Follow-up	○ Not useful

like culture and susceptibility testing, which are still necessary in some cases for accurate diagnosis and treatment guidance [19,20,60,95].

Panel opinion: A comprehensive interpretation of gastrointestinal RMMSP results in pediatric patients should integrate clinical presentation, patient history, and the specific pathogens identified to enhance diagnostic accuracy and guide appropriate clinical management. This integrative approach is expected to improve patient outcomes while minimizing unnecessary interventions [60,61,105,106].

Panel opinion: To address challenges in test interpretation and maximize clinical and economic benefits, the involvement of a multidisciplinary stewardship team specialized in antimicrobial use and diagnostic interpretation is recommended. Such expertise may facilitate appropriate test utilization and result interpretation, particularly in complex cases involving severe illness or immunosuppression.

Table 5 shows the key points to consider for correct interpretation of the test.

Clinical indications for the use of rapid multiplex syndromic panels in patients with suspected infectious AGE

Acute gastrointestinal infections in children encompass a wide range of pathogens and highly heterogeneous clinical scenarios. Understanding this diversity is crucial for implementing personalized

diagnostic approaches and therapeutic interventions that address the specific needs of each patient [5,14-17].

The availability of new tools for etiological identification is leading to a review and update of current guidelines to adapt to the new diagnostic potential [29-31].

Although multiple scientific societies from different regions establish management guidelines for infectious AGE in children including the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [29], the Infectious Diseases Society of America [30], the American Academy of Pediatrics [107], and the Spanish Society of Pediatrics [108], the availability of new molecular diagnostic techniques necessitates their revision, including these tools in clinical management algorithms, for more efficient use [30,60,92-95].

Panel opinion: Based on the current body of evidence in both adult and pediatric populations [15,23,24,29-31,75,90,91,110-113] and extensive clinical experience, the panel has delineated potential clinical indications for the use of RMMSP in diagnosing infectious AGE among pediatric patients. These indications have been stratified into categories of 'highly recommended' and 'recommended' to facilitate the adaptation of local clinical guidelines, considering institutional resources and patient population characteristics. This approach aims to optimize the integration of novel molecular diagnostics into diverse clinical settings, including emergency departments, inpatient wards, outpatient clinics, and special clinical circumstances.

Table 6 summarizes the primary clinical objectives and recommended indications for RMMSP use in pediatric infectious AGE across different care settings.

Roadmap for the pediatric patient with infectious AGE

Based on existing guidelines and on the available evidence and the indications already discussed, the

Table 6. Main clinical indications for the use of multiplex gastrointestinal syndromic panels in pediatric populations according to different clinical contexts. The information presented in this table has been obtained from references [15,23,24,29-31,75,90,91,110-113].

Clinical Indications		
Emergency room / Inpatient Highly recommended	**Recommended**	**Outpatient clinics**
Acute gastroenteritis • Inflammatory gastroenteritis[1] • Traveler's diarrhea > 7 days[2] • Outbreak (possibly epidemic) • HUS /Risk factors HUS[3] • Patients at risk of complications and/or risk of serious infection: age younger than three months younger than, immunosuppressed, asplenia (anatomical or functional), severe chronic illness or severe malnutrition[3]. • IBD (onset, flareups), not justify by the underlaying pathology. • Not inflammatory AGE of in hospital onset.	Acute gastroenteritis • Moderate/severe, without inflammatory symptoms, if the result of the conventional test is negative. • Younger than three months without admission criteria. Other patients without gastroenteritis • Pain in the right ilea fossa and diagnosed/suspected of non-surgical acute abdomen. Differential diagnostic evaluation for acute abdomen.	• Patient with chronic diarrhea with negative conventional tests. • Gastroenteritis in patient with underlying pathology and/or primary or secondary immunosuppression. • Traveler's diarrhea with negative conventional tests.

[1]Diarrhea with mucus, blood, or pus, high fever, septic appearance, or affectations of general conditions.

[2]If it last 14 days, considers parasite testing [30].

[3]See reference 110.

HUS: Hemolytic uremic syndrome. IBD: Inflammatory bowel disease.

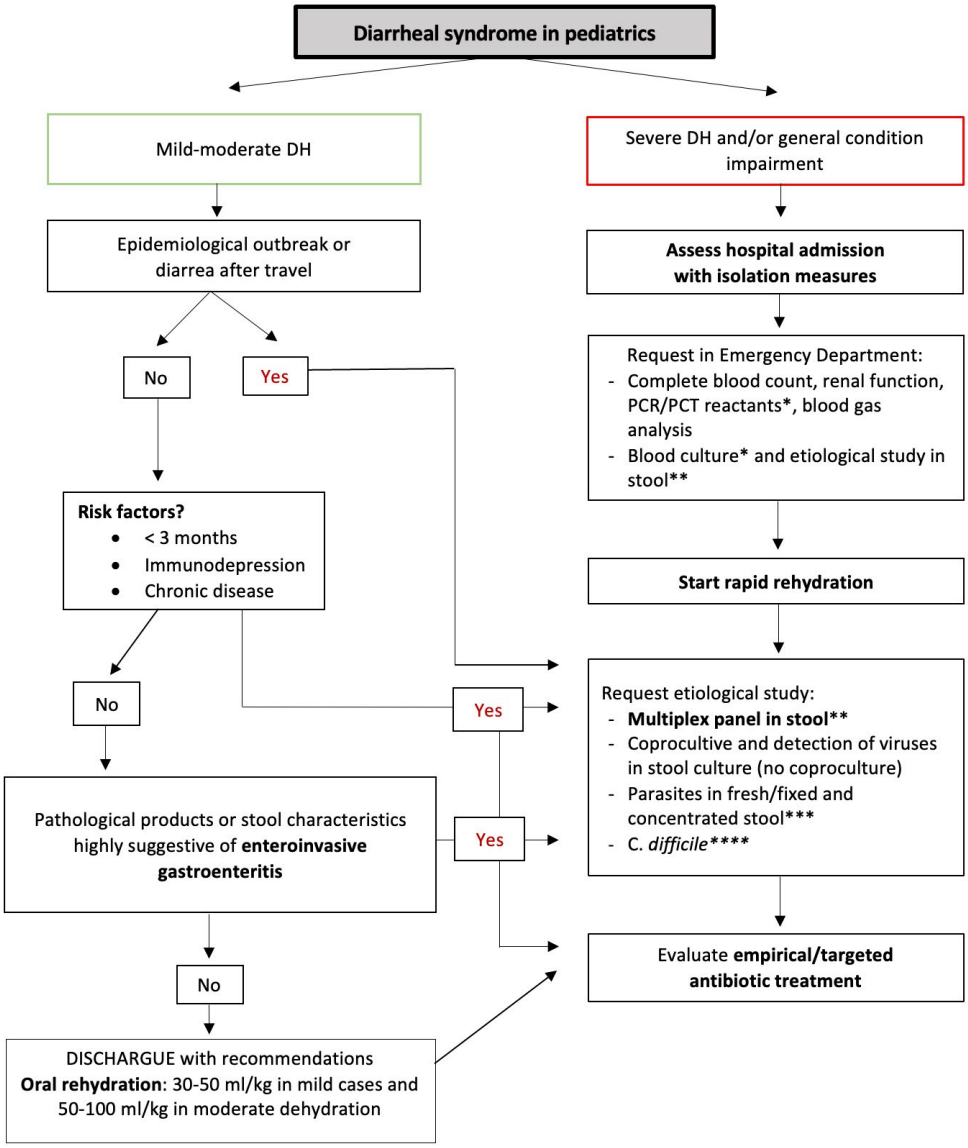

Figure 1. Proposed clinical roadmap for a child with infectious acute gastroenteritis.

Adapted from Menasalvas et al. [15].

DH: dehydration. *Infants <3 months with fever or suspected sepsis: Immediate evaluation and management are required.

**Multiplex panel testing: If available, urgent testing is recommended in cases of severe acute gastroenteritis (AGE) requiring hospitalization, children with risk factors, diarrhea associated with an epidemic outbreak, or traveler's diarrhea. In enteroinvasive AGE without admission criteria, consider multiplex testing upon presentation to the Emergency Department.

***Stool culture indications:Recommended in cases of prolonged symptoms, immunosuppression, or traveler's diarrhea.

****_Clostridioides difficile_ testing: Indicated in the presence of risk factors, including immunosuppression, recent antibiotic exposure, or pre-existing gastrointestinal conditions (e.g., Hirschsprung's disease, inflammatory bowel disease). Routine testing is generally not recommended in infants <2 years, except in highly selected cases.

diagnostic algorithm shown in **Figure 1** for acute gastroenteritis in children is proposed.

Development and validation of the proposed algorithm

The proposed algorithm represents an original contribution developed by the panel members, grounded in both the available scientific evidence and their accumulated clinical experience. All experts have experience using of RMMSP in routine clinical practice, in their sites across Spain. The recommendations presented here reflect a synthesis of both clinical practice and evidence-based outcomes.

To date, no comparable protocol has been described or validated in the literature. Therefore, a rigorously designed prospective study is deemed essential

to assess the impact of the algorithm on the use of diagnostic tests before and after its implementation. Such a study would enable validation of its effectiveness and provide greater clarity regarding its clinical applicability according to the proposed indications.

Conclusions

In pediatric patients with infectious AGE, the use of gastrointestinal RMMSP facilitates rapid identification of the pathogens causing the infection. Although they have limitations intrinsic to detecting DNA rather than viable microorganisms, their advantages compared to stool culture and other traditional microbiological techniques have proven to be relevant.

The use of gastrointestinal RMMSP panels is highly recommended in emergency and inpatient settings for patients with infectious AGE (especially inflammatory types, traveler's diarrhea lasting >7 days, or those at risk for complications such as HUS or severe illness). It is also considered useful in outpatient clinics for cases of moderate/severe gastroenteritis without inflammatory symptoms and when conventional tests are negative, as well as for chronic diarrhea or gastroenteritis in immunocompromised patients or those with underlying pathology.

When used within a diagnostic stewardship framework, in more severe cases of infectious AGE or patients at risk, robust evidence supports their benefits in helping reduce the use of complementary tests and lenght of hospitalization, facilitating outbreak control or the establishment of isolation measures and, above all, enabling a more appropriate use of antibiotics.

While further scientific evidence is needed to establish optimized workflows for rapid result delivery, RMMSP appear to be essential tools in the comprehensive management of infectious AGE in children, particularly in the proposed clinical scenarios.

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Conflict of interest

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Authors' contributions

All the authors have made substantial contributions to the conception and design of the study; acquisition, review, and interpretation of the data; and have drafted the paper or substantively revised it. All authors have read and approved the final manuscript.

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