Olivia Jocelyn, O., et al. International Journal of Biomedical Science and Travel Medicine (IJBSTM)
Volume 1, Number 1, 2024

International Journal of Biomedical Science and Travel Medicine (IJBSTM)

Case Report Open Access

# Syndromic testing as a diagnostic modality for gastrointestinal infection: an evidence-based case report

Olivia Jocelyn[1], David Hutajulu[2], Erni Juwita Nelwan[2]

**Abstract**

Indonesia continues to grapple with sanitation issues, contributing to high incidence of gastrointestinal infections. Timely and accurate diagnosis is crucial to minimize the use of empirical antibiotics and medical expenses. Microbial culture, the current gold standard for diagnosing infections, has certain limitations in terms of duration and accuracy. There is a novel multiplex PCR (mPCR)-based diagnostic approach for infections called syndromic testing that can identify up to 20 pathogens simultaneously within 1–2 hours. This evidence-based case report aims to evaluate its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in diagnosing gastrointestinal infections. Literature search was conducted on February 21, 2024, across several databases which were PubMed, Scopus, Wiley Online Library, and ProQuest. Two prospective cross-sectional studies met the inclusion and exclusion criteria which were then critically appraised. Both studies measured the diagnostic accuracy of syndromic testing for Salmonella and Shigella, yielding sensitivity of 75–95.2%, specificity of >98%, PPV up to 88.2%, and NPV of >99%, indicating its good accuracy. Syndromic testing presents as a promising alternative diagnostic modality for infections, addressing the limitations of culture-based methods.

**Keywords:** culture; multiplex PCR; gastrointestinal infection; syndromic testing

Correspondence:
Olivia Jocelyn
erni.juwita@ui.ac.id

1. Faculty of Medicine, Universitas Indonesia, Jakarta
2. Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta

## Introduction

Infection is one of the leading causes of mortality and morbidity in the world, with about 25% of deaths caused by infectious diseases.[1] Diarrhea, as one of the common infectious diseases, remains an endemic disease in Indonesia and has the potential to become an epidemic that often causes death.[2] Acute diarrheal infections are mainly caused by viruses, bacteria, and, less commonly, parasites. Viral infections are the most common cause, usually causing mild, non-inflammatory acute diarrhea.[3] The prevalence of diarrhea in Indonesia in 2020 had reached 9.8% based on the results of the Indonesian Nutrition Status Survey.[4] Enteric viruses, particularly rotavirus A, were the primary cause of febrile diarrhea in children under five, while bacterial pathogens were more prevalent in febrile cases among adults, with nontyphoidal *Salmonella* and diarrheagenic *Escherichia coli* being the main causes.[5] A previous study conducted in Ethiopia revealed that 77% of antibiotic treatments for diarrhea were inappropriate which may contribute to increasing antimicrobial resistance and lead to increased health care costs.[3]

The most important thing in the treatment of infectious diseases is a rapid and accurate diagnosis.[6] The sooner the diagnosis is established, the less empirical treatments such as broad spectrum antibiotics will be needed.[7] Microbial culture has been long recognized as the gold standard of diagnostic examination for infections. However, culture takes quite a long time and requires well-trained staff.[6] It becomes an obstacle in its own right, especially in an attempt to diagnose a rapidly deteriorating patient. This drives microbiologists to continue to develop new diagnostic technologies or innovations that are faster, more effective, and more accurate.

Advanced microbiology technologies such as multiplex molecular assays (i.e. syndromic diagnostic tests) is a novel approach to the rapid diagnosis of common infectious diseases. Multiplex PCR (mPCR) allows clinicians to identify pathogens and resistant genes using a

single test. Syndromic testing simultaneously targets multiple pathogens with overlapping signs and symptoms. Syndromic testing can help eliminate the guesswork of diagnosing infectious diseases and aids in making prompt clinical decisions. This diagnostic method indirectly improves infection control, support antimicrobial stewardship programs, improve patient outcomes and reduce overall healthcare costs.[7] This evidence -based case report aims to evaluate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of syndromic testing in the diagnosis of gastrointestinal infection.

## Clinical Case

A 70-year-old male came to the emergency department due to stomach discomfort since three days prior to admission. Eighteen days earlier, the patient complained of discomfort in the left chest and consulted a doctor. Examination was done and no abnormalities were found in the heart. The patient's complaint was then suspected to be due to GERD. Several days after the initial complaint, the patient complained of fever with chills and fatigue alongside loose stool without blood or mucus. No other symptom was reported and no other focus of infection was found. Stool sample was taken and a gastrointestinal panel testing was done. The results found enteropathogenic *E. coli* in the stool sample and the patient was given antibiotics. The patient complained of stomach pain and nausea after consuming the antibiotics and went to the emergency department with persisting symptoms.

During hospitalization, the patient had defecated soft stool which was then examined. Results showed yellow colored stool, soft consistency, negative for pus, negative for blood, negative for mucus, leukocytes 1-3/LPF, erythrocytes 2-4/LPF, epithelium 1+, negative for starch, fat with ethanol 1+, negative for acetic acid, yeast cells 1+, negative for amoeba, negative for worm eggs, pH 5.5, blood +, negative for gram-positive cocci, gram-negative rods 1+. Blood test was done with the results of hemoglobin 13.8 g/dL, hematocrit 37.8%, erythrocytes 4.49 x $10^6$/µL, thrombocytes 127.000/ µL, leukocyte 3.500/µL, basophil 0%, eosinophil 0%, stem neutrophil 1%, segment neutrophil 75%, lymphocytes 14%, monocyte 8%, SGOT 42 U/L, SGPT 38 U/L, urea 22 mg/ dL, creatinine 0.96 mg/ dl, eGFR 79.8 mL/ min/1.73$m^2$, blood glucose at 105 mg/dL, sodium 125.0 mmol/ L, potassium 3.30 mmol/L, chloride 96.0 mmoL, and quantitative CRP 16.05 mg/L.

In this particular patient, management of the diarrhea was administered based on the attending physician's assessment and the patient was discharged in a good condition. The utilization of syndromic panel testing in this case raises a clinical question about the diagnostic capability of this test compared to culture testing as the gold standard in diagnosis of infection cases.

## Clinical Question

Problems discussed in this evidence-based case report can be formulated into a clinical question, "What is the accuracy of syndromic testing in the diagnosis of patients with suspected gastrointestinal infections compared to culture examination as the gold standard?". Problems in this case report consists of four components, namely Population (P): stool samples of patients suspected of gastrointestinal infection, Intervention (I): syndromic testing, Comparison (C): culture, Outcome (O): diagnostic accuracy (sensitivity, specificity, positive predictive value, and negative predictive value).

## Strategy and Article Search

Article search was conducted on February 21$^{st}$, 2024, through several databases, namely PubMed, Scopus, Wiley Online Library, and ProQuest. The keywords used were "syndromic test*", "syndromic diagnostic test*", "syndromic panel", "culture", "gastrointestinal infection", and "diagnostics" which were combined using Boolean operators "AND" and "OR". Article screening was conducted based on the inclusion and exclusion criteria. Inclusion criteria in this EBCR were: (1) studies comparing the use of syndromic testing (multiplex PCR) to stool culture as the gold standard to diagnose patients with suspected gastrointestinal infections; (2) study design including systematic review/meta-analysis of cross -sectional studies, cross-sectional studies, case control studies, or cohort studies; (3) studies written in Indonesian or English. Exclusion criteria in this EBCR were: (1) studies without full-text available; (2) studies with outcomes other than sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Article selection was done through title and abstract screening, elimination of duplicate articles, and full-text articles readings to obtain articles that met the PICO, inclusion, and exclusion criteria. The article selection process can be seen in Figure 1.

There were two cross-sectional studies — by Knoth, et al. and Beckman, et al. — which met the specified criteria and proceeded to be critically appraised. A summary of each study can be seen in Table 1 and the results of the critical appraisal can be seen in Table 2, Table 3, and Table 4.


ISSN (online) 3047-7433
ISSN (print) 3047-7441

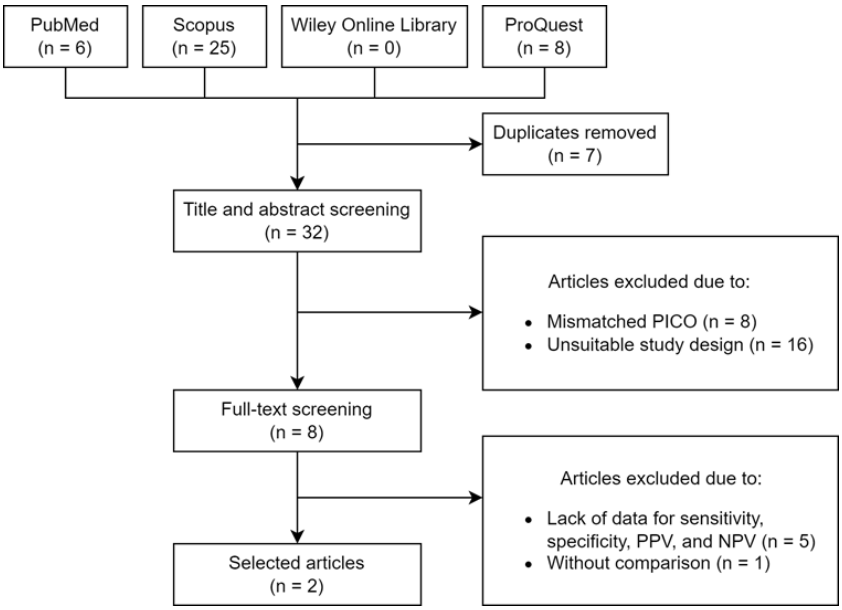


**Figure 1.** Article selection process

**Table 1.** Summary of the studies used in this EBCR.

| Author (Year) | Study design | Patient (P) | Intervention (I) | Comparison (C) | Outcome (O) |
|---|---|---|---|---|---|
| Knoth C, et al.. (2024) | Prospective cross-sectional study | n = 1554 (stool sample) | Syndromic testing [BioCode Gastrointestinal Pathogen Panel (BioCode GPP)] | Bacterial culture | Sensitivity, specificity, PPV, and NPV |
| Beckman AK, et al. (2019) | Prospective cross-sectional study | n = 3687 (stool sample) | Syndromic testing [Verigene Enteric Pathogens (EP) Test] | Bacterial culture | Sensitivity, specificity, PPV, and NPV |

**Table 2.** Validity analysis of studies by Knoth C, et al.[8] dan Beckman AK, et al.[9] based on The Centre for Evidence-Based Medicine (CEBM) Oxford.

| Question | Study | |
|---|---|---|
| | Knoth C, et al. (2024) | Beckman AK, et al. (2019) |
| Was the diagnostic test evaluated in a Representative spectrum of patients (like those in whom it would be used in practice)? | Yes | Unclear |
| Was the reference standard applied regardless of the index test result? | Yes | Yes |
| Was there an independent, blind comparison between the index test and an appropriate reference ('gold') standard of diagnosis? | Yes | Yes |


ISSN (online) 3047-7433
ISSN (print) 3047-7441

**Table 3.** Importance analysis of studies by Knoth C, et al.[8] and Beckman AK, et al.[9] based on The Centre for Evidence-Based Medicine (CEBM) Oxford.

| Study | Pathogen | Importance | | | | Level of evidence |
|---|---|---|---|---|---|---|
| | | Sensitivity | Specificity | PPV* | NPV* | |
| Knoth C, et al. (2024) | Salmonella | 83.3% | 99.2% | 67.6% | 99.7% | II*** |
| | Shigella | 75% | 98.9% | 26.1% | 99.9% | |
| Beckman AK, et al. (2019) | Salmonella | 95.2% | 99.8% | 88.2% | 99.9% | II*** |
| | Shigella | 87.5% | 99.8% | 72.4% | 99.9% | |

*PPV: positive predictive value
**NPV: negative predictive value
***Based on the criteria levels of evidence Oxford CEBM 2011

**Table 4.** Applicability analysis of studies by Knoth C, et al.[8] and Beckman AK, et al.[9] based on The Centre for Evidence-Based Medicine (CEBM) Oxford.

| Question | Study | |
|---|---|---|
| | Knoth C, et al. (2024) | Beckman AK, et al. (2019) |
| Were the methods for performing the test described in sufficient detail to permit replication? | Yes | Yes |

## Discussion

Traditional diagnostic methods such as culture and susceptibility testing have still been widely used to identify the cause of an infection. However, these tests have limitations, such as taking quite a long time to obtain results which prolongs the administration of broad-spectrum antimicrobials. This can affect patient outcomes and increased hospital length of stay. The use of multiplex polymerase chain reaction (mPCR), also known as syndromic testing, is a faster diagnostic method for infections compared to culture. Multiplex PCR can detect many pathogens simultaneously, it detects viruses, bacteria, and parasites that cause diarrhea or gastrointestinal diseases, which helps shorten time of decision making.[7]

This evidence-based case report used two studies as data sources to evaluate the accuracy of syndromic testing in identifying two common enteropathogens, *Salmonella* and *Shigella.* Both studies by Knoth C, et al.[8] and Beckman AK, et al,[9] met the validity criteria so they are considered valid to be used as data sources. The study by Knoth C, et al.[8] conducted culture testing (*Salmonella* and *Shigella*) and GI syndromic panel on 1554 samples from four different sites. The samples used were leftover stool samples sent as part of the routine screening for patients with suspected infections. Cultures were also performed by the home site of each sample according to each site's procedures. On the other hand, the study by Beckman AK, et al,[9] tested 3687 stool samples using GI panel and culture methods for *Salmonella* and *Shigella.*

Based on the study of Knoth C, et al.,[8] GI panel yielded sensitivity of 83.3%; specificity of 99.2%; PPV of 67.6%; and NPV of 99.7% for *Salmonella* and sensitivity of 75%; specificity of 98.9%; PPV of 26.1%; and NPV of 99.9% for *Shigella*. On the other hand, Beckman AK, et al.[9] reported sensitivity of 95.2%; specificity of 99.8%; PPV of 88.2%; and NPV of 99.9% for *Salmonella* and sensitivity of 87.5%; specificity of 99.8%; PPV of 72.4%; and NPV of 99.9% for *Shigella.* The exceptional specificity and NPV values (>98%) indicates that syndromic testing has good accuracy in declaring negative results in healthy patients (specificity) and the probability of patients being healthy when the results are negative (NPV). On the other hand, the sensitivity and PPV of syndromic testing have considerable variation, with the sensitivity for *Salmonella* and *Shigella* ranging from 75–95.2% and PPV up to 88.2%. This variation in sensitivity indicates that only about 75–95.2% of patients that are truly infected with *Salmonella* and/or *Shigella* will yield a positive test result. The method also has the ability to produce up to 88.2% positive results in patients who are truly infected with these pathogens. Thus, syndromic testing is more likely to produce false positives than false negatives. This phenomenon may be due to the principle of the PCR method that identifies the genetic material of pathogens regardless of whether the pathogen is alive or dead. Hence, the detection of dead pathogens' genetic material will result in false positives and is not clinically relevant.[10,11] However, this drawback can

also be an advantage of syndromic testing, as this test is still able to identify dead pathogens after empirical antibiotics administration that may not be identified through conventional culture methods.[11]

The implementation of syndromic testing in clinical practice has the potential to increase diagnostic efficiency for patients with suspected infections. In just a short period of time, negative results from syndromic testing can confirm the absence of a particular pathogen so that further evaluation can be carried out for pathogens that are positively detected. Study by Axelrad JE, et al.[12] found that patients who received GI panel testing were less likely to undergo endoscopic evaluation, abdominal radiology, and antibiotic treatment. Study by Torres-Miranda D, et al.[13] also found that the use of GI panels aided shortening hospital length of stay and improving antibiotic stewardship. Although the cost of GI panel is greater than other conventional methods, the excess cost is offset by decrease in hospital length of stay and reduction of inappropriate antibiotic administration. Thus, the implementation of syndromic panels should be more cost efficient than conventional methods.

The use of GI panels testing on our patient was proven advantageous in terms of aiding prompt diagnosis and reducing empirical antibiotics administration. These findings were consistent with those from previous studies mentioned in this evidence-based case report, which further supports the need for broader implementation of this diagnostic method across Indonesia. However, sourcing and funding are significant issues that must be addressed to facilitate this method across Indonesia.

## Conclusion

Syndromic testing, which is based on the identification of genetic materials using PCR, has the potential to become the breakthrough in infectious diseases diagnostics with a relatively good sensitivity, specificity, PPV, and NPV. The short amount of time needed for examination can improve the effectiveness of clinical management.

## References

1. Liu Q, Jin X, Cheng J, Zhou H, Zhang Y, Dai Y. Advances in the application of molecular diagnostic techniques for the detection of infectious disease pathogens (Review). Mol Med Rep. 2023 Apr 3;27 (5):104.
2. Isnawati A, Gitawati R, Raini M, Alegantina S, Setiawaty V. Indonesia basic health survey: Self-medication profile for diarrhea with traditional medicine. Afr Health Sci. 2019;19(3):2365–71.
3. Misganaw D, Abtew K. Evaluation of Antibiotic Utilization Pattern During Acute Diarrheal Disease at Chefa-Robit Health Center, Kemissie, North East Amhara, Ethiopia. Drug Healthc Patient Saf. 2020 Sep;Volume 12:169–75.
4. Kementerian Kesehatan. Laporan kinerja Direktorat Pencegahan dan Pengendalian Penyakit Menular. Jakarta: Kementerian Kesehatan Republik Indonesia; 2022.
5. Wang T, Wang G, Shan CX, Sun YQ, Ren X, Yu LJ, et al. Comparative study on epidemiological and etiological characteristics of patients with acute diarrhea with febrile or non-febrile symptoms in China. Infect Dis Poverty. 2023;12(1):1–12.
6. Hu ZD, Gu B. Laboratory diagnosis of infectious diseases: a call for more rapid and accurate methods. Akimkin VG, editor. Ann Transl Med. 2020 May;8 (9):600–600.
7. Dumkow LE, Worden LJ, Rao SN. Syndromic diagnostic testing: a new way to approach patient care in the treatment of infectious diseases. J Antimicrob Chemother. 2021 Sep 23;76 (Supplement_3):iii4–11.
8. Knoth C, Humphries R, Johnson JK, Patel A, Lima A, Silbert S, et al. Multicenter evaluation of BioCode GPP for syndromic molecular detection of gastrointestinal pathogens from stool specimens. Ledeboer NA, editor. J Clin Microbiol. 2024 Feb 8;0 (0).
9. Beckman AK, Ferrieri P. Prospective investigation of an automated PCR/nucleic acid microarray-based platform for enteric pathogen testing. Lab Med. 2019 Oct 10;50(4):390–5.
10. Kramme S, Dähne T, Fomenko A, Panning M. Acute viral gastrointestinal (GI) infections in the tropics—a role for cartridge-based multiplex PCR panels? Trop Med Infect Dis. 2022 May 19;7(5):80.
11. Săndulescu O, Streinu-Cercel A, Moțoi MM, Streinu -Cercel A, Preoțescu LL. Syndromic testing in infectious diseases: from diagnostic stewardship to antimicrobial stewardship. Antibiotics. 2022 Dec 21;12(1):6.
12. Axelrad JE, Freedberg DE, Whittier S, Greendyke W, Lebwohl B, Green DA. Impact of gastrointestinal panel implementation on health care utilization and outcomes. J Clin Microbiol. 2019;57(3):1–8.
13. Torres-Miranda D, Akselrod H, Karsner R, Secco A, Silva-Cantillo D, Siegel MO, et al. Use of BioFire FilmArray gastrointestinal PCR panel associated with reductions in antibiotic use, time to optimal antibiotics, and length of stay. BMC Gastroenterol. 2020;20(1):1–7.