Typhoid Fever in Indonesia: Pitfalls in the Diagnosis of Typhoid Fever

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ABSTRACT

Typhoid fever remains a major public health issue in Indonesia, with its true burden likely underreported due to diagnostic challenges. The clinical manifestations of typhoid fever are often nonspecific and overlap with other endemic febrile illnesses such as dengue, leptospirosis, and rickettsial infections, leading to frequent misdiagnosis. Although blood culture and PCR are the gold standards, their limited accessibility in Indonesia has resulted in reliance on suboptimal diagnostic tools such as the Widal test and TUBEX TF. Recent advances, including the Nelwan Score and CRP-based differentiation, have shown promise in improving early clinical screening. Furthermore, antibody-based proteomic diagnostics offer enhanced accuracy but remain largely confined to research settings. A combined approach utilizing validated clinical scores, affordable biomarkers, and selective use of serological tests is essential to improve diagnostic accuracy and patient care. Misdiagnosis not only endangers patient outcomes but also contributes to inappropriate antibiotic use, accelerating the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella Typhi. Resistance to first-line antibiotics and fluoroquinolones has been increasingly reported in Indonesia, although some regions still demonstrate preserved susceptibility. Cautious and evidence-based antibiotic prescribing is therefore critical to mitigating resistance. This article underscores the urgent need to strengthen diagnostic strategies and antimicrobial stewardship to address the persistent challenge of typhoid fever in Indonesia.

Keywords: *Typhoid fever, Diagnostics, Salmonella, Salmonella Typhi*

INTRODUCTION

Typhoid or enteric fever remains a persistent public health concern in Indonesia and other endemic regions. Globally, the disease affects an estimated 11 to 21 million people each year and causes approximately 148,000–161,000 deaths, with the highest burden occurring in South-Central and Southeast Asia.[1-3] In Indonesia, the incidence of typhoid fever is estimated at around 900,000 cases annually, resulting in approximately 20,000 deaths.[4] The number of cases continues to increase each year, with reported mortality rates ranging from 2% to as high as 10.4%.[5,6] However, these figures may not accurately represent the true disease burden due to substantial challenges in diagnosis and surveillance.

One major issue is the non-specific clinical presentation of typhoid fever, which often resembles other causes of acute febrile illness.[7] In routine clinical practice in Indonesia, patients presenting with prolonged fever, diarrhea, or nausea are frequently labeled as having "typhus," a colloquial and inaccurate term that actually

refers to infections caused by *Rickettsia Typhi*. As a result, many individuals resort to self-diagnosis and self-medication without formal medical evaluation. This widespread misconception contributes to significant diagnostic errors.

A study by Gasem et al.[8] reported that a substantial proportion of hospitalized patients in Indonesia with acute febrile illness initially suspected to be typhoid fever were ultimately diagnosed with other etiologies, including rickettsial infections, leptospirosis, and viral illnesses such as chikungunya and influenza. The study found that rickettsial infections accounted for 10.3% of confirmed cases, often misdiagnosed as *Salmonella* spp. or dengue infections. Furthermore, *Salmonella* spp. were among the three most common microbiological causes of fatal cases, identified in 5.6% with a mortality rate of 4.9% among those infected.[8] A distinguishing feature of *Salmonella Typhi* compared with other *Salmonella* species is its ability to survive and replicate within host macrophages, facilitating systemic infection.[9]

The second major challenge lies in the limitations of diagnostic modalities. Although blood culture and polymerase chain reaction (PCR) are considered the gold standards for confirming typhoid fever, these methods are expensive, not widely accessible, and often have long turnaround times.[10] In many cases, empirical antibiotic therapy is initiated and completed before diagnostic results are available.[7] Moreover, the clinical presentation of typhoid fever frequently overlaps with other conditions. For instance, symptoms such as diarrhea do not always indicate typhoid fever. A cross-sectional study conducted in Southeast Asia found that *Salmonella Typhi* was rarely detected in patients with acute diarrhea.[11] Consequently, serological tests such as Widal, TUBEX, and IgM or IgG ELISA are commonly used despite their limited accuracy.

Culture-based diagnosis is available only in a minority of healthcare facilities—primarily referral and urban hospitals—and therefore serves as the standard of care in only a small proportion of cases in Indonesia.[12] Most patients are instead diagnosed based on serological tests or clinical features alone, particularly in rural and resource-limited settings where advanced diagnostic infrastructure is lacking.[13]

The combination of non-specific clinical signs and suboptimal diagnostic testing contributes to a third challenge: the inappropriate use of antibiotics and the growing problem of antimicrobial resistance. Misdiagnosis, whether through overdiagnosis or underrecognition, often leads to unnecessary antibiotic prescriptions.[7,12] Over time, this practice has driven increasing resistance of *Salmonella Typhi* strains to commonly used antibiotics, including fluoroquinolones and third-generation cephalosporins. Resistance to first-line agents such as chloramphenicol, ampicillin, and cotrimoxazole has also been reported in several Southeast Asian regions, particularly Indonesia.[14-16]

This article examines the diagnostic pitfalls associated with typhoid fever in Indonesia by highlighting the gap between clinical suspicion and laboratory confirmation, evaluating the performance of available diagnostic tools, and discussing the broader implications of misdiagnosis on antimicrobial resistance and patient outcomes.

CLINICAL PRESENTATION AND MISDIAGNOSIS

The clinical spectrum of typhoid fever in Indonesia is broad and frequently overlaps with other endemic febrile illnesses such as dengue fever, malaria, leptospirosis, and viral infections.[8] This overlap poses a considerable diagnostic challenge, particularly in resource-limited settings where laboratory confirmation is not readily available. Typical clinical features of typhoid fever include persistent fever, abdominal discomfort, nausea, loss of appetite, headache, fatigue, myalgia, and diarrhea or constipation. Although the classic step-ladder fever pattern is a well-recognized sign, it is now rarely observed due to the widespread use of early antibiotic therapy. Other notable findings include relative bradycardia and a coated tongue, which, when present, can support the clinical diagnosis of typhoid fever. While these symptoms are widely recognized, they are nonspecific and often lead to presumptive diagnoses based solely on clinical judgment.[17-20]

The clinical presentation of typhoid fever is closely associated with its pathogenesis. Following ingestion of *Salmonella enterica serovar Typhi*, the bacteria invade the intestinal mucosa and replicate within the reticuloendothelial system, initially producing nonspecific gastrointestinal symptoms such as abdominal discomfort, diarrhea or constipation, and anorexia. As the infection progresses to the systemic phase, the hallmark step-ladder fever pattern typically develops, often accompanied by malaise, headache, and relative bradycardia. In prolonged or severe cases—particularly when fever persists beyond one week—various complications may arise, some presenting as atypical manifestations. This temporal progression underscores the importance of considering the timing of symptom onset when selecting diagnostic tests and maintaining vigilance for potential complications in patients with persistent fever.[21]

Atypical manifestations of typhoid fever have been reported and may lead to delayed diagnosis, inappropriate treatment, and an increased risk of complications or mortality. These uncommon presentations often involve organ systems beyond the gastrointestinal tract and may mimic other conditions such as viral hepatitis, pneumonia, meningitis, or even acute surgical emergencies. In endemic regions, such manifestations are frequently underrecognized, especially in settings with limited diagnostic capacity.[22,23] **Table 1** summarizes several rare clinical presentations of typhoid fever reported in the literature.

Table 1. Atypical Presentations of Typhoid Fever Reported in Various Case Studies

System / Diagnosis	Reported Clinical Manifestations	Confirmatory Typhoid Diagnosis
Gastrointestinal		
Appendicitis-like presentation[24,25]	Lower abdominal pain without initial fever, normal ultrasound findings	Positive IgM and Widal test
Acute pancreatitis[26]	Epigastric and right hypochondriac tenderness, ascites, elevated lipase levels	Positive blood culture for *Salmonella Typhi*
Acalculous cholecystitis[27]	Fever, jaundice, right upper quadrant tenderness, gallbladder wall thickening, pericholecystic fluid, positive Murphy's sign	Positive blood culture for *Salmonella Typhi*
Hepatitis[28,29]	Fever, jaundice, hepatomegaly, elevated bilirubin, increased AST and ALT	Positive blood culture; clinical diagnosis
Intestinal hemorrhage[30]	Hypotension, gastrointestinal bleeding from the ileocecal valve observed via colonoscopy	Positive blood culture and endoscopic findings
Intestinal perforation[31]	High-grade fever, lower abdominal pain, free air on abdominal X-ray, intraoperative confirmation of ileal perforation	Positive blood culture and histopathological biopsy
Pulmonary		
Typhoid pneumonitis[32]	Mild cough, sputum production, chest radiograph showing lobar to diffuse infiltrates, bradycardia, diarrhea	Positive blood culture for *Salmonella Typhi*
ARDS[33]	Rapid clinical deterioration, bilateral pulmonary infiltrates, impaired oxygenation	Positive cultures from blood, stool, and urine
Neuropsychiatric		
Encephalopathy[34]	Seizures, altered consciousness, normal cerebrospinal fluid, persistent fever	Positive blood culture for *Salmonella Typhi*
Acute psychosis[35]	Behavioral changes, auditory hallucinations, fever	Positive blood culture
Ataxia and upper motor dysfunction[36]	Spasticity, clonus, bradykinesia, hyperreflexia	Rapid diagnostic assays and cultures
Sensorineural hearing loss[37]	Progressive bilateral hearing loss, fever, watery stools, confirmed with audiometry	Positive blood culture for *Salmonella Typhi*
Renal		
Typhoid nephritis / Glomerulonephritis[38]	Fever, hypertension, pedal edema, hematuria, proteinuria	Positive blood culture, high Widal titers

DIAGNOSTIC LIMITATIONS IN CLINICAL PRACTICE

Accurate diagnosis of typhoid fever remains a major challenge in endemic settings such as Indonesia, primarily due to the nonspecific nature of its clinical presentation and the limited availability of reliable diagnostic tools. While the gold standard diagnostic methods remain blood culture and polymerase chain reaction (PCR), their limited accessibility, high cost, and delayed turnaround time often necessitate alternative approaches in routine clinical practice.[39,40]

A widely adopted clinical screening tool is the Nelwan Score, a point-based system developed in Indonesia in 1991 to assess the likelihood of typhoid fever based on specific clinical symptoms and signs. This scoring system serves as an effective screening method in resource-limited settings and may help reduce inappropriate antibiotic use.[7]

In the early phase of illness characterized by gastrointestinal symptoms and fever lasting less than one week clinical scoring systems such as the Nelwan Score can be applied to identify suspected cases, although confirmatory diagnostic testing remains essential. Nonspecific but supportive laboratory findings may also assist in clinical decision-making.[7]

A study by Pohan *et al.* on the clinical and laboratory manifestations of typhoid fever in a Jakarta hospital reported that most patients diagnosed with typhoid fever presented with leukopenia in 45.3% of cases or normal leukocyte counts in 51.3% of cases. Thrombocytopenia was observed in 61.5% of patients. Elevated SGOT and SGPT levels were found in 92.1% and 68.3% of patients, respectively. These findings indicate that leukocytosis is uncommon in typhoid fever; patients often present with normal or reduced leukocyte counts, which may shift to lymphocytosis with aneosinophilia. Other common abnormalities include thrombocytopenia and elevated transaminase levels (SGOT and SGPT).[41]

Table 2. Nelwan Score for Typhoid Fever: A 10 out of 20 score is considered the optimal cut-off value for screening purposes.[7]

Symptom	Score
Fever ≤ 1 week	1
Fever > 1 week	2
Headache	1
Weakness	1
Nausea	1
Abdominal pain	1
Anorexia	1
Vomiting	1
Motility disorder	1
Insomnia	1
Hepatomegaly	1
Splenomegaly	1
Relative bradycardia	2
Typhoid tongue	2
Melena stools	2
Impaired consciousness	2

The C-reactive protein (CRP) test is a rapid, affordable diagnostic tool for assessing the causes of acute fever. A study by Idhayu *et al.* in Indonesia demonstrated significantly different CRP levels in acute fever cases caused by dengue infection and typhoid fever. At the 99th percentile cut-off, a CRP level greater than 45.91 mg/L was diagnostic for typhoid fever, while a CRP level lower than 8 mg/L indicated dengue infection. These findings suggest that CRP differentiation levels can support early and accurate diagnosis, particularly in distinguishing between dengue and typhoid fever, which often present with similar clinical features.[42]

Immunodiagnostic tests play a central role in diagnosing typhoid fever, particularly in resource-limited and endemic regions where culture or molecular diagnostics are not feasible. These tests detect antibody responses to *Salmonella Typhi* antigens and are widely used due to their low cost, ease of use, and rapid turnaround. A systematic review by Najib *et al.*assessed the performance of various serological assays and found that anti-lipopolysaccharide (LPS) IgA demonstrated the highest sensitivity (96%) and specificity (96%) for distinguishing typhoid cases from healthy controls. Combining multiple antibody targets significantly enhanced diagnostic accuracy when differentiating typhoid from other febrile illnesses. The combination of anti-LPS and anti-flagellin total IgGAM achieved the highest sensitivity (93%) and specificity (95%). Anti-hemolysin E (HlyE) antibodies also exhibited strong diagnostic performance across different infection phases, showing potential for acute diagnosis and carrier

detection. These findings suggest multiplex antibody-based strategies may provide more accurate and feasible alternatives where culture and PCR are inaccessible.[13]

Antibody proteome arrays represent a more advanced diagnostic approach, enabling the simultaneous detection of immune responses to a broad panel of *S. Typhi* antigens. This method offers greater diagnostic precision than conventional serological tests by analyzing multiple antibody isotypes (IgM, IgA, and IgG) against diverse antigens. Key immunoreactive targets identified through this platform include HlyE, outer membrane protein A (OmpA), and LPS, which have shown strong potential as biomarkers for acute typhoid infection. Evaluations in Nepal demonstrated that the most effective antibody combinations achieved area under the curve (AUC) values exceeding 0.87, indicating excellent diagnostic performance. Notably, this proteome-based strategy facilitates the discovery of candidate markers that may be adapted into rapid diagnostic tests with multiplex capabilities, providing a promising solution for use in resource-limited, high-burden regions.[43,44]

Blood culture and PCR remain the gold standard diagnostic methods for typhoid fever.[39,45] Blood culture is widely recommended due to its ability to isolate *S. Typhi* directly, although sensitivity is influenced by factors such as low bacterial load and prior antibiotic use.[46] Stool cultures typically become positive during the second week of illness, while urine cultures may yield results in the second or third week.[41] Bone marrow cultures offer higher sensitivity but are invasive and less feasible in routine clinical practice.[47] PCR provides a more rapid and sensitive alternative, especially in early disease or low bacterial load conditions. Still, its use in endemic regions remains limited by high costs and the need for specialized equipment.[48,49] PCR may also exhibit reduced diagnostic sensitivity when performed on peripheral blood samples.[50] Recent advances, such as combining blood culture with PCR (culture-PCR), have improved diagnostic accuracy by enriching *S. Typhi* before amplification. This method reduces blood volume requirements and shortens turnaround time, enabling same-day diagnosis and prompt initiation of antimicrobial therapy.[51]

In many Indonesian healthcare settings, serological tests remain the most commonly used diagnostic tools due to their affordability, rapid turnaround, and ease of use. Several commercial tests are widely utilized in clinical practice, including the Widal test, TUBEX TF, Typhidot, and ELISA-based assays. Among these, the Widal test remains the most commonly used despite its limited specificity and the confounding effect of endemic background antibody levels.[52]

The Widal test is most reliable when antibodies typically appear in the second or third week of illness.[4] Its limited specificity arises from cross-reactivity, as positive results may also occur in non-typhoidal *Salmonella* infections such as enteritis.[53] The Widal test continues to be widely used in Indonesia despite these limitations, as baseline antibody titers may be positive even among healthy individuals. This underscores the importance of establishing population-specific cutoff values to improve diagnostic accuracy. A repeat Widal test may be performed to assess rising titers, although a fourfold increase is uncommon. A study by Pohan *et al.* in hospitalized patients in Jakarta showed that titer increases were usually one- to twofold, with fourfold rises being rare.[41]

The TUBEX TF test, which detects anti-O9 IgM antibodies using a color change inhibition format, provides faster results than Widal. A score of 4 is considered weakly positive, while scores between 6 and 10 indicate positivity.[3] The TUBEX test demonstrates higher sensitivity than the Widal test; however, its diagnostic accuracy is time-dependent, and false-negative results may occur during the early phase of illness before antibody production develops.[54] Typhidot, which detects IgM and IgG antibodies against *S. Typhi* outer membrane proteins, is a simple test that does not require specialized equipment or trained personnel, making it a widely adopted and cost-effective method in low-resource settings.[49] ELISA-based assays, particularly IgM/IgG assays targeting specific *S. Typhi* antigens, have shown promising accuracy and may represent a superior diagnostic alternative in endemic areas.[56,57]

The Widal test, TUBEX TF, and Typhidot are commonly utilized in clinical practice in Indonesia due to their affordability, rapid turnaround, and minimal requirement for advanced laboratory infrastructure. In contrast, culture, PCR, and certain ELISA-based assays are more frequently performed in research settings or larger referral hospitals, given their higher costs, technical complexity, and the need for specialized equipment. Blood cultures may yield negative results during the early phase of typhoid fever, as the infection is initially confined to the gastrointestinal tract. Systemic involvement, including bacteremia, typically develops during the second week of illness, explaining the limited sensitivity of blood-based diagnostic tests in the initial stages.[3,5,13,48,57] Stool culture, while useful particularly in later stages of the disease, cannot establish a definitive diagnosis since typhoid fever is primarily a systemic infection. A positive stool culture may merely indicate a carrier state. Therefore, evidence of systemic involvement—such as the presence of *Salmonella* in the bloodstream—is required for confirmation.[58] When performing PCR for typhoid diagnosis, the use of multiplex PCR is recommended, as it allows simultaneous detection of *Salmonella Paratyphi*.[59]

The performance of currently available diagnostic methods for typhoid fever varies substantially in terms of sensitivity, specificity, and clinical applicability. **Table 3** summarizes the primary diagnostic tools currently used, highlighting their mechanisms, diagnostic performance, and practical considerations.

Table 3. Performance Summary of Diagnostic Methods for Typhoid Fever

Diagnostic Method	Mechanism	Sensitivity	Specificity	PPV	NPV
Nelwan Score[7]	Scoring system based on clinical signs and symptoms	81.8%	60.8%	9.3%	98.5%
Widal Test[52]	Detection of anti-O and anti-H antibodies	79.3% (fever onset >5 days), 46.6% (<5 days)	59.9% (fever onset >5 days), 38.5% (<5 days)	6.8%	100%
TUBEX TF[3,4]	IgM antibody detection against LPS	70.7–97.6%	38.3–67.2%	48.5%	92.9%
IgM ELISA[3,48,56,60]	Detection of IgM antibodies to *S. Typhi*	59.3-92.9%	68.8-95.5%	93.3%	93.4%
IgG ELISA[3,48,56,60]	Detection of IgG antibodies to *S. Typhi*	90.7%	82.7%	93.0%	91.1%
Typhidot[55,61]	IgM/IgG detection against outer membrane protein (OMP)	67–75.5%	54–85.5%	56.6–85%	81–93.3%
Blood Culture[46]	Isolation of *S. Typhi* from blood	40–87%	≈100%	-	-
Bone Marrow Culture[47]	Isolation of *S. Typhi* from bone marrow	Up to 90%	≈100%	-	-
PCR[40]	Detection of *S. Typhi* DNA in blood	>90%	≈100%	-	-

DIFFERENTIAL DIAGNOSIS IN TYPHOID FEVER

The most common differential diagnoses of typhoid fever include other acute febrile illnesses frequently reported in the literature, such as dengue fever, rickettsial infections, salmonellosis, and leptospirosis.[8] Typhoid fever can often be differentiated by its characteristic step-ladder fever pattern, gastrointestinal manifestations, gradual rise in body temperature, and the persistence of fever beyond seven days. A normal leukocyte count is often observed because *Salmonella Typhi* is an intracellular pathogen capable of evading neutrophil detection. Elevated C-reactive protein (CRP) levels are also frequently reported.

In contrast, dengue infection typically presents as an acute febrile illness accompanied by headache, retro-orbital pain, severe myalgia ("breakbone fever"), rash, and bleeding tendencies, often in individuals with a history of mosquito exposure. Dengue is further characterized by marked thrombocytopenia during the acute febrile phase and generally low CRP levels.[42,62] Rickettsial infections usually manifest with fever, rash, arthralgia, and the presence of an eschar at the tick bite site—often resembling a cigarette burn—and may also be associated with severe thrombocytopenia.[63] Leptospirosis should be suspected in individuals with a history of exposure to water contaminated by rodent urine. It may present with fever, conjunctival suffusion, gastrocnemius tenderness, and jaundice. In severe cases, Weil's disease may develop, characterized by jaundice, rash, and acute kidney injury.[64]

ANTIBIOTIC RESISTANCE AND TREATMENT CHALLENGES

Current treatment guidelines for typhoid fever in Indonesia have been established, with chloramphenicol remaining the first-line therapy. However, widespread resistance to chloramphenicol has been reported. Other commonly used antibiotics include ampicillin, cotrimoxazole, fluoroquinolones, and third-generation cephalosporins.[65]

Chloramphenicol has been used for a long time, but increasing resistance and associated side effects have necessitated the use of alternative antibiotics.[66] The improper use of first-line antibiotics has led to the emergence of multidrug-resistant (MDR) strains. Consequently, fluoroquinolones were introduced as an alternative treatment following the development of resistance to first-line antibiotics. Misuse of antibiotics has contributed to the emergence of MDR *Salmonella Typhi*, defined as resistance to chloramphenicol, ampicillin, and cotrimoxazole. Extensively drug-resistant (XDR) *Salmonella Typhi* exhibits additional resistance to fluoroquinolones and third-generation cephalosporins.[14,67]

Several studies have reported varying resistance levels to multiple antibiotics used in typhoid fever treatment. A comparison between ceftriaxone and chloramphenicol demonstrated that *S. Typhi* is more sensitive to ceftriaxone, with clinical evidence indicating better efficacy of ceftriaxone in treating typhoid fever.[68]

Although fluoroquinolones have been used as an alternative therapy, resistance to this antibiotic class has emerged in various regions despite their widespread application.[69] In Indonesia, a study conducted at a general hospital in Tangerang between 2011 and 2015 reported low resistance rates to ampicillin, trimethoprim-sulfamethoxazole, ceftriaxone, and fluoroquinolones.[15] However, a systematic review of antibiotic resistance in Jakarta revealed increasing resistance to fluoroquinolones such as ciprofloxacin and β-lactam antibiotics, including ampicillin and ceftriaxone. Other studies have also reported high resistance levels to β-lactam antibiotics—commonly used agents for treating *Salmonella Typhi* infections.[16] This underscores the heterogeneity of antimicrobial resistance patterns in typhoid fever across different regions in Indonesia.

Antibiotic resistance remains a major challenge in the management of typhoid fever, as it complicates treatment particularly in resource-limited settings and increases morbidity. A review of antimicrobial resistance trends in Southeast Asia highlighted a significant rise in fluoroquinolone resistance in *Salmonella Typhi*, leading to delayed fever resolution. In light of reduced fluoroquinolone efficacy, third-

generation cephalosporins (e.g., ceftriaxone, cefixime) or azithromycin are now preferred for treating typhoid fever in developing countries.[69] However, a recent study from Jakarta reported continued susceptibility of *Salmonella Typhi* to first-line antibiotics, including chloramphenicol, ampicillin, cephalosporins, and fluoroquinolones over the past decade, suggesting that these agents remain viable treatment options in Indonesia, particularly in areas lacking microbiological diagnostic facilities.[70]

CONCLUSION

Accurate diagnosis of typhoid fever remains challenging, especially in endemic regions such as Indonesia, due to its nonspecific clinical presentation. To improve clinical outcomes and minimize antibiotic misuse, clinicians should employ a combination of validated diagnostic tools, such as the Nelwan Score, C-reactive protein (CRP) testing, and reliable rapid diagnostic assays based on antigen or serological detection. Given the high risk of misdiagnosis and its contribution to antimicrobial resistance, typhoid fever should not be treated presumptively without clear clinical evidence.

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Study design (ERY, KCL); manuscript writing (ERY); critical revision (ERY, KCL, AP, NL).

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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