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Beyond Classical Diphtheria: Nontoxigenic *Corynebacterium diphtheriae* Isolated from Blood Culture in a Child : A Case Report and Public Health Implication

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A B S T R A C T

Nontoxigenic *Corynebacterium diphtheriae* has increasingly been recognized as a clinically relevant pathogen capable of causing invasive and non-invasive infections. However, reports from Southeast Asia, particularly among pediatric populations, remain limited. This study describes two pediatric cases identified during laboratory-based surveillance in North Sumatra, Indonesia. Clinical specimens were examined using culture, microscopic examination, biochemical identification, Elek toxigenicity testing, and polymerase chain reaction (PCR) for diphtheria toxin gene detection at the National Health Biology Laboratory. The first case involved a 5-year-old child whose blood culture yielded *C. diphtheriae* var. gravis without classical respiratory manifestations. The second case involved a 13-year-old child with a wound infection in which wound swab culture identified the same organism. Both isolates were confirmed as nontoxigenic. These findings highlight the expanding clinical spectrum of nontoxigenic *C. diphtheriae* and emphasize the importance of laboratory confirmation and surveillance integration for early detection of atypical diphtheria-related infections.

INTRODUCTION

Diphtheria is a vaccine-preventable infectious disease caused by toxigenic strains of *Corynebacterium diphtheriae*, characterized by upper respiratory tract infection and potentially fatal systemic complications mediated by diphtheria toxin (World Health Organization, 2017; Efstratiou & George, 1999).Hstorically, the pathogenicity of *C. diphtheriae* has been attributed almost exclusively to toxin production, leading to the long-standing assumption that nontoxigenic strains are of limited clinical importance (MacGregor & McKee, 1986).

Over the past two decades, this paradigm has been increasingly challenged. Multiple studies have demonstrated that nontoxigenic *C. diphtheriae* is capable of causing invasive infections, including bacteremia, septic arthritis, and infective endocarditis, particularly among individuals with underlying comorbidities (Tiley et al., 1993; Rasmussen et al., 2020). These infections often occur in the absence of classical respiratory manifestations, making clinical suspicion and diagnosis more challenging.

Epidemiological data from Europe and North America suggest a gradual increase in invasive infections caused by nontoxigenic *C. diphtheriae*, even in settings with high vaccination coverage (Zasada & Rzeczkowska, 2019; Dangel et al., 2018). In the United States, surveillance reports have documented a rise in nontoxigenic *C. diphtheriae* cases since 2018, affecting vulnerable populations and resulting in both cutaneous and invasive disease. (CDC, 2023. These findings indicate that vaccination, while effective against toxin-mediated disease, does not prevent colonization or infection by nontoxigenic strains (Wagner et al., 2012). In addition, cutaneous diphtheria-like infection has gained recognition as an important clinical and public health entity, as skin lesions may serve as a reservoir for transmission and may be underdiagnosed when wound isolates are dismissed as non-pathogenic "diphtheroids" without further confirmation (Lowe et al., 2011; Reacher et al., 2000). In addition, limitations in laboratory identification contribute to underreporting. Many laboratories do not perform species-level identification for Corynebacterium isolates, especially from non-respiratory specimens. This gap may obscure the true burden of disease.

Despite these observations, reports of invasive nontoxigenic *C. diphtheriae* infection from Southeast Asia remain scarce, particularly in pediatric populations. Indonesia, which continues to report diphtheria cases and maintains active surveillance programs, represents an important setting in which atypical presentations may be underrecognized. Most published reports describing invasive infections caused by nontoxigenic *C. diphtheriae* originate from Europe and North America, while evidence from Southeast Asia remains scarce. Furthermore, pediatric cases involving bloodstream infection or wound-associated infection without classical diphtheria manifestations are rarely documented in the region. This lack of documentation creates an important knowledge gap regarding the clinical spectrum and epidemiological significance of nontoxigenic *C. diphtheriae* infections in Indonesia. Therefore, this study aims to describe two pediatric cases of nontoxigenic *Corynebacterium diphtheriae* identified in North Sumatra, Indonesia, and to discuss their clinical

characteristics and public health implications within the context of diphtheria surveillance.

In many clinical settings, *Corynebacterium* species isolated from non-respiratory specimens are frequently regarded as contaminants or part of normal flora, particularly when identified from wound swabs or blood cultures without classical diphtheria symptoms. This assumption may lead to underdiagnosis and underreporting of clinically significant infections caused by nontoxigenic *C. diphtheriae*. Studies have shown that inadequate species-level identification and lack of toxigenicity testing contribute significantly to the misclassification of these organisms, thereby obscuring their true epidemiological and clinical impact (Funke et al., 1997; Efstratiou & George, 1999).

From a public health perspective, the emergence of nontoxigenic *C. diphtheriae* infections presents new challenges for surveillance systems that are primarily designed to detect toxin-mediated disease. In endemic countries such as Indonesia, where diphtheria remains a public health concern, atypical presentations may go unnoticed without strong laboratory-based surveillance. The integration of clinical findings with laboratory confirmation is therefore essential to improve case detection, monitor evolving epidemiological patterns, and support timely public health response. These considerations underscore the importance of documenting and reporting atypical cases, particularly in pediatric populations, to strengthen the evidence base in Southeast Asia.

Case Presentation

Case 1

A 5-year-old female patient was hospitalized in a pediatric cardiac care unit in Deli Serdang district, North Sumatra. The patient did not exhibit signs or symptoms consistent with classical diphtheria, such as sore throat, pseudomembrane formation, cervical lymphadenopathy, or respiratory distress. As part of inpatient evaluation, blood culture examination was performed.

The blood culture revealed bacterial growth suggestive of *Corynebacterium* species. Due to the unexpected finding and potential public health concern, the isolate, along with throat and nasopharyngeal swab specimens, was referred to the National Health Biology Laboratory (BBLBK), Ministry of Health of Indonesia, for confirmatory testing. Laboratory investigations at BBLBK included microscopic examination, culture, biochemical identification, Elek test, and polymerase chain reaction (PCR) for diphtheria toxin gene detection. The results showed that both throat and nasopharyngeal swab specimens were negative for *C. diphtheriae*. In contrast, the blood culture isolate was identified as *Corynebacterium diphtheriae* var. gravis and confirmed to be nontoxigenic based on negative Elek test and PCR results.

Case 2

A 13-year-old male was identified as part of a suspected diphtheria public health investigation in North Sumatra. In response to this event, blood culture was obtained and yielded bacterial growth compatible with *Corynebacterium* species. Given the epidemiological context and the importance of ruling out toxigenic diphtheria, the blood culture isolate was referred through the

provincial surveillance network to the national reference laboratory for confirmation.

Confirmatory laboratory testing included culture-based identification and toxigenicity assessment, supporting the diagnosis of **nontoxigenic *Corynebacterium diphtheriae*** isolated from blood culture. This second case further emphasizes that invasive infection due to *C. diphtheriae* may occur outside the typical presentation of toxin-mediated diphtheria and highlights the importance of laboratory-based surveillance for sterile-site isolates during suspected diphtheria events. *Corynebacterium diphtheriae* var. gravis and confirmed to be nontoxigenic based on negative Elek test and PCR results

THEORETICAL REVIEW

Pathogenesis of Corynebacterium diphtheriae

Corynebacterium diphtheriae is a Gram-positive bacterium recognized as the etiological agent of diphtheria, a toxin-mediated disease primarily affecting the upper respiratory tract. The pathogenicity of this organism is mainly associated with the production of diphtheria toxin encoded by the *tox* gene, which is responsible for severe systemic complications such as myocarditis and neuropathy Historically, clinical attention has focused on toxigenic strains because of their role in classical diphtheria outbreaks. As a result, nontoxigenic strains were previously considered to have limited pathogenic potential and were often regarded as commensals or laboratory contaminants.

Infections Caused by Nontoxigenic Corynebacterium diphtheriae

However, increasing evidence has demonstrated that nontoxigenic *C. diphtheriae* can cause clinically significant infections independent of toxin production. Several studies have reported invasive infections caused by these strains, including bacteremia, infective endocarditis, septic arthritis, and osteomyelitis. These findings suggest that nontoxigenic strains possess alternative virulence mechanisms that enable them to invade host tissues.

Cutaneous Infection as a Potential Reservoir of Transmission

In addition to invasive disease, cutaneous infections caused by *C. diphtheriae* have been increasingly reported and may serve as reservoirs for bacterial transmission within communities. Epidemiological studies from Europe and North America have also documented an increase in infections caused by nontoxigenic strains in recent years

Global Epidemiological Trends of Corynebacterium diphtheriae

Molecular epidemiological investigations have further revealed substantial genetic diversity among circulating *C. diphtheriae* strains, suggesting ongoing bacterial evolution and adaptation. These findings highlight the importance of laboratory-based surveillance and accurate species-level identification in detecting atypical presentations of diphtheria-related infections.

Host Susceptibility and Risk Factors

Host susceptibility plays an important role in the development of invasive infections caused by nontoxigenic *Corynebacterium diphtheriae*. Several studies have identified underlying medical conditions such as cardiac abnormalities, immunosuppression, chronic skin lesions, and poor hygiene as contributing risk factors (Rasmussen et al., 2020; Tiley et al., 1993). In particular, individuals with compromised immune systems or pre-existing comorbidities are more susceptible to bloodstream infections and endocarditis. In pediatric populations, risk factors may include malnutrition, incomplete immunization, and prolonged hospitalization. Although vaccination protects against toxin-mediated disease, it does not prevent bacterial colonization. This creates a scenario in which nontoxigenic strains may persist and potentially invade sterile sites, especially in vulnerable individuals.

Mechanisms of Invasion and Disease Progression

The pathogenesis of invasive disease caused by nontoxigenic *C. diphtheriae* is not yet fully understood. However, it is believed that bacterial entry may occur through breaches in mucosal or skin barriers, followed by hematogenous spread. Once in the bloodstream, the organism may adhere to endothelial surfaces and establish infection, particularly in cardiac tissues, leading to complications such as infective endocarditis (Tiley et al., 1993). Additionally, the ability to form biofilms and adhere to host tissues may contribute to persistence and resistance to host immune responses. These mechanisms suggest that nontoxigenic strains possess sufficient virulence capacity to cause severe disease even in the absence of toxin production.

Potential for Genetic Transformation and Tox Gene Acquisition

An important concern in the epidemiology of *C. diphtheriae* is the potential for nontoxigenic strains to acquire the *tox* gene through lysogenic conversion mediated by bacteriophages. This process has been well documented and represents a mechanism by which previously non-toxigenic strains may become toxigenic and capable of causing classical diphtheria (Efstratiou & George, 1999). The circulation of nontoxigenic strains in the population may therefore represent a hidden risk, as these strains can serve as a genetic reservoir. Continuous surveillance is essential to detect such changes early and prevent potential outbreaks.

Implications for Clinical Management

The recognition of nontoxigenic *C. diphtheriae* as a potential pathogen has important implications for clinical management. Clinicians should consider this organism as a possible cause of infection when isolated from sterile sites such as blood or from clinically significant wound specimens. Appropriate antimicrobial therapy should be guided by susceptibility testing, as resistance patterns may vary. Furthermore, infection control measures should not be overlooked. Even in the absence of toxin production, patients with confirmed *C. diphtheriae* infection may require isolation precautions to prevent transmission, particularly in

healthcare settings. Early diagnosis and appropriate management are therefore essential to reduce morbidity and prevent further spread.

METHODOLOGY

This study employed a descriptive case report design based on laboratory-confirmed cases detected through routine diphtheria surveillance activities in North Sumatra, Indonesia. Clinical specimens were obtained from pediatric patients during hospital evaluation and public health investigation. Blood culture specimens and wound swab samples were initially processed at local hospital laboratories. Due to the identification of Corynebacterium species and the potential public health significance, the isolates were referred to the National Health Biology Laboratory (Balai Besar Laboratorium Biologi Kesehatan – BBLBK), Ministry of Health of Indonesia, for confirmatory testing. Laboratory investigations included microscopic examination, bacterial culture, and biochemical identification to determine the species. Toxigenicity testing was performed using the Elek immunodiffusion test. In addition, polymerase chain reaction (PCR) targeting the diphtheria toxin (tox) gene was conducted to determine whether the isolates were toxigenic or nontoxigenic. Clinical and laboratory findings were reviewed descriptively to characterize the cases and evaluate their potential public health implications. Patient identities were anonymized to maintain confidentiality.

RESULTS AND DISCUSSION

The present report describes two pediatric cases of infection caused by nontoxigenic *Corynebacterium diphtheriae* identified through laboratory-based surveillance in North Sumatra, Indonesia. These findings highlight the expanding clinical spectrum of nontoxigenic *C. diphtheriae*, which may manifest as invasive bloodstream infection or cutaneous infection even in the absence of classical diphtheria symptoms. Traditionally, the pathogenicity of *C. diphtheriae* has been strongly associated with diphtheria toxin production. Consequently, nontoxigenic strains were historically considered to have limited clinical relevance. However, increasing evidence indicates that these strains are capable of causing clinically significant infections independent of toxin production (MacGregor & McKee, 1986; Zasada & Rzeczkowska, 2019).

Isolation of *C. diphtheriae* from blood culture, as observed in the first case, should be regarded as clinically significant and not merely as laboratory contamination. Several studies have reported that *C. diphtheriae* isolated from sterile sites such as blood is frequently associated with true invasive infections, including bacteremia and infective endocarditis. Invasive infections caused by nontoxigenic strains have been reported in various populations, particularly among individuals with underlying medical conditions or compromised host defenses (Rasmussen et al., 2020). In the present case, the patient was admitted to a pediatric cardiac care unit, which may represent a potential risk factor for invasive infection, as cardiac abnormalities have been associated with increased susceptibility to *C. diphtheriae* bacteremia and endocarditis (Rasmussen et al., 2020; Tiley et al., 1993).

The isolation of nontoxigenic *Corynebacterium diphtheriae* from blood culture, as observed in this study, should be interpreted with caution and clinical relevance. While coryneform bacteria are often considered contaminants, increasing evidence indicates that *C. diphtheriae* isolated from sterile sites is frequently associated with true infection rather than contamination (Rasmussen et al., 2020). This distinction is particularly important in pediatric patients, where early recognition of bloodstream infection is critical for appropriate management.

An important feature of the first case is the absence of respiratory tract involvement. Both throat and nasopharyngeal swabs tested negative for *C. diphtheriae*, suggesting that bloodstream infection may occur without detectable respiratory colonization. Similar findings have been reported in several studies in Europe, where invasive infections caused by nontoxigenic *C. diphtheriae* were documented in patients without classical respiratory diphtheria manifestations (Dangel et al., 2018; Gubler et al., 1998). These observations suggest that alternative routes of entry, including transient colonization of mucocutaneous surfaces or breaches in the skin barrier, may play a role in the pathogenesis of invasive infection (Funke et al., 1997).

The second case further illustrates the role of cutaneous infections in the epidemiology of *C. diphtheriae*. Cutaneous diphtheria and wound infections caused by *C. diphtheriae* have been increasingly reported in several countries and are recognized as potential reservoirs for bacterial transmission (Lowe et al., 2011; Reacher et al., 2000. Skin lesions may facilitate bacterial persistence in the community and contribute to the spread of the organism, particularly in settings where laboratory identification of coryneform bacteria is limited (Lowe et al., 2011). In some clinical settings, wound isolates of C. diphtheriae may be misclassified as non-pathogenic diphtheroids and therefore not subjected to further identification, which may lead to underestimation of their epidemiological importance.

From an epidemiological perspective, the increasing recognition of infections caused by nontoxigenic *C. diphtheriae* reflects changing patterns in diphtheria epidemiology. Surveillance studies in Europe have documented a gradual increase in infections caused by nontoxigenic strains, even in regions with high vaccination coverage (Zasada & Rzeczkowska, 2019; Dangel et al., 2018). Similarly, recent surveillance data from the United States have reported a rise in nontoxigenic *C. diphtheriae* cases in recent years (Centers for Disease Control and Prevention, 2023). These findings suggest that while vaccination effectively prevents toxin-mediated disease, it does not prevent colonization or infection by nontoxigenic strains (Wagner et al., 2012).

From a laboratory and public health perspective, these cases highlight the importance of accurate species-level identification and toxigenicity testing. Differentiating between toxigenic and nontoxigenic strains requires specialized diagnostic methods such as Elek testing and polymerase chain reaction (PCR), which are typically available only in reference laboratories (Efstratiou & George, 1999). Strengthening laboratory capacity and specimen referral systems is

therefore essential for improving detection of atypical *C. diphtheriae* infections (Efstratiou & George, 1999).

In addition, documenting infections caused by nontoxigenic *C. diphtheriae* may contribute to improved understanding of the evolving epidemiology of diphtheria. Some authors have suggested that invasive infections caused by nontoxigenic strains should be incorporated into surveillance systems as sentinel events reflecting changing transmission dynamics (Clarke et al., 2019; Bonmarin et al., 2009). The cases presented in this report provide additional evidence from Southeast Asia and support the need for strengthened laboratory-based surveillance to detect both toxigenic and nontoxigenic C. diphtheriae infections.

The presence of nontoxigenic *C. diphtheriae* in the population raises important concerns regarding its potential evolution. Through bacteriophage-mediated gene transfer, these strains may acquire the *tox* gene and become toxigenic (Efstratiou & George, 1999). This possibility underscores the importance of continuous surveillance and molecular monitoring. Furthermore, the findings of this study highlight the need for a broader perspective in diphtheria control strategies. In addition to maintaining high vaccination coverage, public health programs should also focus on improving laboratory detection, surveillance integration, and documentation of atypical cases.

CONCLUSIONS AND RECOMMENDATIONS

This report describes two pediatric cases of infection caused by nontoxigenic *Corynebacterium diphtheriae* identified through laboratory-based surveillance in North Sumatra, Indonesia. The findings demonstrate that nontoxigenic *C. diphtheriae* can cause clinically significant infections, including bloodstream infection and wound-associated infection, even in the absence of classical diphtheria manifestations. These cases highlight the importance of considering *C. diphtheriae* as a potential pathogen when isolated from clinically significant specimens such as blood cultures or wound swabs.

The cases also illustrate the expanding clinical spectrum of nontoxigenic *C. diphtheriae* infections and emphasize the need for accurate laboratory identification and toxigenicity testing. Recognition of such atypical presentations is essential for improving clinical diagnosis and for strengthening surveillance systems aimed at detecting changes in the epidemiology of diphtheria-related infections.

Several measures are recommended to improve the detection and management of infections caused by *Corynebacterium diphtheriae*. First, clinical microbiology laboratories should perform species-level identification for Corynebacterium isolates obtained from sterile sites or clinically significant specimens to avoid misclassification as non-pathogenic diphtheroids. Second, strengthening laboratory referral systems is essential to ensure that suspected isolates can be confirmed at national reference laboratories capable of performing toxigenicity testing using Elek test and molecular methods.

In addition, integration of laboratory findings into existing surveillance systems would improve the monitoring of both toxigenic and nontoxigenic *C. diphtheriae* infections. Documenting such cases as part of routine surveillance may provide valuable insights into emerging epidemiological trends and support early

detection of potential public health threats. Strengthening collaboration between clinical laboratories, surveillance units, and public health authorities will therefore be essential to improve the overall response to diphtheria-related infections

FURTHER STUDY

This case report was generated as part of a public health investigation conducted in response to a suspected public health emergency. In accordance with national public health regulations, ethical review and individual informed consent were waived, as the activities described were undertaken for disease surveillance, outbreak investigation, and public health response purposes. All patient data were anonymized prior to analysis and publication, and no identifiable personal information is disclosed in this report. The investigation was conducted under the mandate of the national health authority in accordance with applicable public health laws and regulations.

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