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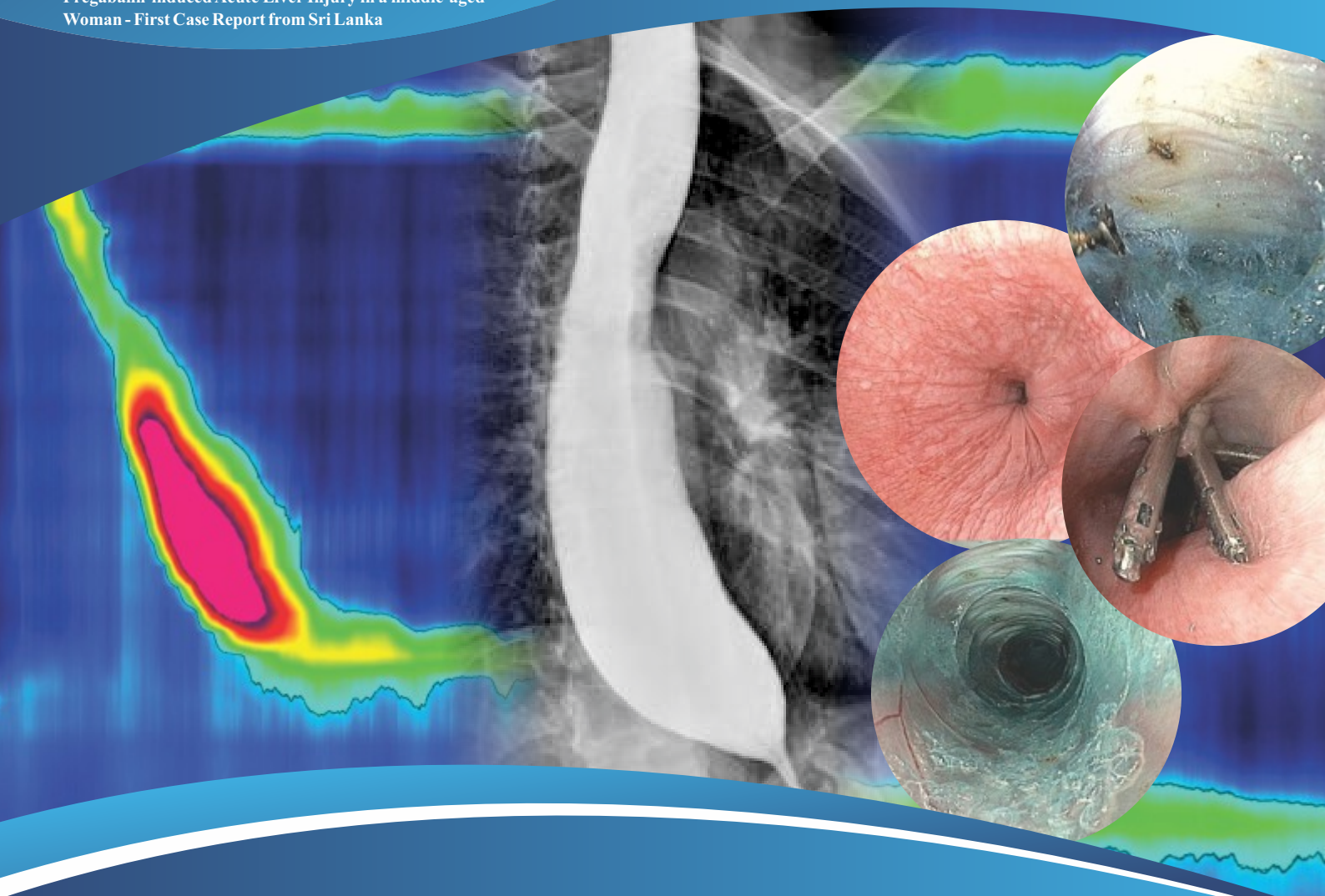

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EDITORIAL TEAM

RESEARCH REPORT

Clinical and Microbiological Characteristics of Cholangitis in Patients Undergoing Endoscopic Biliary Drainage: An Observational Study in Sri Lanka

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ABSTRACT

Background: Cholangitis is a life-threatening condition secondary to biliary obstruction. While clinical diagnosis and timely intervention can significantly reduce mortality, local epidemiological and microbiological data are limited in Sri Lanka.

Objectives: This study aimed to describe the clinical features, etiologies of biliary obstruction, microbial spectrum of bile, and antimicrobial resistance patterns among patients undergoing endoscopic drainage for cholangitis.

Methods: A prospective observational study was conducted among 106 patients with cholangitis at the National Hospital of Sri Lanka, in which demographic, clinical, endoscopic, and microbiological data were collected.

Results: The median age was 56 years with a female predominance (69.8%). Choledocholithiasis (67.9%) was the most common aetiology. Bile cultures were positive in 52.8%, with Enterobacteriaceae (42.8%) and Enterococcus spp. (21.4%) being most frequent. Resistance to ciprofloxacin was observed in 54.1% of Enterobacteriaceae. Multidrug-resistant organisms were isolated in 12.5% of culture-positive cases.

CONCLUSION

Early identification and local knowledge of microbial resistance patterns are essential for optimal management of cholangitis.

Keywords: Cholangitis, Bile culture, Multidrug resistance

INTRODUCTION

Cholangitis,an acute infection of the biliary tract, develops when biliary obstruction coincides with bacterial proliferation, typically from ascending duodenal bacteria, with less frequent spread via the portal venous or periportal lymphatic systems(1-3,9).

Common causes of biliary obstruction include choledocholithiasis, strictures, and malignancies obstructing biliary flow. Without timely intervention, cholangitis can lead to sepsis and multi-organ failure, making it a gastroenterological emergency with substantial morbidity and mortality(3).

Though Charcot's classic triad of fever, right upper quadrant pain, and jaundice remains a pathognomonic clinical feature for identifying cholangitis and carries high specificityaround 96%,it yields a sensitivity of approximately 26% (1).The Tokyo Guidelines(TG) have offered improved sensitivity over two revisions. This clinical tool requires a criterion from three diagnostic categories for diagnosis: systemic inflammation, cholestasis, and imaging (biliary dilatation or imaging evidence of aetiology of obstruction) (1,2).

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The management of cholangitis involves supportive care, intravenousantibiotics, and biliary decompression, most commonly via endoscopic retrograde cholangiopancreatography (ERCP) (3-6).

Microbiological analysis of bile can help guide appropriate empirical antibiotic therapy. The most commonly identified bacteria in acute cholangitis are Escherichia coli, Klebsiella species, Enterobacter species, and Enterococcus species(4-6). Anaerobic bacteria including Clostridiumor Bacteroides speciesare more likely tocause infections in elderly patients and in those with prior biliary surgery (6).

Increasing antimicrobial resistance, particularly the growing prevalence of extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, poses a major challenge to empirical therapy selection, especially in regions with limited surveillance data (4).

There is limited Sri Lankan data on biliary obstruction and cholangitis, highlighting the need for further investigation. Existing evidence on biliary microbiology is scarce and constrained by methodological limitations, and many available studies are outdated and may not accurately reflect the current pathogens or resistance patterns. Consequently, there is no clear consensus regarding optimal initial antibiotic therapy, and the paucity of local susceptibility data makes antibiotic selection challenging for clinicians.

This prospective study aims to describe thecharacteristics of cholangitis in patients requiring endoscopic biliary drainage, determine the microbiological spectrumand patterns of drug resistance, and assess the therapeutic implications of these findings.

METHODS

This descriptive observational study was carried out at the Gastroenterology Unit of the National Hospital of Sri Lanka, where all patients diagnosed with cholangitis and undergoing ERCP between March 2019 and February 2020 were prospectively enrolled. Eligible participants included adults aged 18 years or older with a clinical diagnosis of cholangitis who required ERCP for biliary decompression and from whom bile aspirates could be obtained for microbiological analysis.

Patients with incomplete clinical data or those who declined consent were excluded from the study. For each enrolled patient, demographic and clinical information, including presenting symptoms and ERCP findings, was systematically documented.

During the ERCP procedure, bile aspirates were collected under sterile conditions and submitted for culture and antimicrobial susceptibility testing in accordance with standard guidelines, allowing for detailed evaluation of the microbial spectrum associated with biliary obstruction and cholangitis.

RESULTS

Demographics and Clinical Profile

Among the 106 patients included in the study, the median age was 56 years, with a range spanning from 18 to 89 years. A notable female predominance was observed, with 74 females accounting for 69.8% of the study population. The majority of patients presented with classic clinical features of biliary obstruction and infection, with jaundice seen in 96.2%, fever in 83%, and right upper quadrant abdominal pain in 67.9%. Charcot's triadcomprising jaundice, fever, and abdominal painwas documented in 54 patients (50.9%). 8 patients (7.5%) exhibited clinical features of sepsis. All patients received intravenous antibiotic therapy and subsequently underwent successful ERCP for biliary decompression. Despite treatment, the in-hospital mortality rate was 3.7%. Table 1 summarises the clinical characteristics of the patients and causes of biliary obstruction.

Aetiology of Biliary Obstruction

The underlying causes of biliary obstruction varied, with choledocholithiasis being the most common aetiology, accounting for 72 patients (67.9%). Cholangiocarcinoma represented the second most frequent cause at 9.4%, followed by benign biliary strictures in 6.6% of the cohort. Malignant obstruction originating from the pancreatic head was identified in 4.8% of patients, while ampullary malignancies accounted for 2.8%. Additionally, periampullary diverticula contributed to obstruction in 4.8% of cases. In a small proportion of patients (3.7%), no clear aetiology could be identified.

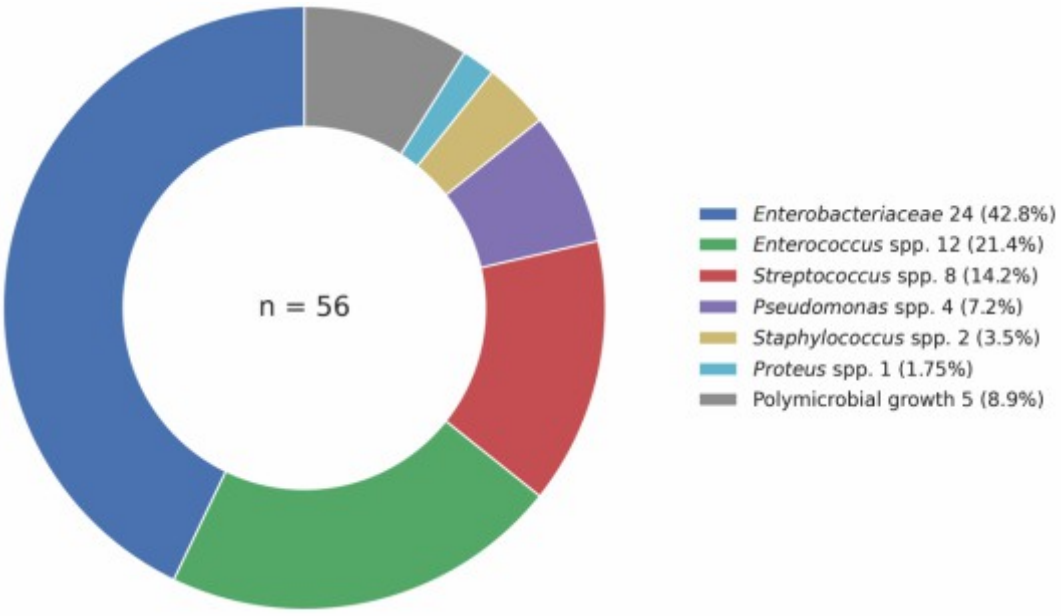
Microbiological Findings

Bile cultures were positive in 56 of the 106 patients, yielding an overall positivity rate of 52.8%. Gram-negative Enterobacteriaceae were the most commonly isolated organisms, found in 42.8% of culture-positive samples (Figure. 1). Enterococcus species were identified in 21.4% of patients, and Streptococcus species in 14.2%. Pseudomonas species were isolated in 7.2% of cases, while Staphylococcus species and Proteus species were less frequently detected at 3.5% and 1.75%, respectively. Polymicrobial infections were observed in 8.9% of patients.

Table 1: Demographic and Clinical Characteristics of the Study Population, Aetiology of Biliary Obstruction

	n (%)
Median age in years (range)	56 (18–89)
Gender	
Male	32 (30.2%)
Female	74 (69.8%)
Presenting features	
Jaundice	102 (96.2%)
Fever	88 (83.0%)
Right upper quadrant pain	72 (67.9%)
Charcot's triad	54 (50.9%)
Clinical sepsis	8 (7.5%)
In-hospital mortality	4 (3.7%)
Aetiology of biliary obstruction	
Choledocholithiasis	72 (67.9%)
Cholangiocarcinoma	10 (9.4%)
Benign biliary strictures	7 (6.6%)
Pancreatic head malignancy	5 (4.8%)
Ampullary malignancy	3 (2.8%)
Periampullary diverticulum	5 (4.8%)
No identifiable cause	4 (3.7%)

Figure 1 Microbiological profile of bilecultures (56 positivecultures)



Antibiotic Resistance

Antibiotic resistance patterns revealed several important trends. Among Enterobacteriaceae isolates, more than half (54.1%) demonstrated resistance to ciprofloxacin. In contrast, high levels of susceptibility (90-95%) were observed to cephalosporins, carbapenems, piperacillin-tazobactam, and aminoglycosides. Enterococcus species showed sensitivity to vancomycin, teicoplanin, and gentamicin; however, one-third (33.3%) exhibited resistance to penicillin and ampicillin. Notably, multidrug-resistant organisms were isolated in 12.5% of culture-positive patients.

Blood Cultures

Of the 88 patients for whom blood cultures were available, 12 patients (13.6%) had positive blood cultures. In nine of these cases (75%), the same organism was isolated from both blood and bile cultures.

DISCUSSION

This study provides important insights into the clinical presentation and microbiological profile of cholangitis in a Sri Lankan tertiary care setting. The median age of the study population was 56 years, with patients ranging from 18 to 89 years. A marked female predominance was observed, with females accounting for 69.8% of the cohort.Choledocholithiasis is the most common cause of acute cholangitis and similarly itwas identified as the predominant cause in our study, followed by malignancy-related obstruction and benign biliary strictures (3,5).

Notably, Charcot's triad was present in only 50.9% with jaundice, fever, and right upper quadrant abdominal pain observed in 96.2%, 83%, and 67.9% of patients respectively. Although the presence of Charcot's triad is highly suggestive of the diagnosis, its sensitivity is very lowas Charcot's triad is not always present in patients with acute cholangitis. The diagnostic sensitivity for acute cholangitis has improved with the TG13/TG18 diagnostic criteria which incorporate clinical features, laboratory findings, and imaging evidence (1).

The two key microbiological tests used to identify the causative organisms in acute cholangitis are blood and bile cultures. In a multicenter study,40% of blood cultures were positive compared with83%positive results in bile cultures, highlighting the clinical significance of bile cultures (7). In our study, blood culture results were available for 88 patients, of whom 12 (13.6%) were positive, whilebile cultures identified the causative organisms in 52.8% of cases. Because bile cultures are valuable in guiding the antibiotic treatment, TG 18 guidelines recommend obtaining the bile sample at the beginning of the drainage procedure (4).

The microbiologicspectrum demonstrateda high prevalence of gram-negative bacteria with Enterobacteriaceaeidentified in 42.8% of positive bile samples, consistent with the previous literature findings (5). Gram-positive bacteria such as Enterococcus spp. andStreptococcus spp. were detected in 21.4% and 14.2% of positive cultures respectively. A notable finding was the high rate of ciprofloxacin resistance among Enterobacteriaceaeisolates (54.1%). Althoughearlier studies reported higher susceptibility rates to ciprofloxacinamong Gram-negative bacteria, recentevidence indicates a significant decline in susceptibility rates (4,8). Enterococcusspecies exhibited resistance to penicillin and ampicillinin 33.3% of isolates. Furthermore, the detection of multidrug-resistant strains in 12.5% of culture-positive patients underscores the growing concern of antimicrobial resistance and the necessity for microbiological surveillance.

CONCLUSION

This study demonstrates that cholangitis in Sri Lanka occurspredominantly in women, with choledocholithiasis being the most commoncause. Selection of empirical antibiotic therapyshould consider local resistance trends, especially the increasing ciprofloxacin resistance among Enterobacteriaceae. Prompt biliary drainage combined with appropriate antimicrobial therapy remains the cornerstone of effective management.

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REVIEW ARTICLE

Clostridioides difficile Infection: What Every Clinician Needs to Know

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ABSTRACT

Clostridioides difficile infection (CDI) is one of the leading causes of healthcare-associated infectious diarrhoea worldwide and remains a major contributor to morbidity, mortality, prolonged hospitalisation, and healthcare expenditure. CDI typically develops following disruption of the normal intestinal microbiota, most commonly after exposure to broad-spectrum antibiotics. Additional risk factors include advanced age, hospitalisation, immunosuppression, inflammatory bowel disease, renal impairment, obesity, hypoalbuminemia, and the use of proton pump inhibitors. Clinical manifestations range from mild self-limiting diarrhoea to fulminant colitis complicated by toxic megacolon, septic shock, and death.

Diagnosis requires a combination of clinical assessment and laboratory stool testing, with multistep diagnostic algorithms improving accuracy and helping differentiate active infection from colonisation. Disease severity assessment is crucial, as it guides therapeutic decision-making and predicts outcomes. Current management strategies emphasise prompt discontinuation of unnecessary antibiotics, severity-based treatment, and prevention of recurrence. Fidaxomicin and oral vancomycin are the preferred first-line therapies, while fulminant disease may require high-dose vancomycin, adjunctive intravenous therapy, and early surgical consultation. Recurrent CDI remains a major challenge, with microbiota-restorative therapies such as faecal microbiota transplantation playing an increasingly important role. Effective infection control measures, antimicrobial stewardship, and appropriate diagnostic testing remain central to prevention.

This review summarises the epidemiology, pathogenesis, risk factors, clinical features, diagnosis, and contemporary management of CDI, highlighting key challenges and emerging therapeutic approaches relevant to everyday clinical practice.

Keywords: Clostridioides difficile infection, Antibiotics, Fecal microbiota transplantation

INTRODUCTION

Clostridioides difficile infection (CDI) is one of the most important causes of healthcare-associated infectious diarrhoea around the world and remains a major contributor to prolonged hospitalisation and healthcare expenditure (1). Clostridioides difficile is a Gram-positive, obligate anaerobic bacillus that primarily causes antibiotic-associated colitis and diarrhoea. The organism was previously known as Clostridium difficile, before being reclassified into the genus Clostridioides. (4).

The life cycle of C. difficile alternates between an infectious, metabolically inactive spore form and an active vegetative form capable of toxin production (2). Spores are the principal mediators of transmission and are highly resistant to heat, antibiotics, and bile acids, enabling prolonged dormancy within the environment and host (2). The incubation period is generally less than two weeks, with a median duration of approximately six days. The progression from colonisation to active infection, including the exact sequence, duration, and timing of these stages, remains incompletely understood (1).

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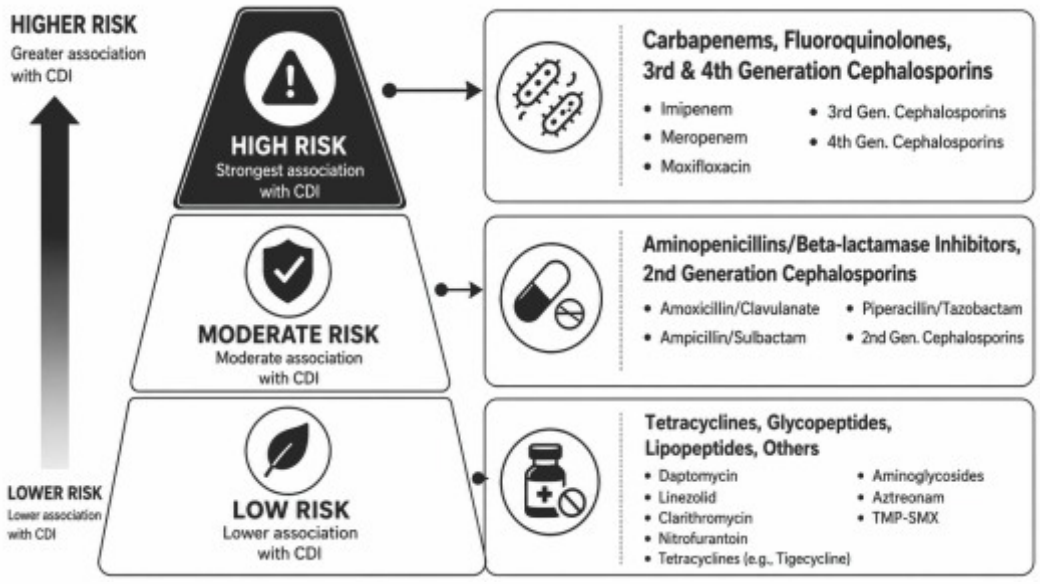
The two major exotoxins produced are toxin A (TcdA) and toxin B (TcdB), which disrupt intestinal epithelial tight junctions and damage the actin cytoskeleton of colonocytes. This leads to breakdown of the mucosal barrier, resulting in increased fluid secretion, neutrophil recruitment, and marked mucosal inflammation and colitis, often culminating in pseudomembrane formation (1-3).

Individuals colonised with C. difficile at the time of hospitalisation have an approximately sixfold increased risk of developing symptomatic infection (2). Asymptomatic colonisation is also common and contributes to disease transmission. Recurrence remains a major clinical challenge, occurring in 15–25% of patients after an initial episode, with progressively increasing risk following subsequent infections. Differentiating relapse from reinfection is often difficult in routine practice due to limited access to molecular genotyping. Mortality is particularly significant among elderly patients and those with severe or fulminant disease (1).

RISK FACTORS

Several host and treatment-related factors contribute to an increased risk of CDI. CDI develops most commonly after systemic antibiotic exposure. Broad-spectrum antibiotics such as clindamycin, fluoroquinolones, and cephalosporins are particularly known to cause this(Figure-1) (1,3). Longer antibiotic exposure further increases CDI risk, with prolonged courses causing greater microbiome disruption and risk persisting for up to three months after cessation(3).

Figure 1 Relative risk of CDI infection with different antibiotic groups



Clinical symptoms may arise during antibiotic therapy, typically within 2–10 days of initiation, but can also occur up to 10 weeks after antibiotic exposure (1)

The use of antisecretory agents, including proton pump inhibitors and histamine-2 receptor antagonists, has been associated with an increased risk through mechanisms such as acid suppression and promotion of intestinal dysbiosis. Other risk factors for CDI include advanced age, female sex, obesity, hypoalbuminemia, renal failure, inflammatory bowel disease, prolonged hospitalisation, immunosuppression, and the presence of multiple medical comorbidities (2,3).

CLINICAL FEATURES

The clinical manifestations range from mild self-limiting diarrhoea to fulminant colitis with toxic megacolon and septic shock. An episode of CDI is defined by the presence of diarrhoea (three or more loose watery stools within 24 hours), compatible clinical features together with detection of C. difficile toxin, or pseudomembranous colitis (1).

Additional symptoms may include abdominal cramping, lower abdominal discomfort, low-grade fever, and constitutional symptoms. Mucus or occult blood can be present in stool, although overt gastrointestinal bleeding such as melena or hematochezia is uncommon (2).

Pseudomembranous colitis represents the classical pathological manifestation of CDI and may be identified on endoscopy or histology. However,

pseudomembranes are present in only 40–60% of cases and may be absent in mild disease or in patients with inflammatory bowel disease. Therefore, the absence of pseudomembranes does not exclude the diagnosis (1).

Rare cases of extraintestinal infection such as bacteremia, abscesses, osteomyelitis, and prosthetic device infections have been reported, particularly in severe disease with significant gastrointestinal disruption. Increasing evidence also suggests that circulating C. difficile toxins can cause systemic "toxaemia," contributing to cardiac, renal, hepatic, and possibly neurologic injury through direct toxicity and inflammatory mechanisms (3).

DISEASE SEVERITY

The severity of Clostridioides difficile infection is variably defined among international guidelines, but classification generally depends on clinical, laboratory, and radiological parameters. More severe cases are often defined by the presence of fever >38.5 °C, leukocytosis >15 × 10^9/L, and/or acute kidney injury with a creatinine level ≥133 µmol/L, while hypoalbuminemia and third spacing may also be present (1).

Clostridioides difficile infection fulminant (or severe-complicated) disease accounts for fewer than 5% of cases and is characterised by severe illness with features such as elevated serum lactate, hypotension, septic shock (with or without ileus), toxic megacolon, and/or colonic perforation (1).

Recurrent Clostridioides difficile infection is characterised by the resolution of symptoms after adequate treatment, followed by the return of symptoms with a positive diagnostic assay within 2–8 weeks after the initial episode (2).

DIAGNOSTIC WORKUP

Clinical history and physical examination alone are insufficient for accurately diagnosing CDI. Laboratory abnormalities frequently include leukocytosis, elevated inflammatory markers, hypoalbuminemia, and acute kidney injury.

Definitive diagnosis relies on laboratory stool testing , supported by clinical assessment and imaging to evaluate disease severity and complications (1).

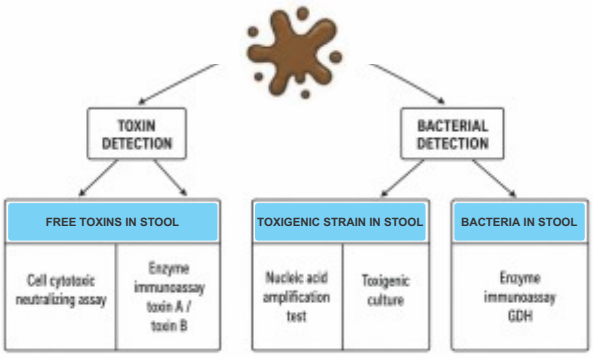
Demonstration of The Organism

Clostridioides difficile infection is diagnosed using stool assays that detect the organism or its toxins(Figure-2). Although cell cytotoxicity neutralisation assay and toxigenic culture are considered the reference standards for diagnosing Clostridioides difficile infection, their routine clinical use is limited because they are technically complex and time-consuming (1,2).

Enzyme immunoassays for toxins A and B provide rapid and highly specific results, although sensitivity may vary depending on specimen processing. Nucleic acid amplification tests , including polymerase chain reaction identify toxigenic strains with sensitivity comparable to toxigenic culture (1).

Glutamate dehydrogenase antigen detection is a highly sensitive screening method with a strong negative predictive value, as both toxigenic and non-toxigenic strains produce this enzyme (2).

Figure 2 Stool testing methods for C.deficille diagnosis

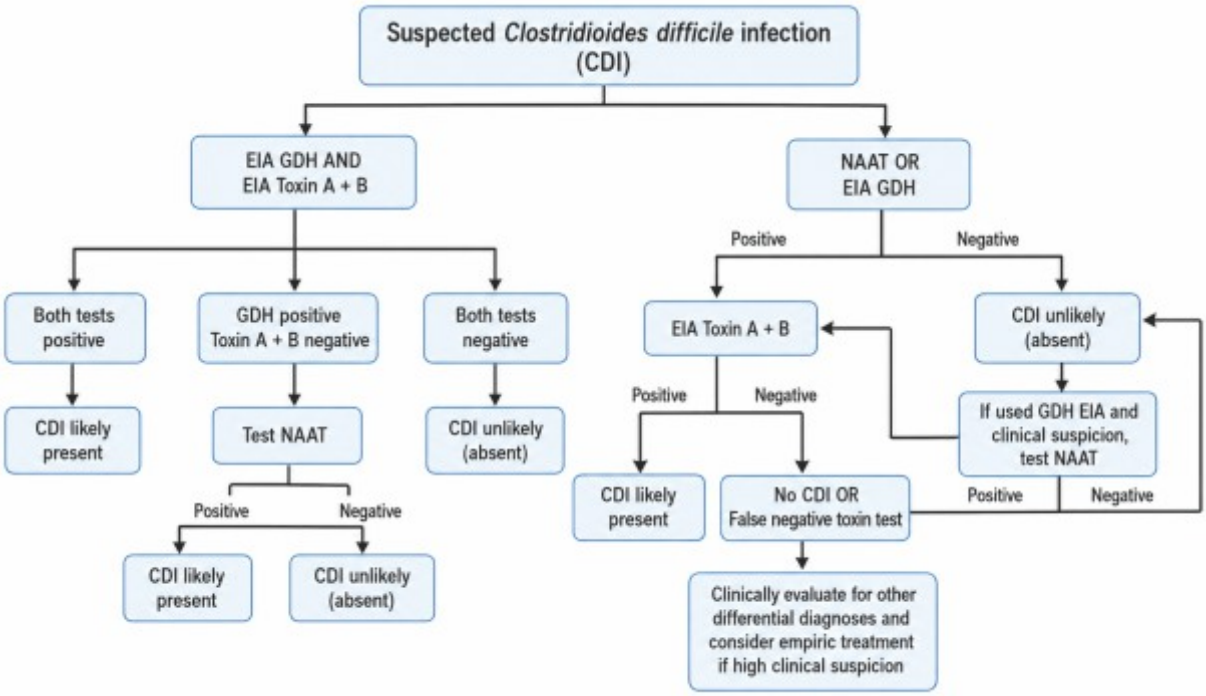


Two-step strategies combining the above tests improve diagnostic accuracy and are commonly employed in clinical practice(Figure -3). Importantly, repeat testing to document cure is not recommended, as PCR assays may remain positive for weeks to months after treatment (1)

RADIOLOGY

Radiological investigations are not routinely required for the diagnosis but may provide supportive evidence and help guide empiric management while awaiting microbiological confirmation. Plain abdominal X ray is useful to detect complications such as toxic megacolon. Computed tomography of the abdomen can demonstrate features of colitis and identify severe complications such as toxic megacolon or bowel perforation.(1).

Figure 3 Diagnostic algorithm for CDI
EIA- enzyme-immuno assay, GDH-glutamate dehydrogenase, NAAT- nucleic acid amplification tests



Endoscopy

Flexible sigmoidoscopy is often preferred with minimal insufflation to reduce the risk of colonic perforation. It may show a spectrum of findings ranging from normal mucosa to mild patchy erythema and mucosal friability to severe pseudomembranous colitis characterised by raised yellow-white plaques. (1,2).

Histology

Histologically, Clostridioides difficile colitis ranges from mild mucosal inflammation to severe pseudomembranous colitis characterised by fibrin, mucin, and inflammatory cell–rich pseudomembranes. Severe disease may demonstrate cryptitis, crypt abscesses, glandular dilation, confluent pseudomembranes, extensive mucosal necrosis, and marked submucosal oedema extending into the muscularis propria(3).

MANAGEMENT

Management of Clostridioides difficile infection begins with reviewing ongoing medications by discontinuing systemic antibiotics if possible or switching to a lower-risk alternative(1).

Patients should then be stratified according to disease severity into non-fulminant or fulminant CDI, while also considering the number of previous CDI episodes, as this influences treatment selection. Routine antimicrobial susceptibility testing is generally not useful in guiding therapy because most strains remain susceptible to the commonly used anti-CDI antibiotics (1).

Table 1 summarises the management options of initial and recurrent CDI.

MANAGEMENT OF NON-FULMINANT CDI

Current guidelines recommend Fidaxomicin 200 mg orally twice daily for 10 days as the first-line treatment for an initial CDI episode. If Fidaxomicin is not available , oral Vancomycin 125 mg four times daily for 10–14 days is recommended.(1,2) Although the optimal treatment duration for both agents has not been firmly established, current guidelines recommend a 10-day course. Extension of vancomycin therapy up to 14 days may be considered in patients who show an inadequate clinical response after 7 days of treatment (1).In non-fulminant Clostridioides difficile infection, oral Metronidazole is now considered a secondary option and is recommended only when first-line agents such as Fidaxomicin and oral Vancomycin are not available (1,3).

MANAGEMENT OF FULMINANT CDI

It differs significantly due to limited randomised controlled trial evidence, leading to variation between guidelines. North American recommendations generally favour high-dose oral Vancomycin 500 mg four times daily, often combined with adjunctive IV Metronidazole 500 mg every 8 hours in severe cases. In contrast, European guidelines tend to recommend standard-dose vancomycin (125 mg four times daily) or Fidaxomicin 200 mg oral twice daily, with consideration of IV Tigecycline in selected patients (1,2).

In cases of ileus, where oral drug delivery to the colon may be impaired, adjunctive rectal vancomycin via enema may be used. The use of IV metronidazole (or alternatives such as tigecycline) is primarily to ensure systemic and colonic antimicrobial activity in the setting of severely impaired gastrointestinal transit (2,3). In severe-complicated cases, early surgical consultation is recommended, particularly in patients with toxic megacolon, acute abdomen, septic shock, or failure of medical therapy. The standard operative management is total abdominal colectomy with end ileostomy and rectal stump closure(1-3).

MANAGEMENT OF RECURRENT CDI

For first recurrences, Fidaxomicin 200 mg twice daily orally for 10 days is an option if it was not used for the first episode.

Another option is a 4–6-week vancomycin pulse-taper strategy(Table-2).If fidaxomicin was used for the first episode, options include: repeat fidaxomicin therapy, using a pulse-and-taper regimen, or using a 4-6 week pulse and taper regimen of vancomycin (1,2).

Management of second and subsequent recurrences of Clostridioides difficile infection remains an area with limited high-quality comparative evidence. If a patient has failed repeated courses of Fidaxomicin, it is reasonable to switch to oral Vancomycin, and vice versa. For multiple recurrences, both fidaxomicin pulse–taper regimens and vancomycin pulse–taper regimens are considered acceptable strategies, although direct comparative effectiveness data are lacking (2).

Microbiota restorative therapies, including faecal microbiota transplantation (FMT) have demonstrated efficacy in recurrent Clostridioides difficile infection by restoring disrupted gut microbiota following completion of standard antibiotic therapy. FMT involves administration of screened and processed stool from healthy donors via endoscopic, colonoscopic, or enema routes to re-establish protective intestinal flora, and is primarily used in recurrent CDI as well as in severe or fulminant cases refractory to antibiotics as well as in patients who are poor candidates for surgery (2,6).

Table 1: Management of CDI

Severity / Situation	Recommended Treatment (Simplified)
Initial Infection –Non-fulminant	Vancomycin 125 mg orallyfour times daily × 10 days or Fidaxomicin 200 mg O BD × 10 days.
Initial Infection – Fulminant	Vancomycin 125/500 mg orally or via NG four times dailyx >10 days. Consider rectal vancomycin if ileus present. Add IV Metronidazole 500 mg 8-hourly especially if ileus is present.
First Recurrence	Vancomycin 125 mg orallyfour times daily × 10 days or Fidaxomicin 200 mg PO BID × 10 days or pulse and taper vancomycin/fidaxomycin regimen (Selection depends on which antibiotics were used in previous CDI)
Subsequent Recurrences	Pulse and tapervancomycin regimen or Oral Vancomycin 125mg four times daily x 10 days followed by oral Rifaximin 400mg three times daily x 20days, or Fidaxomicin 200 mg PO twice dailyx 10 days, or Faecal Microbiota Transplantation (FMT).

Table 2: Pulsed and tapered regimen

Vancomycin -pulse and taper regimen	Oral vancomycin 125 mg 4 times daily for 14 days, followed by 125 mg 3 times daily for 1 week, followed by 125 mg twice daily for 1 week, followed by once daily for a week and then every 2-3 days for 2-8 weeks
Fidaxomycin -pulse and taper regimen	Oral fidaxomicin 200 mg twice daily for 10 days, or Oral fidaxomicin 200 mg twice daily for 5 days, followed by once daily every other day for 20 days

GENERAL MEASURES

Patients with suspected or confirmed Clostridioides difficile infection should be placed in a single room with a dedicated toilet, and contact precautions should be used. Routine screening or isolation of asymptomatic carriers is not recommended. Overall, the effectiveness of preventive strategies is unclear, and stopping unnecessary systemic antibiotics remains a key intervention (1).

As stool tests may remain positive despite clinical recovery, repeat testing to confirm cure is not recommended and treatment of asymptomatic carriers is discouraged. Retesting should be reserved for patients who develop recurrent symptoms after completing effective therapy (2).

Primary prevention of Clostridioides difficile infection focuses on minimising unnecessary exposure to systemic antibiotics and discontinuing unnecessary proton pump inhibitor use, alongside implementation of antibiotic stewardship and contact precautions to reduce healthcare-associated transmission. There is currently insufficient evidence to support routine use of prophylactic CDI-targeted antibiotics for primary prevention (1,2,6).

CONCLUSION

Clostridioides difficile infection is a major healthcare-associated and increasingly community-acquired infection with significant clinical and economic burden.

Despite advances in therapy, important gaps remain in prevention, diagnosis, and optimal treatment selection. Future priorities include better risk stratification, improved diagnostic algorithms to distinguish infection from colonisation, and stronger comparative evidence for first-line and recurrent disease therapies, including adjunctive and microbiome-based approaches.

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CASE REPORT

Intra-thoracic Gastric Perforation Secondary to Ammonium Hydroxide ingestion: A Case Report

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ABSTRACT

Ammonium Hydroxide is commonly used as an industrial caustic solution. Ingestion of caustic solutions accidentally or withsuicidal intent is common around the globe.

This case report describes a rare case of ammonium hydroxide self-ingestion in a 28-year-old female who presented with severe upper gastrointestinal bleeding and subsequently developed gastric perforation with diaphragmatic perforation and pleural effusion on the left hemi-thorax. Prompt imaging, endoscopy and suspicion of complications are essential in patientmanagement.

Keywords: Ammonium hydroxide, Gastric perforation, Diaphragmatic perforation

INTRODUCTION

We report a 28-year-oldSri Lankan female who presented to the National Hospital of Sri Lanka, Colombo, with massive upper gastrointestinal bleeding following ingestion of ammonium hydroxide (NH_4OH) and subsequently developed gastric perforation with diaphragmatic perforation and pleural effusion on the left hemi-thorax. This complication has not beendescribed in relationto alkali ingestion in the literature, to the best of our knowledge.

CASE PRESENTATION

A 28-year-old female who was working in the rubber industry presented with severe hematemesis and melaena following a suicidal intent ammonium hydroxide ingestion of unknown amount.

After admission to the local hospital, Emergency care was given, includingtwounits of red cell concentrate transfusion; she was transferred to a tertiary care hospital for specialised care. Upper gastrointestinal endoscopy was performed on the day of ingestion and found denuded mucosa from the oesophagusup to the visualised extent, i.e., the second part of the duodenum. (Figure 1)

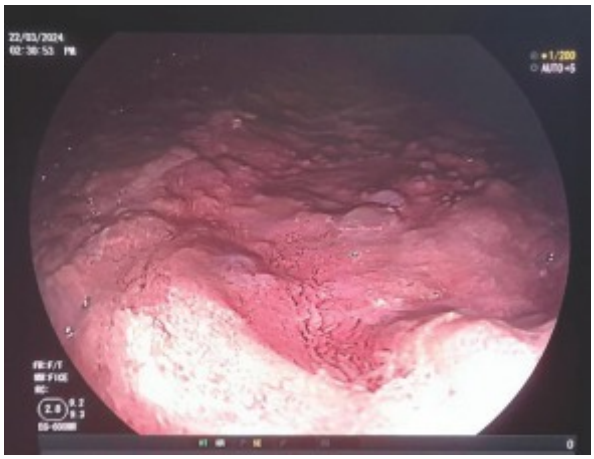

Figure 1 Endoscopic view of the stomach mucosa on day 1 of the ingestion of NH_4OH

She was admitted to the medical intensive care unit and started on IV antibiotics. She was kept nil oral witha nasogastric (NG) tubeinserted, allowing free drainage and started parenteral feeding. Chest X-rayand subsequent HRCT chest revealed left-sided pleural effusion, and an intercostal tube (IC tube) was insertedon theeighth day,followed by a second IC tubeon thetwelfth day after ingestion.

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CECT on theseventh dayafter ingestion showed a large left-sided pleural effusion, a thinned-out gastric wall with athin rim of intramural air within the gastric wall (maximum thickness 4.5mm) and a small pneumoperitoneum due to possible gastric wall rupture, which was conservatively managed.

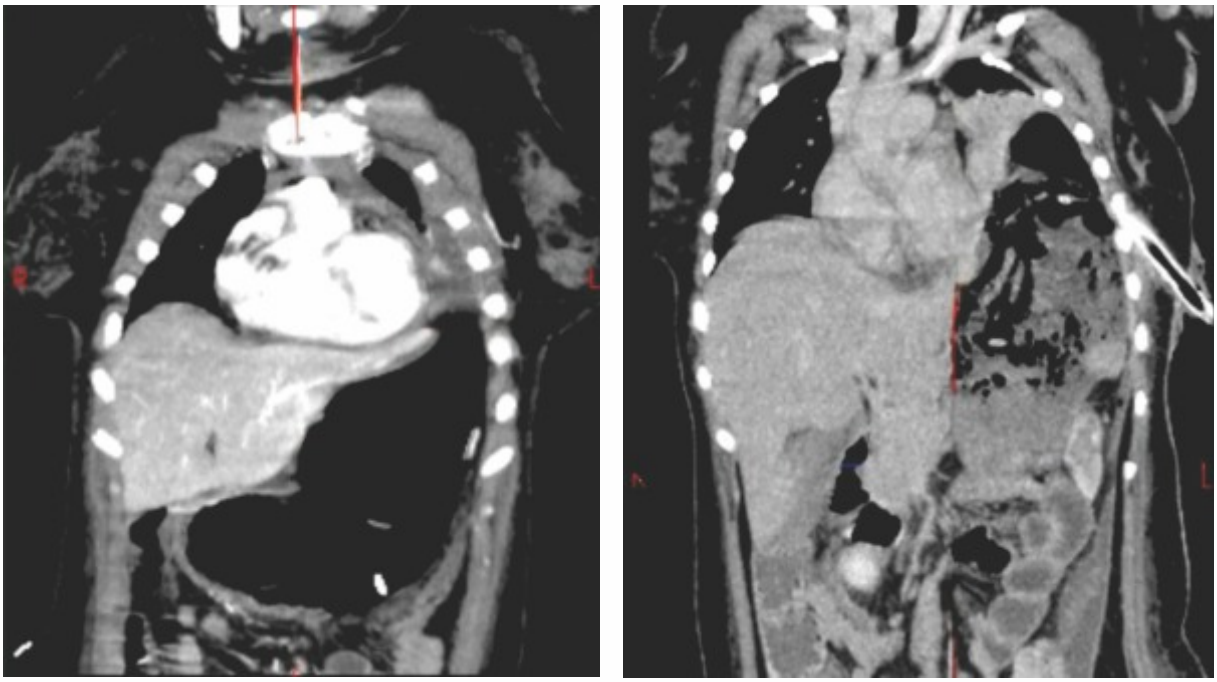

Figure 2 Coronal reconstruction of CECT on D7(Left) D28(Right) after NH_4OH ingestion

CECT performed on the twenty-eighth day after ingestion couldn't identify the left hemidiaphragm separately, and thestomach was distended with thinned-out walls and filled with soft tissue material. Part of the distended stomach was occupying the left hemithorax with both IC tubes traversing through the stomach. An urgent multidisciplinary meeting (MDM) was held, and an emergency surgery (oesophageostomy, gastrectomy and diaphragmatic repair) was decided to be done by the gastroenterological and thoracic surgical teams, but the patient passed away before the surgical intervention.

DISCUSSION

Ammonium hydroxide is an industrial caustic solution with a pH of10.1 to 13.8 (1). Self-ingestion of caustic solutions as a method of suicide iscommon in many countries of the world. Alkali ingestion is more common in the Western world than in Asia.15,000 adult cases were reported per year in theUnited States (2). Ingestion of alkali can cause acute upper gastrointestinal bleeding. In severe cases, peritonitis and mediastinitis can develop following perforation of the gastrointestinal tract (3,4).

Acid ingestion leads to coagulative necrosis with eschar formation, but alkali causes liquefactive necrosis of all layers of the digestive tract (5,6). Intrathoracic gastric perforation has been reported following laparoscopic fundoplication (7) and acid ingestion (8) but not described following alkali ingestion.

Chest X-ray (to detect air under the diaphragm or pneumomediastinum) and upper gastrointestinal endoscopy (to detect extent of injury) are commonly done as investigations. The timing of the endoscopy is still under debate, but many authors suggest endoscopy after 12-48 hours of ingestion. Computed tomography (CT) helps to detect gastrointestinal wall abnormalities, including perforation (9,10).

We put forth the hypothesis that the alkali has caused the gastric and diaphragmatic perforation leading to intrathoracic perforation. The other possibility would have been the asymptomatic presence of a diaphragmatic hernia and gastric perforation alone causing intrathoracic perforation, which is unlikely with the previous imaging displaying the diaphragm intact.

CONCLUSION

Intrathoracic gastric perforation is a rare and serious complication of Ammonium hydroxide ingestion. Knowledge and early suspicion of this potentially fatal complications and early imaging are key to success in the management of patients. Early multidisciplinary approach is beneficial for the optimal management of patients.

CONFLICTS OF INTEREST

None

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CASE REPORT

Pregabalin-induced Acute Liver Injury in a middle-aged Woman - First Case Report from Sri Lanka

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ABSTRACT

A 51-year-old Sri Lankan woman, previously diagnosed with osteoarthritis of the right knee and chronic pain syndrome, was prescribed a daily dose of 75 mg pregabalin.

After 45 days of pregabalin therapy, she reported experiencing symptoms of nausea, vomiting, and right hypochondrial pain. Subsequent investigations revealed elevated liver enzyme levels. The peak values for aspartate transaminase (AST) were 2232 U/L, alanine transaminase (ALT) 2045 U/L, INR 1.6and γ-glutamyltransferase (GGT) 186 U/L. Other potential causes of elevated liver enzymes were ruled out, RUCAM score indicated probable association with pregabalin and liver biopsy confirmed the diagnosis of drug-induced liver injury.

Notably, hepatic enzyme levels only showed improvement after the initiation of steroid treatment and gradually returned to baseline levels over a period of six months. While many medications are known to be associated with hepatic injury, cases of pregabalin-induced liver damage are relatively rare. This case highlights the importance of considering pregabalin as a potential, albeit rare, cause of acute liver injury in patientseven after some time of initiation of the drug. As a precaution, liver function should be monitored when patients on pregabalin therapy present with constitutional symptoms. Early detection and intervention are crucial for managing drug-induced liver damage associated with pregabalin.

Keywords: pregabalin, acute hepatic injury, liver enzymes

INTRODUCTION

Pregabalin, an analogue of the neurotransmitter gamma-aminobutyric acid, is a medication widely employed for the management of various conditions, including painful diabetic neuropathy, neuropathic pain associated with spinal cord injuries, post-herpetic neuralgia, partial convulsive crises in adults and fibromyalgia (1).

Commonly encountered side effects of pregabalin are dose-dependent and encompass weight gain, peripheral edema, headache, dizziness, blurred vision, tremor, confusion, and ataxia (1). Notably, pregabalin is generally well-tolerated, with the advantage of not undergoing hepatic metabolism or inducing/inhibiting liver enzymes (2).

During the preapproval clinical trials conducted by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), hepatic adverse effects were not observed (3). Nevertheless, sporadic cases of acute liver diseases associated with pregabalin use have emerged globally, often presenting with cholestatic and hepatocellular injury patterns (4). Importantly, these cases did not exhibit signs of hypersensitivity reactions such as fever, rash, eosinophilia, or autoimmunity (2).

Remarkably, this case report presents the first documented instance of pregabalin-induced liver injury in Sri Lanka, contributing to the growing body of knowledge surrounding this rare but significant adverse effect (4).

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CASE HISTORY

The patient is a 51-year-old housewife from Mandawala, Sri Lanka, with a history of osteoarthritis and associated chronic pain syndrome, as well as hypertension. She presented with yellowish discolourationof the eyes, vomiting, epigastric pain, and loss of appetite over the course of three days. Notably, she did not have a history of fever, had dark-colored urine and normal stools, and she had experienced mild pruritus. The patient denied high-risk behaviours, previous blood or blood product transfusions, or intravenous drug use, and she primarily consumed self-prepared food and boiled, cooled water. There was no evidence of autoimmune diseases, dry eyes, dry mouth, chronic diarrhoea, nocturnal fever, night sweats, or other constitutional symptoms. The patient did not use alcohol, ayurvedic treatments, or over-the-counter drugs and reported no neurological impairment. Her regular medications included losartan 50 mg twice daily for hypertension, and she occasionally used diclofenac gel, ibuprofen 400 mg with famotidine 40 mg to relieve the symptoms of osteoarthritis. Additionally, she had recently initiated pregabalin at a dose of 75 mg twice daily for chronic pain syndrome. There were no known allergies or significant family history of liver disease, and no prior episodes of jaundice.

Importantly, there was no history of prolonged or acute overdose of paracetamol. Given these findings, the patient's presentation raises concern for hepatic dysfunction, and further investigation is warranted, with consideration of the recent pregabalin initiation as a potential factor.

CLINICAL FINDINGS

Upon examination, the patient was afebrile and presented with icterus but without pallor. Her Glasgow Coma Scale (GCS) score was 15 out of 15, indicating normal cerebral function. Notably, there were no signs of xanthelasma, xanthomata, or Kayser-Fleischer (KF) rings, which are often associated with specific hepatic and metabolic disorders. The patient did not exhibit hepatic flaps, lymphadenopathy, body rashes, or ankle edema, and there were no peripheral stigmata suggestive of chronic liver disease.

Abdominal examination revealed mild tenderness in the right hypochondrial region, but there was no hepatosplenomegaly or ascites. Her blood pressure was measured at 110/70 mmHg, and her pulse rate was 76 beats per minute. Respiratory, central nervous system, and fundoscopy examinations yielded normal findings.

Table 1: Progression of Biochemical Parameters

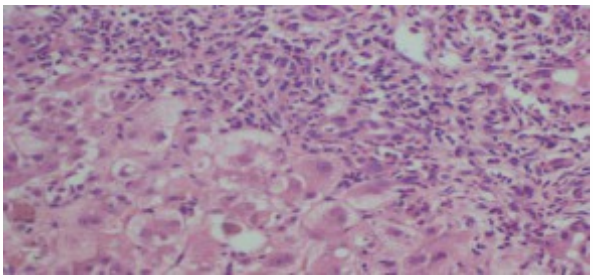
PARAMETERS	DAY 1	DAY 2	DAY 3	DAY 5	DAY 7	DAY 10	DAY 12	DAY 14	DAY 17
SGOT(u/L)	2045	1602	1223	994	601	578	415	379	262
SGPT(u/L)	2232	1917	1890	1715	1333	879	662	525	492
ALKPO4(u/L)	218	185	196	162	138	137	149	148	150
BILI.TOT(mg/dl)	5.9	6.5	12.3	13	14	13.3	11.7	8,9	6.8
BILI. D.(mg/dl)	4.6	5.3	10.2	10.3	11.3	11.7	9.9	7.7	5.6
INR	1.08	1.1	1.2	1.3	1.6	1.4	1.4	1.2	1.2
S.PROTEIN	6.8			6.8					
ALBUMIN(g/dl)	3.9			35					
S.CREATININE(umm ol/L)	58		69		77				

The patient's clinical and laboratory findings reveal a complex medical profile. WBC 9.43 10/ul (N-61%,L-26%,M-9.5%,E-3.5), Hb 12g/dl, Plt-233 10/ul. CRP -6, ESR 24, UFR, serum electrolytes and blood urea amylase levels found to be normal. Retic count 1.5%. Serum γ- glutamyltransferase 186 u/l. Serum ferritin was 1230ng/ml, TSH -2.6miu/l. ECG did not reveal any ischemic changes, and troponin I was normal.

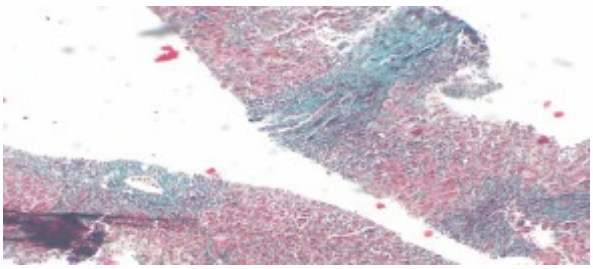
Her CPK and LDH levels were found to be normal. Hepatitis A IgG/IgM, Hepatitis B surface antigen, Hepatitis C antibody, Hepatitis E IgM, E.B virus (IgM), leptospira IgM/IgG were negative. Blood picture revealed a reactive picture, and chest X-ray and ultrasound of the abdomen findings were not significant. Serum ceruloplasmin 18mg/dl which is under the normal range (14-50mg/dl).

Antinuclear antibodies, P-ANCA, C-ANCA, Antimito--chondrial antibodies, Liver kidney microsomal antibodies, Anti smooth musle antibody found to be normal. Immunoglobulin G concentration was 1098mg/dl(800-1800), and CA 19-9 was 28u/ml(<35)

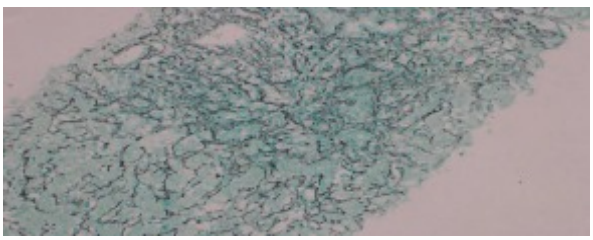
Figure 1 Liver Histology



Liver biopsy-H & E Staining



Liver biopsy-Masson's trichrome staining



Liver biopsy-Reticulin staining

The CT scan of the abdomen revealed inflammatory changes in the gallbladder fossa, likely secondary to hepatitis. Ultrasound-guided liver biopsy (Figure 1) demonstrated chronic active hepatitis with cholestatic features (Batts-Ludwig grade 3/4, stage 2/4). Histology showed portal inflammatory infiltrates containing numerous eosinophils with interface hepatitis. The eosinophil-rich inflammatory infiltrate strongly favored drug-induced liver injury. Plasma cell infiltration was not a dominant feature, making classical autoimmune hepatitis less likely.

Following admission, the primary intervention involved discontinuing the causative drug, pregabalin. The patient received a comprehensive treatment regimen that encompassed medications and monitoring. This included syrup lactulose, oral rifaximin, enemas, pantoprazole, domperidone, ursodeoxycholic acid, and intravenous N-acetylcysteine. Adequate hydration was maintained through IV fluids, and close monitoring of random blood sugar levels and Glasgow Coma Scale scores was performed.

Despite discontinuation of pregabalin, persistent liver enzyme elevation was observed, prompting the initiation of a short course of intravenous methylprednisolone followed by an oral prednisolone regimen. With the introduction of steroids, the patient's liver function gradually improved, leading to her eventual discharge from the hospital with a plan for regular medical clinic follow-ups. Over the subsequent six months of monitoring, the patient's liver function fully normalized, demonstrating the effectiveness of the treatment approach in resolving the drug-induced liver injury.

DISCUSSION

Drug-induced liver injury (DILI) is a well-documented phenomenon, encompassing a spectrum of clinical diseases that range from mild liver function derangement to acute liver failure (7). Most of the time, this damage arises from idiosyncratic reactions and typically occurs between 5 and 90 days after the drug's last administration. Multiple mechanisms have been described in the context of drug-induced liver injury (7).

Among these mechanisms, systemic hypersensitivity (drug allergy), impairment of the structural and functional integrity of the liver directly or by metabolite, and activation of the host defense mechanisms through the production of new antigenic drug proteins binding to hepatic proteins are considered the most crucial factors (8). DILI can be categorised into hepatitis, cholestatic, or mixed based on histology and acute or chronic based on the duration of symptoms (7). The diagnosis is established by identifying the temporal relationship between drug exposure and the development of symptoms and signs of liver toxicity.

It is imperative to rule out other potential causes of liver disease before confirming a diagnosis of DILI. A high degree of clinical suspicion and a comprehensive patient history are fundamental for an accurate diagnosis. Early recognition and prompt discontinuation of the causative drug are essential to prevent the progression to acute liver failure and chronic liver disease.

Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA) and a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system (5). It exhibits a favourable pharmacokinetic profile with predictable oral absorption, lacks hepatic metabolism or significant protein binding, and is primarily excreted through the kidneys (5). The most common dose-related side effects of pregabalin include peripheral edema, weight gain, dizziness, somnolence, confusion, headache, blurred vision, tremor, and ataxia (1). There is limited worldwide data available on pregabalin-induced liver toxicity, and prelicensure clinical trials did not associate it with an increased incidence of liver toxicity (4). The low incidence of significant hepatotoxicity from pregabalin may be attributed to its minimal hepatic metabolism and rapid urinary excretion. The hepatic injury resulting from pregabalin is typically idiosyncratic, with potential immunologic or metabolic causes.

The causality assessment was performed using the Roussel Uclaf Causality Assessment Method (RUCAM). Based on the temporal relationship between pregabalin exposure and onset of liver injury (45 days), improvement following drug withdrawal, exclusion of competing causes including viral, autoimmune and metabolic liver diseases, and supportive liver biopsy findings, the patient achieved a RUCAM score of approximately 8, indicating a "probable" causal relationship between pregabalin and the liver injury.The patient also fulfilled Hy's law criteria for severe drug-induced liver injury, as alanine aminotransferase exceeded three times the upper limit of normal, total bilirubin exceeded twice the upper limit of normal, and no alternative explanation for the liver injury was identified. Although the patient did not progress to acute liver failure, the presence of Hy's law features indicated a significant risk of serious hepatotoxicity and justified close monitoring and aggressive management.

This case further underscores the time-dependent association between pregabalin treatment and the onset of liver injury symptoms, consistent with cases reported in the literature. Symptoms typically manifest within the first week up to 4 months of continuous drug use.

However, in line with other cases reported, the patient's liver function did not return to normal upon discontinuation of the drug; it only normalised after treatment with steroids. Notably, this patient also exhibited a significant cholestatic phase with elevated bilirubin levels. The absence of liver metabolism does not preclude pregabalin-induced liver toxicity.

Autoimmune hepatitis (AIH) was an important differential diagnosis in this patient because liver biopsy demonstrated chronic active hepatitis. However, several findings argued against AIH. Autoimmune serology, including antinuclear antibodies, anti-smooth muscle antibodies, antimitochondrial antibodies, liver-kidney microsomal antibodies, and ANCA, was negative. Serum IgG concentration remained within the normal reference range (1098 mg/dL), and there was no previous history of autoimmune disease. According to the Simplified International Autoimmune Hepatitis Group (IAIHG) scoring system, the patient would receive a score below the diagnostic threshold for probable AIH. Furthermore, the close temporal relationship with pregabalin initiation, eosinophil-rich portal inflammation on liver biopsy, and gradual recovery after drug withdrawal strongly support drug-induced liver injury rather than autoimmune hepatitis

As pregabalin is commonly used in clinical practice, particularly for musculoskeletal pain, clinicians should be aware of the potential for idiosyncratic liver toxicity (6). Therefore, it is crucial to consider pregabalin as a rare cause of acute liver injury and discontinue the drug if a patient presents with elevated liver function tests.

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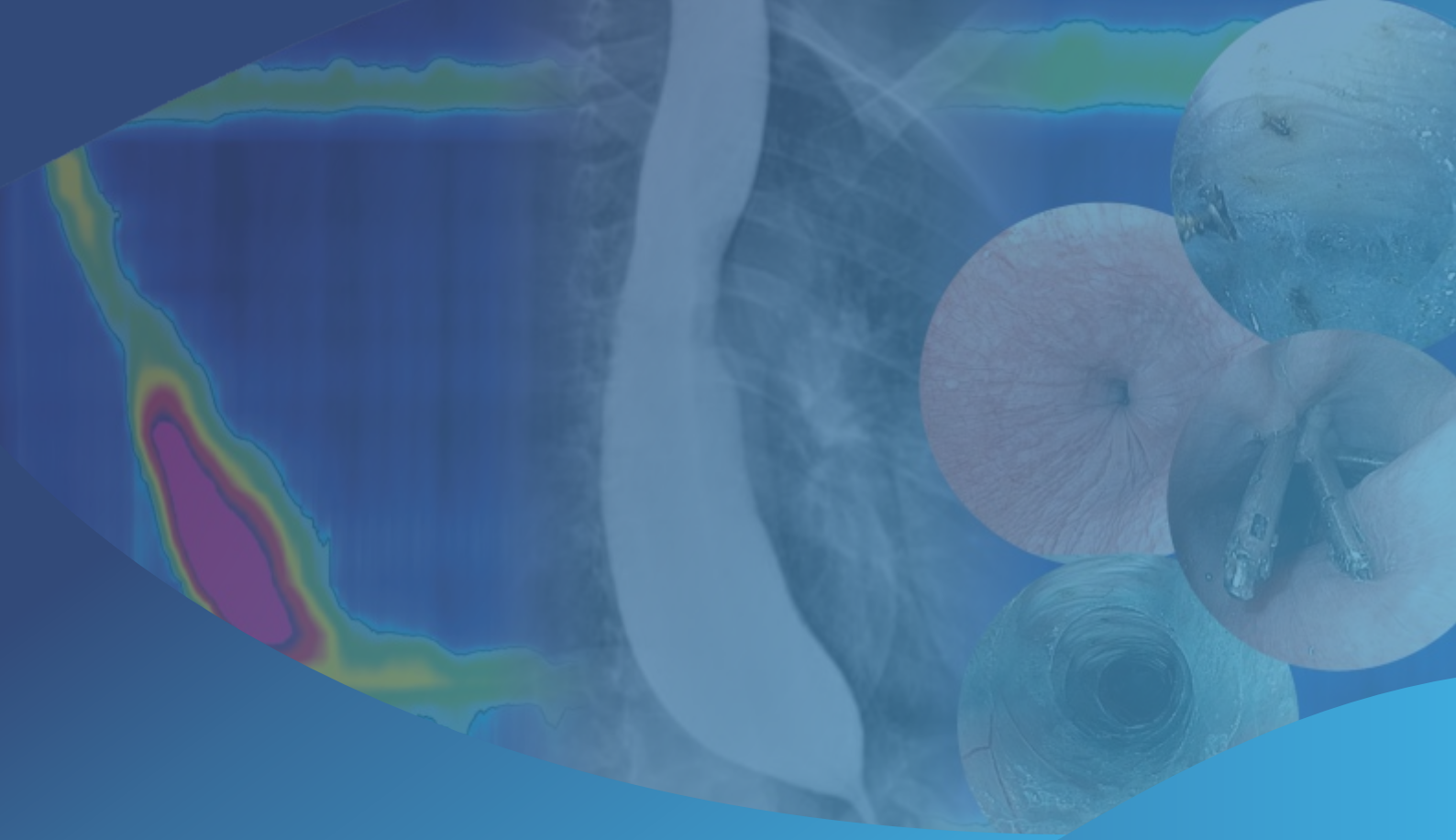

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