

Utilization of the complete blood count in diagnosing endemic diseases in Pakistan

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Abstract

Numerous infectious diseases, including enteric fever, malaria, dengue fever, and, most recently, coronavirus disease-2019, are prevalent in Pakistan. All these diseases have overlapping clinical symptoms and can present a diagnostic challenge for the general practitioner. Since definitive testing for these disorders is time-consuming and expensive, basic clinical testing, such as a complete blood count, should be utilised to supplement clinical diagnosis, when possible. The current narrative review was planned to present specific alterations in haematological parameters for each of these disorders. The review was intended as a guide for practising physicians in their decision-making.

Keywords: Complete blood count, Typhoid fever, Malaria, Dengue, COVID-19.

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Introduction

Complete blood count (CBC) is the most ordered routine investigation in general practice worldwide.¹ It is a low-cost, quick and reliable test that can provide information about almost all common conditions of the blood and can aid in the diagnosis of any underlying pathology. A CBC is also commonly ordered at patient admission as a baseline investigation, with repeat CBCs indicating the clinical course of inpatients.

Over the last few decades, clinicians have used CBC as the first test to aid in the diagnosis of many clinical conditions. Haematological parameters exhibit specific patterns of change in various diseases, which can guide clinicians in their decision-making. This is especially important in the diagnosis of various epidemic and endemic diseases. Definitive diagnostic testing for these conditions takes longer, is more expensive, and is unaffordable for many people, particularly those in developing countries that bear half the global disease burden.

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Most common diseases in Pakistan have distinct haematological patterns that can be detected on a CBC, and aid in diagnosis. A thorough clinical evaluation combined with a CBC can frequently be enough to diagnose a condition and save time, money and resources.

The current narrative review was planned to highlight CBC patterns in various endemic diseases in Pakistan and to guide the decision-making process in general practice. For the purposes of the review, CBC did not include peripheral blood film or erythrocyte sedimentation rate (ESR). However, because a few laboratories do report them along with the CBC, a small section on ESR and peripheral blood films has also been included.

Enteric fever

Enteric fever, commonly referred to as typhoid fever, is a systemic febrile illness caused by bacterium *Salmonella* (*S.*) typhi. Typhoid is transmitted via the faeco-oral route and is typically spread through the consumption of contaminated food or water. Major risk factors that contribute to a high prevalence of enteric fever in low-income nations include a lack of safe drinking water and inadequate sanitary facilities. The World Health Organisation (WHO) estimates that 11-20 million people are infected with typhoid each year.²

In Pakistan, typhoid fever is highly endemic: 493.5 out of 100,000 cases in South Asia in 2018 were reported from Pakistan.³ This number is the highest among countries in the region, and various regional factors put Pakistan at high risk of a widespread typhoid outbreak including but not limited to lack of sanitation, poor socioeconomic status (SES) of majority of the population, and limitations in terms of access to safe drinking water.³ During the summer and monsoon seasons, typhoid outbreaks are common, and patients typically present with a gradual onset of high-grade fever often reaching a plateau of 102-104°F, fatigue, rash and gastrointestinal (GI) symptoms. If left untreated, typhoid can lead to life-threatening complications, such as intestinal perforation and bleeding.⁴

Blood cultures have traditionally been described as the gold standard for the diagnosis of enteric fever, but blood cultures are expensive and often take several days to produce results. According to a 2016 systematic review, the

sensitivity of blood cultures in diagnosing typhoid fever is 66%, which means that one out of every three culture results can be a false-negative outcome.⁵ The other serological tests have the drawback of being non-specific and non-confirmatory.⁴ As a result, clinicians in endemic areas, particularly those in low- and middle-income countries (LMICs), must actively seek to diagnose typhoid fever using clinical suspicion and certain diagnostic clues from basic laboratory testing.

Haematological changes are common in typhoid fever and may include anaemia, leukopenia or leukocytosis, and sometimes thrombocytopenia.⁶ Haemoglobin (Hb) counts are typically unaffected, but certain complications, such as GI bleeding, haemophagocytosis, bone marrow suppression, and prolonged toxemia may result in anaemia.⁷ As a rule, patient's Hb level is always normal at the initial stage of infection and may decline slowly, depending on the progression of the disease.⁶ Significant anaemia at the onset of a fever may point to an alternative diagnosis, like malaria.

Leukopenia has been described as a classical finding in typhoid infections, and occurs secondary to a bacterial-mediated leukocyte shift from the circulation to the marginal zone.⁸ In actual clinical practice, leukopenia is seen only in approximately one-fourth of patients, and studies report the incidence of leukopenia in typhoid fever to be around 20-25%. Leukopenia, when present, can be an important indicator for the diagnosis of enteric fever, but a normal or elevated white blood cell (WBC) count on the CBC does not rule out typhoid infection.⁷ The differential WBC counts frequently show a decrease in neutrophils and an increase in the lymphocyte percentage, which suggests relative lymphocytosis.⁹

Notably, enteric fever in children more commonly presents with leukocytosis than in adults, in whom leukopenia may be more common.¹⁰ Leukocytosis may also be due to complications, such as intestinal perforation.⁴ However, a study conducted on paediatric patients in Pakistan found leukopenia to be present in approximately half of typhoid patients, indicating that leukopenia is an important diagnostic marker in local clinical settings.⁸

Eosinopenia, defined as a decrease in the number of eosinophils, is often described as an important independent predictor for typhoid fever, and current literature has described its frequency to be 30-50%.⁷ In a study conducted on Pakistani population in 2020, 35% of patients with enteric fever were found to have eosinopenia, with an odds ratio (OR) of 9.63.¹¹ In paediatric patients in Pakistan, this frequency was found to be 67.1%.⁸

Thrombocytopenia, although more important in other febrile illnesses, can also be observed in enteric fever. A transient decrease in platelet (PLT) count can be observed in typhoid patients after almost one week of illness. It is important to note that thrombocytopenia, if present, is mild in contrast to thrombocytopenia seen in other viral fevers.^{4,7}

Malaria

Malaria is a potentially life-threatening febrile illness caused by the protozoan *plasmodium* (*P.*), which is transmitted via the bite of the female Anopheles mosquito. There are five different parasite species that cause disease in humans, of which malaria caused by *P. falciparum* is the most severe. Malaria is endemic in tropical and subtropical regions, and in the year 2020, a total of 241 million people were infected, with an estimated 627,000 deaths.¹²

Pakistan has a high number of malaria cases, with an annual incidence reported to be greater than 300,000. According to WHO malaria statistics, Pakistan is one of the seven countries in the Eastern Mediterranean Region that account for 98% of the total malaria burden. The number of people estimated to be at moderate and high risk for malaria are 217 million and 63 million, respectively.¹³ More than two-thirds of these cases are caused by the species *P. vivax*, and peak incidence is observed from July to November after the monsoon rains.¹⁴ Malaria usually presents with a non-specific intermittent fever with chills, GI symptoms, such as vomiting and generalised fatigue. In severe cases, organ dysfunction may occur, including the involvement of central nervous system (CNS), called cerebral malaria, and kidneys, which is the blackwater fever.¹⁵

Traditionally, the visualisation of protozoans using microscopy has been described as the gold standard method for the diagnosis of malarial infections. However, microscopy is often not accessible in rural areas where malaria is common, and up to three blood smears taken during a fever spike must be examined independently by an expert to rule out the diagnosis of malaria.¹⁶ For this reason, malaria is usually diagnosed on clinical grounds, which often leads to the indiscriminate use of antimalarial drugs.

Certain haematological abnormalities invariably accompany malaria; these include anaemia, thrombocytopenia and atypical leukocytosis or leukopenia.¹⁷ Anaemia is haemolytic in nature and occurs due to a combination of different factors, including haemolysis of parasitised cells, hypersplenism leading to increased red blood cell (RBC) removal and/or pooling, and other factors such as RBC structural changes and increased

RBC clearance.¹⁷ In addition, complicated malaria is linked to bone marrow depression, which can result in anaemia.

A study comparing haematological parameters between febrile illnesses in Thailand demonstrated that anaemia with Hb <11.0 was frequently observed in patients with malaria. Other RBC indices, including haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC), were also found to be significantly low.¹⁸ Anaemia in malarial infections is often progressive and correlates with the severity of the infection. Hb <7.0g/dL in adults and <5.0g/dL in children is an important diagnostic criterion for severe malaria, indicating need for hospitalisation.¹⁹

Malaria is known to cause both leukocytosis and leukopenia, with varying findings reported in literature.¹⁷ Leukopenia occurs secondary to splenic sequestration and marginal localisation of WBCs, but this finding is not universal. A study conducted on malaria patients in Pakistan found no significant change in total leukocyte count (TLC), irrespective of the degree of parasitaemia.¹⁶ Eosinophilia can be observed among the differential WBC counts. Malaria does not by itself cause an increase in eosinophil counts; neutrophils containing hemozoin are responsible for pseudo-eosinophilia commonly reported in CBC analysis.²⁰ Plasmodium infections may result in monocytosis, owing to the large number of activated monocytes in the circulation.²⁰

Thrombocytopenia is the most common haematological abnormality observed in malaria patients, and in endemic areas, the presence of a low PLT count in patients with acute febrile illness is considered virtually diagnostic for malaria.²¹ Increased peripheral destruction and increased PLT consumption both contribute to thrombocytopenia, and counts are negatively correlated with the parasite index.¹⁶ A PLT count of <150,000/ μ l has been described to have a sensitivity and specificity of approximately 80% in the detection of malaria in endemic regions.²¹

A low PLT count can also be observed in dengue fever (DF), but PLT counts tend to fall later in dengue and are often normal at the onset of infection; a finding that can help differentiate DF from malaria. Kumar et al. analysed haematological parameters between the two diseases and suggested a combination of four variables, which, when taken together, have a post-test probability of 69% and a positive likelihood ratio of 7.2 for malaria if all 4 are present; Hb <10.0g/dL, TLC <5.0 \times 10⁶, PLT <100,000/ μ l, and red cell distribution width (RDW) >15.¹⁷

Dengue fever

DF is a mosquito-borne febrile illness caused by a flavivirus transmitted via the bite of the female mosquito *Aedes aegypti*. Four distinct, but closely related virus serotypes are responsible for infection: dengue virus-1 (DENV-1), DENV-2, DENV-3 and DENV-4.²² According to the WHO, the number of dengue cases have increased dramatically over the last two decades, 96 million people every year present with clinical symptoms of dengue infection, with Asia accounting for 70% of the global disease burden.²³

DF is endemic in Pakistan, and the number of cases is constantly increasing. Data for 2021 reported 48,091 cases and 183 deaths due to the virus.^{24,25} This situation is highly alarming due to the steep rising trend over the years (Figure 1). Dengue usually presents as DF, a nonspecific febrile illness with myalgia, headache, retro-orbital pain, and rash. In some cases, patients develop dengue haemorrhagic fever (DHF), a severe form of infection characterised by bleeding, plasma leakage and organ impairment, which can also result in shock and collapse, called the dengue shock syndrome (DSS).²²

DF is usually confirmed by rapid diagnostic tests for the dengue nonstructural protein-1 (NS-1) antigen during days 1-5 of illness, and by serological testing after the 5th day.²² However, patients in LMICs frequently cannot afford these tests due to the high cost. They may also be unreliable early in the course of the disease.²⁶ Since early diagnosis and management of DF is important to avoid complications, basic blood testing combined with clinical suspicion in endemic areas must be used to diagnose and treat dengue patients in a timely manner.

Haematological parameters, such as HCT, TLC and PLT count show specific variations in DF and can be used as reliable parameters to diagnose dengue infection. In patients with simple DF, RBC indices, such as Hb and HCT,

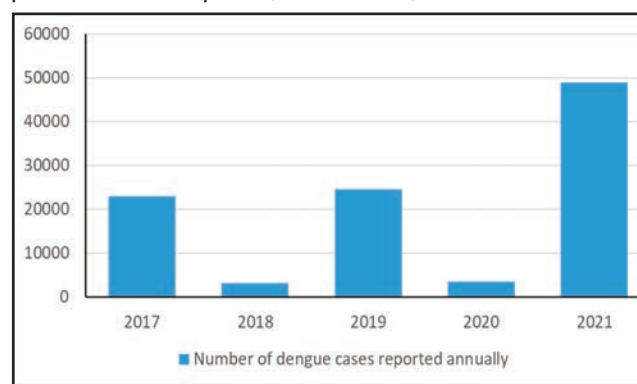


Figure-1: Annual number of dengue cases reported in Pakistan over the years. Data source: National Institute of Health (NIH), Islamabad, and Disaster Response Emergency Fund (DREF) Final Situation Report, Pakistan (June 2022).^{24,25}

are frequently unchanged. In DHF, plasma leakage and haemoconcentration occur, leading to an increase in both the parameters. An increase in the HCT level of $\geq 20\%$ is one of the WHO defining criteria for DHF.²⁷ An increased HCT level, while important in diagnosis, is not prognostic and cannot be used to predict disease severity.²⁸

Leukopenia, defined as TLC count $< 4.0 \times 10^6$, can be observed as early as day 2 of illness and can be used as an early marker for diagnosis.²⁹ Leukopenia has a positive predictive value (PPV) of 70-80% for DF in endemic areas.²² The decrease in TLC is primarily due to a decrease in neutrophil count, which occurs as a result of decreased granulocyte production secondary to virus-mediated bone marrow suppression.¹⁸ In contrast, the lymphocyte count is increased owing to the presence of atypical lymphocytes in response to viral infections.³⁰ DF is characterised by a low

neutrophil-to-lymphocyte ratio (NLR), which can help distinguish it from other febrile infections.³⁰

Among other WBCs, an increase in the number of monocytes can be seen in the early stages of illness, whereas an increase in the number of basophils and eosinophils is frequently seen in the convalescent phase.^{30,31} In approximately 80% cases, the resurgence of the TLC precedes the recovery of the PLT count during the recovery phase.³¹

Thrombocytopenia is the most common haematological abnormality seen in dengue patients, and it can be caused by increased peripheral destruction and bone marrow depression. PLT counts may be normal in the early stages of DF, which helps distinguish it from malaria. PLT counts are typically lowest 3-6 days after disease onset, when the patient is no longer febrile.¹⁸ PLT count is also a prognostic indicator, with higher values indicating disease progression. Lower PLT counts are linked to more haemorrhagic manifestations.²⁸

The haematocrit-platelet index (HPI) has recently been introduced as a prognostic marker for severe dengue, and is strongly associated with length of hospital stay. According to Haider et al., an HPI of 1.0 or higher on day 3 is associated with a severe clinical course.³² As a result, a CBC can not only help diagnose DF, but also predict its clinical course and severity.

Kotepui et al. in Thailand in 2017 determined the haematological parameters that could be used to differentiate DF and malaria. The study had 683 patients, and, after analysis, a decision tree was devised that could be used to differentiate between the two fevers (Figure 2).¹⁸

COVID-19

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting coronavirus disease-2019 (COVID-19) pandemic resulted in over six million deaths, making it the deadliest global health crisis since the 1918 influenza pandemic.³³ The virus is highly contagious and spreads from person to person via respiratory droplets. COVID-19 has now entered an 'endemic phase' as a result of vaccine development and global vaccination efforts.³⁴ New strains of the virus continue to emerge and spread in the community, infecting people.³⁴

Pakistan, like other countries, was severely affected by the virus, with approximately 1.57 million reported cases and over 30,000 deaths.³⁵ COVID-19 has a broad clinical spectrum, from asymptomatic or mildly symptomatic forms to severe pneumonia, that causes organ failure and frequently necessitates mechanical ventilation.³³ Among

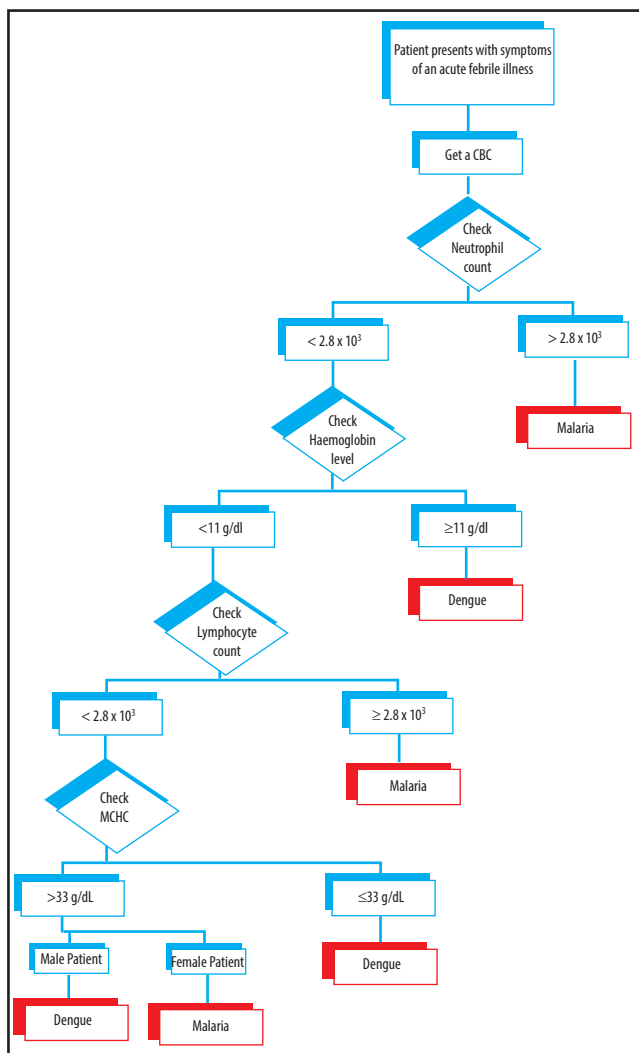


Figure-2: Algorithm to differentiate between malaria and dengue fever based on complete blood count (CBC) parameters.¹⁸

MCHC: Mean corpuscular haemoglobin concentration.

those who are symptomatic, the most common symptoms are fever, cough, dyspnoea, sore throat, anosmia and myalgias.³³

The standard test for COVID-19 diagnosis is molecular testing for the virus using polymerase chain reaction (PCR) on nasopharyngeal or oropharyngeal swab samples. The drawbacks of this test include its high cost, sample collection errors, low sensitivity, and prolonged waiting time for the results.³⁶ The gold standard for diagnosing COVID-19 is a high-resolution computed tomography (HRCT) chest scan, but radiological testing is costly and not widely available. Other tests, such as rapid antigen testing, serological testing, and plain chest films, have low sensitivity and are frequently not used for diagnosis.³³

The CBC of COVID-19 patients shows several changes that can be used to predict infection and guide diagnostic testing. COVID-19 patients' mean Hb and HCT levels are frequently unchanged or mildly decreased, except in critically ill patients, where the Hb level may be significantly low.³⁷ RDW is typically increased, as are serum ferritin levels.³⁸

Lymphopenia has been identified as the most common and significant CBC abnormality in COVID-19 patients.³⁹ When compared to baseline levels, TLC is low, and the neutrophil count is often high. Lymphopenia is progressive, and people with severe disease frequently become more lymphopenic as the disease progresses.⁴⁰ These findings are similar to those of DF, but NLR is higher in COVID-19 patients than in DF patients, which can help distinguish between the two.⁴¹

An important finding observed in COVID-19 patients is eosinopenia. Tanni et al. found that 60% of COVID-19 patients had an eosinophil count of 0 at the time of presentation.⁴² Persistently, low eosinophil counts are also associated with severe disease and low recovery rates. The pathophysiology behind this abnormality is uncertain and is most likely multifactorial.³⁸ Among the other types of WBCs, basophil counts are low, whereas monocyte counts remain unchanged.³⁷

COVID-19, like other viral infections, also causes thrombocytopenia, which is usually mild. Unlike DF, where the PLT count drops during defervescence days 3-5, thrombocytopenia in COVID-19 occurs later in the clinical course.⁴¹ PLT counts remain above 100,000/ μ l on average. A progressively falling PLT count, on the other hand, may indicate the presence of an underlying coagulopathy and is associated with a severe clinical course.³⁷ It is interesting to note that in COVID-19, the immature platelet fraction (IPF) is elevated even when the total PLT count is normal.⁴³

These immature PLTs are more functional and may contribute to an increase in COVID-19 thrombotic events.

Formica et al. developed a clinical score based on CBC parameters with >80% sensitivity and specificity for the diagnosis of COVID-19. Each of these parameters were scored accordingly; MCV \leq 90fL, age \geq 45 years, PLT \leq 180,000/ μ l, and eosinophil count $<$ 0.1/ μ L. Individuals with a mean absolute percentage error (MAPE) score \geq 173 have a high probability of testing positive by COVID-19 PCR testing.⁴⁴ Such scores have yet to be clinically applied, but they highlight the importance of a CBC in diagnosing endemic diseases early and effectively.

Erythrocyte sedimentation rate (ESR)

The erythrocyte sedimentation rate (ESR) is a test that measures the descent of RBCs in a vertical column of anticoagulated blood over a period of one hour. ESR is a simple and inexpensive test that is often used as a nonspecific marker of inflammation in the body.⁴⁵ ESR values, like the other CBC parameters already discussed, frequently show characteristic patterns in infectious diseases, and, when available, can aid in diagnosis. In typhoid fever, ESR levels do not increase in the first few weeks, rather show a significant decrease when compared to ESR levels in healthy individuals.⁴⁶ Approximately 80% of individuals with malaria have an elevated ESR during the acute phase of illness, which returns to normal during recovery.⁴⁷ Most DF patients have normal ESR levels, but in cases of DHF with shock, ESR levels are low.⁴⁸ COVID-19 has significantly elevated ESR levels, as well as other inflammatory markers, such as C-reactive protein (CRP) and serum ferritin levels.³⁹

Role of the blood peripheral film

While the role of the peripheral blood smear has been widely recognised for malaria diagnosis, the utility of the blood film in diagnosis of other infectious fevers remains unclear and less well recognised. For malaria, a drop of blood is smeared on a slide and stained with Giemsa to visualise the plasmodium parasites, which results in definitive diagnosis. Often, both thin and thick blood smears are prepared and visualised under a microscope. In *P. falciparum* infections, the infected RBCs will show either ring forms or crescent-shaped gametocytes. Trophozoite and schizont forms are rarely visualised.⁴⁹ In DF, plasmacytosis has been suggested as a diagnostic marker on blood film in some cases.⁵⁰

Literature suggests that morphological abnormalities on blood smear can be used to predict disease severity in COVID-19 rather than using it for diagnostic purposes.⁵¹

Table: A simplified summary of the most common changes in haematological parameters amongst endemic infectious diseases in Pakistan.

Disease	Changes in CBC parameters									
	Hb	HCT	TLC	Neutrophils	Lymphocytes	NLR	Eosinophils	Monocytes	Basophils	Platelets
Typhoid	N	N	↓ (↑ in children)	↓	N or ↑	↓	↓	N	↓ (often zero)	N or ↓ (late)
Malaria	↓	↓	N or ↓	↓	↓↓	↑↑	↑	↑	N or ↓	↓↓ (early)
Dengue	N or ↑	N or ↑	↓ (early)	↓	↑	↓	↑ (late)	↑ (early)	↑ (late)	↓↓ (late)
COVID-19	N or ↓	N or ↓	↓	↑↑	↓	↑↑	↓↓ (often zero)	N	↓	↓

CBC: Complete blood count, Hb: Haemoglobin, HCT: Haematocrit, NLR: Neutrophil-to-lymphocyte ratio. N: Normal, ↑: Increased, ↓: Decreased, COVID-19: Coronavirus disease-2019.

Clinical application and limitations

The primary infectious diseases in Pakistan have particular alterations in CBC values (Table). In real life, the outcomes might not be as uniform, and a diagnosis might be difficult. Since the majority of these disorders share comparable CBC readings and overlapping clinical characteristics, a single CBC test might not provide a conclusive diagnosis. Moreover, most of these diseases have CBC patterns that differ based on the day after infection. It is crucial to keep in mind that routine laboratory testing should always support clinical judgement, and caution must be taken to account for all confounding variables when utilising CBC as a diagnostic tool.

Conclusion

Certain infectious diseases that are endemic in Pakistan carry a significant burden on the healthcare system in terms of economic and healthcare resources. When there is a high degree of clinical suspicion, a simple and inexpensive CBC test can often be the only investigation needed for diagnosis. It can also help direct prompt management, saving valuable time and resources.

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