Mini-Review

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Approach to acute febrile illness during the COVID-19 pandemic

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SUMMARY Coronavirus disease 2019 (COVID-19) is a febrile respiratory illness that has spread rampantly across the globe and has emerged as one of the biggest pandemics of all time. Besides the direct effects of COVID-19 on mortality, collateral impacts on diagnosis and management of acute febrile illnesses (AFI) is a matter of great concern. The overlap in presentation, shunting of available resources and infection control precautions in patients with suspected COVID-19 result in a significant delay in diagnoses and management of AFI. This review highlights the challenges in the management of acute febrile illness during COVID pandemic and possible solutions for the same.

Keywords Dengue, scrub typhus, leptospirosis, chikungunya, malaria

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by a virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was first reported in December of 2019 and has evolved into a pandemic with more than 75 million cases as on December 20, 2020. The number of reported deaths due to COVID-19 is more than 1.6 million (*1*). However, there are no official reports on the number of deaths in non-COVID patients who suffered as collateral damage of COVID-19. One such group of patients who are speculated to be affected is patients with acute febrile illnesses (AFI) who may present with similar manifestations as COVID-19 but remain undiagnosed. AFI is an umbrella term used for infectious febrile illness of short duration (< 14 days) in tropical and sub-tropical countries (*2*). The most common AFIs include dengue, chikungunya, malaria, enteric fever, scrub typhus, leptospirosis, Zika virus, and Kyasanur forest disease (KFD) (*3*). The aim of this review is to discuss the interplay between COVID-19 and AFIs.

2. Epidemiology

Acute febrile illness is one of the most common causes of admission in the monsoon/post-monsoon season in both the public and private sectors. With the increase in the human population and overcrowding, the prevalence of AFIs has been increasing throughout the world. Due to the lockdown instituted in several geographical regions, interventions such as seasonal chemotherapy prophylaxis, insecticidal measures, and environmental surveillance may take a hit, thereby increasing the incidence further.

These AFIs are either mosquito-borne (dengue, chikungunya, malaria, Zika) with a higher number of reported cases in the monsoon season or are tick (KFD)/ louse-borne (scrub typhus) with predominant activity in the post-monsoon season. Waterborne illnesses such as leptospirosis and enteric fever can be seen throughout the year, but a spike is noticed in their reports in the monsoon season. Mosquito-borne AFIs like dengue, malaria, chikungunya, and Zika have wide geographic distribution spanning the continents of Asia, Africa, and South Americas. In a recent review of literature, 262 dengue outbreaks were identified throughout the world from 1990-2015, with the highest number of them reported from India (58/262) (*4*). Malaria affects more than 90 countries and territories in the tropical and subtropical regions with Africa. According to the World Malaria Report 2017, in the year 2016, more than half of the population (698 million) was at risk of malaria (*5*). India accounted for 6% of all malaria cases in the world, 6% of the deaths, and 51% of the global *Plasmodium vivax* cases. The report estimates the total cases in India at 1.31 million (0.94-1.83 million) and deaths at 23,990 (1,600-46,500) (*6*). Following the initial outbreak at Tanganyika in the year 1952, Chikungunya epidemics have been reported from several parts of the world including Africa, Asia, and elsewhere. As of September 2015, 1.7 million cases and 240 deaths were reported from 45 of the 53 countries or territories reporting to the Pan American Health Organization (*7*). The three major outbreaks of Zika virus disease occurred in the Yap Islands (2007), French Polynesia (2013-14), and South

Americas (2015-16) after years of sporadic reports from Africa. The first proven cases of ZIKV from India were reported in the year 2017. This was followed by major outbreaks in the states of Rajasthan and Madhya Pradesh in 2018 (*8,9*).

Tick/louse-borne AFIs like scrub typhus and KFD have a more defined geographical distribution. Scrub typhus, a rickettsial infection caused by *Orientia tsutsugamushi*, is supposed to be endemic in major parts of Asia and Australia. It accounts for up to 23% of all febrile episodes, with an estimated 1 million cases occurring annually in endemic areas (*9*). The KFD virus is transmitted by the bites of infected *Haemaphysalis spinigera* ticks. This is predominantly reported from five states in Southern India (Karnataka, Kerala, Goa, Maharashtra, and Tamil Nadu) (*10*).

Water-related diseases like leptospirosis and enteric fever have a world-wide distribution. Leptospirosis infection occurs from exposure to water contaminated with animal urine, while enteric fever is associated with the intake of contaminated food or water. As a part of a multi-centric study from India, of 3,682 patients with acute febrile illness, 469 (12.7%) were found to have a leptospiral infection (*11*). The global annual burden of typhoid was estimated at approximately 12 million cases for 2010, with a case fatality rate of 1% (*12*).

3. Clinical manifestations

The most common clinical manifestations of patients with mild COVID 19 are fever and upper respiratory tract symptoms. There are a significant fraction of patients with COVID-19 who present with fever but without upper respiratory tract symptoms. In patients with moderate/severe disease, there is concomitant respiratory distress and hypoxemia (*13*). Similar to the manifestations of COVID-19, patients with acute febrile illness present with fever with accompanying symptoms (Table 1) (*14*). Respiratory involvement as a consequence of increased vascular permeability or direct involvement as a part of multi-organ dysfunction is seen in many of the febrile illnesses (*15*). Consequently, the distinction between COVID-19 and AFI on clinical grounds alone is difficult. Some of the AFIs like dengue fever present commonly with a rash, but these rashes are often difficult to appreciate in dark-skinned individuals residing in the tropics. Besides, a similar rash has been described in a small percentage of patients with COVID-19. Characteristic eschar in scrub typhus help in differentiating from COVID in some cases, but its frequency is variable and may go unnoticed in many cases unless looked for carefully (*16*). Conjunctival suffusion and jaundice are characteristic of leptospirosis and are not commonly reported with COVID-19. However, a larger proportion of patients with leptospirosis do not have either of these signs (*17*). The presence of arthralgia is common to both AFIs (Chikungunya, Zika virus disease) and COVID-19. However, the presence of small joint arthritis is not commonly reported in COVID-19, which may help in diagnosing chikungunya.

4. Laboratory manifestations

The laboratory manifestations of COVID-19 and AFIs have been summarized in Table 2. Similar to patients with COVID-19, AFIs such as dengue, chikungunya, and KFD also present with leucopenia. Leucocytosis seen in some cases of scrub typhus or leptospirosis is rare in COVID-19. Thrombocytopenia (dengue, chikungunya, scrub typhus, leptospirosis, enteric fever, KFD) is, however, more common in most acute febrile illnesses when compared to COVID-19. Elevated transaminases (scrub typhus, enteric fever, dengue) are common to several AFI and COVID-19, but hyperbilirubinemia seen in leptospirosis is uncommon in COVID-19. Acute kidney injury in leptospirosis or scrub typhus can also be seen with severe COVID-19. Raised inflammatory markers such as C-reactive protein (scrub typhus, leptospirosis) is common to both AFI and moderate/severe COVID-19.

5. Diagnosis

Healthcare workers in resource-limited settings often diagnose patients presumptively on the basis of clinical features and region-specific prevalence of the pathogens.

Table 1. Clinical manifestations of COVID-19 and acute febrile illnesses

Disease	Fever	Cough	Rash	GI Symptoms	Jaundice	Conjunctival suffusion	Lymph adenopathy	Hepato splenomegaly
COVID-19 (*23*)	Y	Y	N	N	N	N	N	N
Dengue (*24*)	Y	?Y	Y	Y	-	Y	?Y	
Malaria (*15*)	Y		N	?Y	Y	-	-	?Y
Chikungunya (*25*)	Y		Y	N	-	-	?Y	-
Scrub typhus (*26*)	Y	?Y	?Y	N	?Y	?Y	?Y	Y
Leptospirosis (*27*)	Y	?Y		?Y	Y	Y	-	-
Enteric fever (*28*)	Y	Y		Y		-	-	Y
KFD (*29-31*)	Y	Y		?Y	N	Y	-	-
Zika (32-33)	Y		Y	?Y	N	Y	-	-

Abbreviations- Y, feature commonly present; ?Y, present but not very common; N, not commonly present.

Table 2. Laboratory manifestations of COVID-19 and acute febrile illnesses

Disease	Anemia	Leukopenia	Leukocytosis	Thrombocytopenia	Deranged LFT	Raised Creatinine	Raised CRP	Coagulopathy
COVID-19 (*23,34*)	N	?Y	N	N	N	N	?Y	Y
Dengue (*24,35*)	N	Y	N	Y	Y	N	-	Y
Malaria (*15,36*)	Y	N	N	Y	Y	Y	-	Y
Chikungunya (*25*)	N	Y	N	Y	-	N	-	-
Scrub typhus (*25,34-36,40*)	?Y	N	Y	Y	Y	?Y	Y	?Y
Leptospirosis (*27,41*)	?Y	N	Y	Y	Y	Y	Y	-
Enteric fever (*42*)	?Y	?Y	Y	Y	?Y		-	-
KFD (*29-31*)	N	Y	-	Y	Y	-	-	-
Zika (*33*)	-	Y	-	?Y	-	-	-	-

Abbreviations- Y, feature commonly present; ?Y, present but not very common; N, not commonly present.

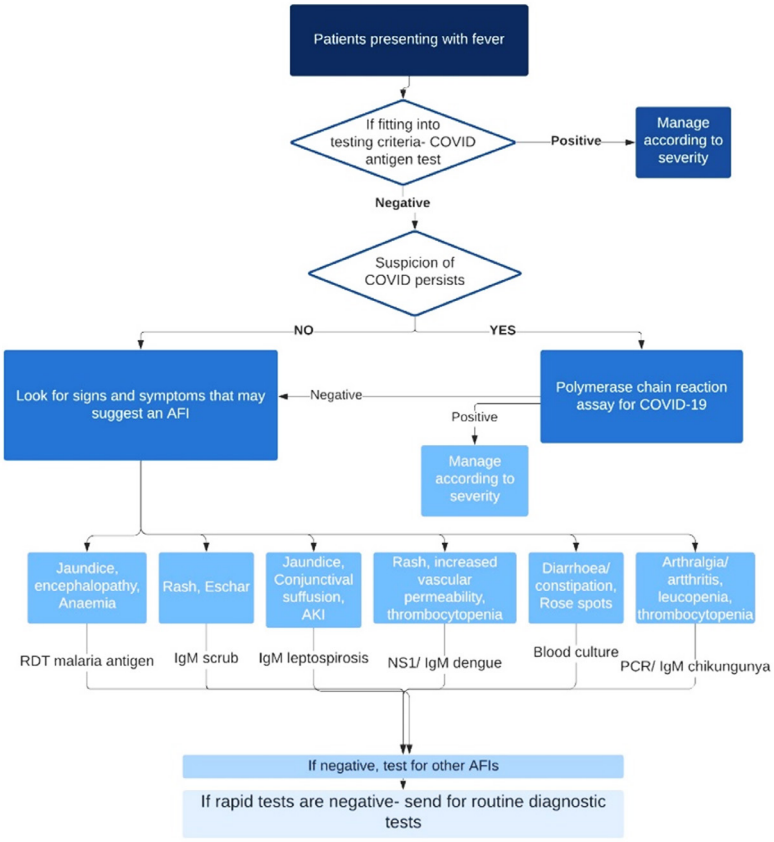

Figure 1. Proposed algorithm for the approach to Acute febrile illness during COVID time. Abbreviations: AFI- Acute febrile illness, AKI- Acute kidney injury, RDT- Rapid diagnostic test, PCR- Polymerase chain reaction assay.

However, the accurate determination of the aetiology of AFI requires laboratory tests, as many of the AFIs have similar clinical presentations. The overlap of the clinical spectrum of acute febrile illnesses with COVID 19 has further added fuel to the fire by presenting as a diagnostic and management conundrum for the health care system in resource-limited settings. Besides, due to the infection control precautions that are mandated in most hospitals, tests for acute febrile illnesses are often not sent until the COVID tests return negative. Depending on the turn-around time of COVID-19 tests, the diagnosis of AFI is often delayed. Also, due to unreal concerns of infection from the blood of suspected patients, peripheral smear and quantitative buffy coat are discontinued in many hospitals resulting in significant difficulty in diagnosing malaria. It has to be also kept in mind that some of the serological tests for AFI are not perfect and may yield false-positive results. As a result, a patient with COVID-19 may be falsely diagnosed with AFI, and infection control precautions may be discontinued. This can lead to unnecessary exposure to healthcare professionals. A report from Singapore highlighted patients with false-positive rapid serological testing for dengue, who later confirmed to

have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection- the causative virus of COVID-19 (*18,19*). A similar report published by Ullah *et al.* described a patient with COVID 19 presenting with arthralgia and a false positive chikungunya test (*20*). Also, considering the current endemicity of both groups of illnesses, coinfections cannot be ruled out. During the pandemic, the routine non-COVID diagnostics have been severely compromised due to the shunting of resources (manpower and materials) in the COVID area. In such a scenario, the use of rapid diagnostic testing for the diagnosis of COVID-19 and AFIs will be beneficial in early diagnosis and prompt initiation of treatment (*21*). However, it must be kept in mind that rapid diagnostic tests suffer from poor sensitivity. In the presence of high clinical suspicion, they should be confirmed by routine gold standard diagnostics. An integrated algorithm has been proposed for the management of a patient with suspected AFI. (Figure 1) (*22-42*).

6. Treatment

The rapidly evolving use of experimental COVID-19 therapies is gaining importance globally. While most of these therapies are initiated without proof of their efficacy in COVID-19, they may have potential clinical harms. Biologicals like anakinra and tocilizumab may suppress the cytokine storm, a potential defence mechanism against febrile illnesses. Pharmacokinetic and pharmacodynamic interactions involving the HIV protease inhibitor lopinavir/ritonavir may affect the absorption, distribution, and metabolism of other systemic therapy administered to the patient. The rampant off-label use of chloroquine derivatives for COVID 19 prophylaxis may increase resistance in malaria in endemic regions. The use of agents like doxycycline and azithromycin as empiric therapy can decrease the sensitivity of molecular diagnostics by many folds (*43*).

7. Conclusion

It is of prime importance that the infrastructure and manpower at the healthcare facilities should be expanded to avoid neglect of endemic acute febrile diseases. The primary care physicians should be sensitized about the importance of suspecting AFIs in COVID-19 suspects. There is a need for formulating integrated clinical algorithms for the management of AFIs, keeping into account the epidemiology and seasonal prevalence of febrile diseases.

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References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Inf Dis. 2020; 20:533-534.
2. Mørch K, Manoharan A, Chandy S, *et al*. Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. BMC Infect Dis. 2017; 17:665.
3. Shrestha P, Roberts T, Homsana A, Myat TO, Crump JA, Lubell Y, Newton PN. Febrile illness in Asia: gaps in epidemiology, diagnosis and management for informing health policy. Clin Microbiol Infect. 2018; 24:815-826.
4. WHO Global Strategy for dengue prevention and control, 2012-2020. Available from: *https://www.who.int/denguecontrol/9789241504034/en/* (accessed September 1, 2020).
5. Nghochuzie NN, Olwal CO, Udoakang AJ, Amenga-Etego LN, Amambua-Ngwa A. Pausing the fight against malaria to combat the COVID-19 pandemic in Africa: Is the future of malaria bleak? Front Microbiol. 2020; 11:1476.
6. Malaria in India. Malaria Site. 2015. Available from: *https://www.malariasite.com/malaria-india/* (accessed August 29, 2020).
7. Petersen LR, Powers AM. Chikungunya: epidemiology. F1000Res. 2016; 5:F1000 Faculty Rev-82.
8. Gupta N, Kodan P, Baruah K, Soneja M, Biswas A. Zika virus in India: past, present and future. QJM. 2019:hcz273.
9. Biswas A, Kodan P, Gupta N, *et al.* Zika outbreak in India in 2018. J Travel Med. 2020; 27:taaa001.
10. Mourya DT, Yadav PD, Patil DY. Expediency of dengue illness classification: the Sri Lankan perspective highly infectious tick-borne viral diseases: Kyasanur forest disease and Crimean-Congo haemorrhagic fever in India. WHO South East Asia J Public Health. 2014; 3:8-21.
11. Sehgal SC, Sugunan AP, Vijayachari P. Leptospirosis disease burden estimation and surveillance networking in India. Southeast Asian J Trop Med Public Health. 2003; 34 (Suppl 2):170-177.
12. John J, Van Aart CJ, Grassly NC. The burden of typhoid and paratyphoid in India: Systematic review and meta-analysis. PLoS Negl Trop Dis. 2016; 10:e0004616.
13. Guan WJ, Ni ZY, Hu Y, *et al.* Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382:1708-1720.
14. Chanda-Kapata P, Kapata N, Zumla A. COVID-19 and malaria: A symptom screening challenge for malaria endemic countries. Int J Infect Dis. 2020; 94:151-153.
15. Echeverri M, Tobón A, Alvarez G, Carmona J, Blair S. Clinical and laboratory findings of *Plasmodium vivax* malaria in Colombia, 2001. Rev Inst Med Trop Sao Paulo. 2003; 45:29-34.
16. Le Van N, Pham Van C, Nguyen Dang M, Dao Van T, Le T Do Q, Vu Hoang H, Tran Viet T, Nhu Do B. Clinical features, laboratory characteristics and prognostic factors of severity in patients with Rickettsiaceae at two military hospitals, Northern Vietnam. Infect Drug Resist. 2020; 13:2129-2138.
17. Sambasiva RR, Naveen G, PB, Agarwal SK. Leptospirosis in India and the rest of the world. Braz J Infect Dis. 2003; 7:178-193.
18. Yan G, Lee CK, Lam LTM, *et al.* Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis. 2020; 20:536.
19. Lorenz C, Azevedo TS, Chiaravalloti-Neto F. COVID-19

and dengue fever: A dangerous combination for the health system in Brazil. Travel Med Infect Dis. 2020; 35:101659.
20. Ullah W, Tran A, Roomi S, Saeed R, Sarwar U. COVID-19 masquerading as Chikungunya fever. Am J Infect Dis. 2020:73-76.
21. Gupta N, Nischal N. Management of acute febrile diseases in limited resource settings: a case-based approach. Infez Med. 2020; 28:11-16.
22. Lim JH, Baek EJ. A case of false-negative malaria rapid diagnostic test induced by treatment with doxycycline. Laboratory Medicine Online. 2019; 9:194-196.
23. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, *et al.* Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020; 34:101623.
24. Daumas RP, Passos SR, Oliveira RV, Nogueira RM, Georg I, Marzochi KB, Brasil P. Clinical and laboratory features that discriminate dengue from other febrile illnesses: a diagnostic accuracy study in Rio de Janeiro, Brazil. BMC Infect Dis. 2013; 13:77.
25. Lakshmi V, Neeraja M, Subbalaxmi MV, Parida MM, Dash PK, Santhosh SR, Rao PV. Clinical features and molecular diagnosis of Chikungunya fever from South India. Clin Infect Dis. 2008; 46:1436-1442.
26. Kumar R, Thakur S, Bhawani R, Kanga A, Ranjan A. Clinical profile and complications of scrub typhus: hospital-based study in sub-himalayan region. J Assoc Physicians India. 2016; 64:30-34.
27. Becirovic A, Numanovic F, Dzafic F, Piljic D. Analysis of clinical and laboratory characteristics of patients with leptospirosis in five-year period. Mater Sociomed. 2020; 32:15-19.
28. Azmatullah A, Qamar FN, Thaver D, Zaidi AK, Bhutta ZA. Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever. J Glob Health. 2015; 5:020407.
29. Webb HE, Rao RL. Kyasanur forest disease: a general clinical study in which some cases with neurological complications were observed. Trans R Soc Trop Med Hyg. 1961; 55:284-298.
30. Gupta N, Varma M, Saravu K. Difference in clinical presentation between the first and second phases of Kyasanur Forest disease: an experience from a teaching hospital in South India. Infez Med. 2020; 28:597-602.
31. Gupta N, Wilson W, Neumayr A, Saravu K. Kyasanur Forest disease: State-of-the-art review. QJM. 2020:hcaa310.
32. Azeredo EL, Dos Santos FB, Barbosa LS, Souza TM, Badolato-Corrêa J, Sánchez-Arcila JC, Nunes PC, de-Oliveira-Pinto LM, de Filippis AM, Dal Fabbro M, Romanholi IH. Clinical and laboratory profile of zika and dengue infected patients: lessons learned from the co-circulation of dengue, zika and chikungunya in Brazil. PLoS curr. 2018; 10.
33. Wilder-Smith A, Chang CR, Leong WY. Zika in travellers 1947-2017: a systematic review. J Travel Med. 2018; 25.
34. Wright FL, Vogler TO, Moore EE, Moore HB, Wohlauer MV, Urban S, Nydam TL, Moore PK, McIntyre RC Jr. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J Am Coll Surg. 2020; 231:193-203.
35. Kannan A, Narayanan KS, Sasikumar S, Philipose J, Surendran SA. Coagulopathy in dengue fever patients. Int J Res Med Sci. 2014; 2:1070-1072.
36. Conroy AL, Hawkes M, Elphinstone RE, Morgan C, Hermann L, Barker KR, Namasopo S, Opoka RO, John CC, Liles WC, Kain KC. Acute kidney injury is common in pediatric severe malaria and is associated with increased mortality. Open Forum Infect Dis. 2016; 3:ofw046.
37. Thakur CK, Chaudhry R, Gupta N, Vinayaraj EV, Singh V, Das BK, Jadon RS, Wig N, Lodha R, Kabra SK, Dey AB. Scrub typhus in patients with acute febrile illness: a 5-year study from India. QJM. 2020; 113:404-410.
38. Narayanasamy DK, Arun Babu T, Vijayadevagaran V, Kittu D, Ananthakrishnan S. Predictors of severity in pediatric scrub typhus. Indian J Pediatr. 2018; 85:613-617.
39. Premraj SS, Mayilananthi K, Krishnan D, Padmanabhan K, Rajasekaran D. Clinical profile and risk factors associated with severe scrub typhus infection among non-ICU patients in semi-urban south India. J Vector Borne Dis. 2018; 55:47-51.
40. Park SW, Lee CS, Kim JH, *et al.* Severe fever with thrombocytopenia syndrome: comparison with scrub typhus and clinical diagnostic prediction. BMC Infect Dis. 2019; 19:174.
41. Furlanello T, Reale I. Leptospirosis and immune-mediated hemolytic anemia: A lethal association. Vet Res Forum. 2019; 10:261-265.
42. Khosla SN, Lochan R. Renal dysfunction in enteric fever. J Assoc Physicians India. 1991; 39:382-384.
43. Gupta N, Chaudhry R, Kabra SK, *et al.* Comparative evaluation of serological and molecular methods for the diagnosis of scrub typhus in Indian settings. Jpn J Infect Dis. 2017; 70:221-222.

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