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 (7). 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
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.

| 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   | N           | Y        | -                      | -               | Y                   |
| Chikungunya (25)                 | Y     | Y     | N    | N           | Y        | -                      | -               | Y                   |
| Scrub typhus (26)                | Y     | ?Y    | ?Y   | N           | ?Y       | ?Y                     | -               | Y                   |
| Leptospirosis (27)               | Y     | ?Y    | ?Y   | Y           | Y        | -                      | Y               | Y                   |
| Enteric fever (28)               | Y     | Y     | Y    | N           | Y        | -                      | -               | Y                   |
| KFD (29-31)                      | Y     | Y     | ?Y   | N           | Y        | -                      | -               | -                   |
| Zika (32-33)                     | Y     | Y     | ?Y   | N           | Y        | -                      | Y               | Y                   |

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

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          | Y            | N                | Y            | N                | ?Y         | Y            |
| Dengue (24,35)    | N      | Y          | N            | Y                | N            | N                | N          | N            |
| Malaria (15,36)   | Y      | N          | N            | Y                | Y            | Y                | Y          | -            |
| Chikungunya (25)  | Y      | N          | 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                | 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.
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, coinfestions 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 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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