Review

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Management of dengue with co-infections: an updated narrative review

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SUMMARY Dengue is a life-threatening mosquito borne viral disease. We are still in the era of supportive treatment where morbidity and mortality are a major concern. Dengue infection in presence of other co-infections makes this scenario rather worse. Timely recognition and raising alarm to be intensive is the need of the hour for primary care physicians practicing in the community and indoors. This review provides a comprehensive knowledge about the recent trends of coinfection in dengue as well as their management consideration which will be particularly helpful for physicians practicing in rural and remote areas of India.

Keywords Dengue, co-infection, management, approach, atypical Dengue

1. Introduction

Dengue infection has rapidly emerged as the most important mosquito-borne viral disease in the last few decades. According to the World Health Organization (WHO) estimates, the disease is endemic in more than 100 countries, with about 390 million new dengue infections occurring annually, and there has been a steady increase in these numbers (*1*). Dengue fever typically presents as a self-limiting disease, with a mortality rate of less than 1%. Severe dengue accounting for 3-4% of dengue fever cases, has a mortality rate of 2-5% when adequately treated, but if not treated, the mortality rate rises to as high as 50%. Dengue patients having co-infections with other microorganisms are associated with a greater risk of severe disease and mortality (*2*). Adding to this picture is the risk of morbidity and mortality associated with coinfections. The aim of this review was to give a comprehensive picture about the different clinical presentation and management issues of dengue with different coinfection particularly in respect to Indian setting.

2. Dengue serotypes and association with virulence

The dengue virus has four antigenic groups (serotypes) and each serotype is further divided into one to six genetic groups (genotypes) as shown in Table 1. The four serotypes dengue virus 1-4 (DENV 1-4) of the virus share almost 65-70% sequence homology with each other. These viruses have the highest mutation rate among the flaviviruses, leading to the generation of different genotypes and lineages within each serotype. More recently, a fifth serotype has been discovered in 2013 from the forests of Sarawak, Malaysia.

Infection with any of the four dengue serotypes can progress to severe dengue infection. However, DENV-2 is found to be most virulent amongst the four strains having association with most of the severe cases. With the advent of newer technologies for the genetic analyses of viruses, studies from the Western hemisphere have deciphered that severe dengue is mostly associated with infection with specific genotypes of dengue virus within each serotype (*3*). The initial descriptions of differences in DENV virulence came from epidemiologic and entomologic studies conducted in the South Pacific by Gubler *et al*. (*4*). Some outbreaks in this region had very few or no cases of severe dengue, and the transmitted viruses were considered to be of lower virulence as compared to other outbreaks that had many cases of severe dengue, after primary infection and thus considering the latter viruses to be more virulent (*5*).

3. When to suspect co-infections?

Differentiating patients of dengue fever from patients with other co-infections such as malaria, chikungunya, enteric fever, scrub typhus, leptospirosis on clinical grounds alone is difficult on many occasions. The clinical presentations may be similar in few cases of co-infection, but majority of them present with more severe manifestations and complications. Hence having a high index of clinical suspicion for co-infection is essential in order to make a timely diagnosis and administration of the specific treatment required. Symptoms and clinical findings that may suggest co-infections are depicted in Table 2.

Enteric fever can manifest with a wide variety of symptoms and is essentially a clinical diagnosis. However, much of the knowledge on the clinical manifestations of the same disease as a coinfection in dengue are largely based on case reports. In patients with dengue, enteric fever should be suspected when there is persistence of fever beyond first week of illness with prominent gastrointestinal symptoms (*5,6*).

Patients can have urinary tract infection (UTI) with gram negative bacilli during the course of hospital stay. The symptoms of superadded UTI are usually prolonged fever beyond first week with or without lower urinary tract symptoms (LUTS) like dysuria, increased frequency, urgency (*6*). Appropriate culture based antibiotics is usually adequate for treatment of UTI in dengue (Table 3).

Dengue when presents with any coinfection will have additional laboratory abnormalities apart from those caused by DENV depending on the co-infecting pathogen. Table 4 represents prominent laboratory features of some of the common infections that can occur during dengue season in India.

Table 1. Different dengue virus serotypes

Serotype	Number of genotypes
DENV 1	5
DENV 2	6
DENV 3	4
DENV 4	4
DENV 5	Sylvatic

4. Reinfection by dengue serotype

Several epidemiologic studies have shown that prior dengue exposure is significantly associated with

Table 2. Clinical features distinguishing different aetiologies of co-infection in dengue

Dengue with	Fever more than 5-7 days	Cough	AKI	Jaundice	GI	Spleen	Eschar	HRS	LN	Altered mental status, seizures	Rash	Red eyes	Myalgia	Joint pain
Enteric fever	√				√	√				√	+/-			
UTI	√													
Leptospirosis	√		√					√				√	√	
Malaria	√		√							√				
Scrub	√	+/-	√			√	√	√	√	√	√			
Chikungunya										+/-	√			√
Zika											√	√	√	√
COVID 19		√	+/-	+/-	Diarrhoea								√	

AKI, acute kidney injury; GI, gastrointestinal; HRS, hepato renal syndrome; LN, lymph node; UTI, urinary tract infection; COVID, corona virus disease.

Table 3. The diagnostic tests for co-infection

Diseases	Tests	Sample
Dengue	NS1 antigen ELISA or RT PCR: For < 5 days of illness IgM capture ELISA (MAC-ELISA): For > 5 days of illness	Blood/Serum
Chikungunya	Early disease: RT PCR After first week of illness: IgM capture ELISA	Blood/Serum
COVID 19	Acute phase: RT PCR	Nasopharyngeal/ Oropharyngeal swab
Malaria	RDT (bi-valent both Pf/Pv detection) Quality microscopy for slide positivity confirmation	Blood Blood
Leptospirosis	In endemic areas: IgM ELISA and MAT tests Non-endemic areas: IgM ELISA followed by MAT test for confirmation	Serum Serum
Scrub Typhus	Detection of IgM antibodies by Weil-Felix Test (WFT) Enzyme linked Immunosorbent assay (ELISA)	Serum Serum

Table 4. Prominent laboratory features of different mono-infections

Items	Leucocytosis	Leucopenia	Anemia	TCP	Transaminitis	Raised bilirubin	Raised cre-atinine	Coagulopathy
Enteric fever	√	Lymphopenia						
Chikungunya		Lymphopenia		√				
UTI	√						√	
Malaria			√	√	√	√	√	√
Leptospirosis	√Neutrophilia		√	√	√	√	√	√
Scrub	√				√		√	√
Zika	Eosinopenia			+/-				
COVID 19		√			√			√

TCP- thrombocytopenia

greater risk of severe disease when encountered with a secondary dengue virus infection, than during the primary infection. This phenomenon can be explained by the Halstead theory of antibody mediated immune enhancement and has been supported by several observations. Cuba experienced an outbreak of DENV-2 in 1981, which was preceded by DENV-1 in 1977. The outbreak of 1981 affected 45% of the nation's population, with 98% of severe cases occurring in children and adults being associated with secondary infections (*7,8*). A prospective study conducted in Bangkok in 1980 showed that hospitalization was not required in any of the 47 children with primary dengue infection as compared to the children with secondary infections, of whom 7 of 56 required hospitalization (*9*).

5. Different serotypes

Dengue infection can occur with various serotypes at the same time in any permutation and combination. Depending on infection with specific combination of serotypes the severity also differs. According to a meta-analysis by Soo *et al*., primary infection with DENV2 followed by a secondary infection with DENV 2, DENV3 and DENV4 were associated with a more severe outcome in south east Asian region (*3*).

6. Malaria

Malaria, another mosquito-borne disease, is a common co-infection with dengue fever. It is widely endemic in the countries where dengue also causes a menace, including India. The transmission period of malaria also coincides with dengue infection. Exclusion of the diagnosis of malaria should be done as early as possible as malaria treatment requires administration of artemisinin combined treatment (ACT), which yields very good results. There have been recent reports of complicated vivax malaria being on rise, with a large number of the patients presenting with fever and thrombocytopenia. In endemic areas for dengue and malaria, jaundice (in dengue patients) and spontaneous bleeding (in malaria patients) should raise the suspicion of co-infection. Testing of blood with rapid diagnostic test (RDT) kit for malaria should be done at the first presentation in all the patients suspected with malaria.

Antimalarial treatment should be begun at the earliest in order to prevent complications and ensure better outcome in case of co-infection. In a bi-variate analysis study conducted in French Guiana from 2004 to 2010 amongst 104 hospitalized patients with dengue co-infection and 208 controls with dengue and malaria mono-infections, the results revealed that the clinical picture of dengue and malaria co-infection was more severe than mono-infections, and the co-infected patients were at a greater risk of severe thrombocytopenia and anaemia (*10*). A cross-sectional study was conducted from 2009 to 2011 in Brazilian Amazon, among the 1,578 hospitalized patients, of which, 176 (11.1%) presented with *P. vivax* malaria mono-infection, 584 (37%) had dengue fever mono-infection, and 44 (2.8%) of them were co-infected. It was observed that the co-infected patients had a higher incidence of presenting with severe disease (*vs*. dengue mono-infected), with features such as severe bleeding (*vs*. *P. vivax* mono-infected), and hepatic manifestations such as hepatomegaly, and jaundice (*vs*. dengue mono-infected) (*11*). The below mentioned Table 5 shows different studies worldwide on dengue and malaria co-infection.

7. Enteric fever

Incidence of water borne diseases such as enteric fever and gastroenteritis also rises during the monsoon season, when the dengue infection is also reported in large numbers. There is scarcity of data on dengue-typhoid co-infection in medical literature from both developed and developing countries. There are many features common to both the diseases, including leucopenia and high grade fever. Early administration of antibiotics is essential in cases of dengue-typhoid co-infection in order to prevent the development of complications. In patients with high index of suspicion of enteric fever and dengue co-infection (*i.e*. with fever > 5 days), early blood cultures should be sent for detection of typhoid fever and empirical antibiotics need to be started (*12-14*). The list of studies in dengue-typhoid coinfection is depicted in Table 6.

In a study conducted by Capeding *et al*., in 2013 in 5 Asian countries, out of 71 patients positive for dengue,

Table 5. Studies on malaria and dengue coinfection

S.N	Author	Title	Journal	Year	Place	Outcome /Conclusion	Finding/Significance (*p* value)
1	Magalhaes BM, *et al*., 2014 (*11*)	*P. vivax* malaria and dengue fever co-infection: a cross-sectional study in the Brazilian Amazon.	PLoS Negl Trop Dis	2014	Brazil	Jaundice in dengue and spontaneous bleeding in malaria should raise the suspicion of coinfection.	
2	Epelboin L, *et al*., 2013 (*12*)	Discriminating malaria from dengue fever in endemic areas	Plos Negl Trop Dis	2013	French Guiana	CRP > 5 mg/dL independently associated with malaria compared to dengue.	< 0.001
3	Kotepui M, *et al*.,2017 (*13*)	Differentiating between dengue fever and malaria using hematological parameters in endemic areas of Thailand.	Infect Dis Poverty	2017	Thailand	Decision tree model starting with node as neutrophil count and ending in leaf as dengue or malaria.	
4	Barua A, *et al*., 2016 (*14*)	A comparative study of concurrent dengue and malaria infection with their mono infection in a teaching hospital in Mumbai.	JAPI	2016	India	Epigastric discomfort, anemia, low haematocrit and transaminitis in coinfection group	< 0.001

Table 6. Dengue Typhoid co-infection

S.N	Author	Title	Year	Place	Journal	Finding
1	SharmaY, *et al*., 2014 (*16*)	Dengue and Typhoid Co-infection–Study from a Government Hospital in North Delhi	2014	New Delhi, India	J Clin Diagn Res	7.8% of dengue cases coinfected with enteric fever
2	See KC, *et al*., 2013 (*17*)	Identification of concurrent bacterial infection in adult patients with dengue	2013	Singapore	Am J Trop Med Hyg	4.65% culture proven enteric fever coinfection on dengue cases
3	Thein TL, *et al*., 2017 (*18*)	Risk factors for concurrent bacteremia in adult patients with dengue	2017	Singapore	J Microbiol Immunol Infect	17.2% of enteric fever among bacteremia detected in dengue cases

17 of them had co-infection with enteric fever (*15*). In an observational study from North India, the prevalence of dengue and enteric fever coinfection was found in 7.8% of proven dengue cases (*16*). In another study from Singapore, the prevalence of culture proven enteric fever was found to be 4.65% (*17*). A similar study from Singapore in 2017 showed 17.2% prevalence of enteric fever among bacteremia detected in dengue cases (*18*). Co-infections with enteric fever if present can modify the clinical presentation of dengue, thus resulting in missed or delayed diagnosis and management of dengue shock. The management should include administration of ceftriaxone and/or azithromycin at the earliest suspicion to avoid complications.

8. Chikungunya

Chikungunya and dengue fever have been reported to be prevalent at the same time from many geographical areas. Halstead *et al*. in 1969 reported the first cases of dengue-chikungunya co-infection in Thailand. They detected four co-infected cases among 150 patients diagnosed with either dengue or chikungunya virus (CHIKV) (2.6%) (19). Acute severe complications have sometimes been reported in cases of chikungunya co-infection with dengue fever. Predominant joint involvement along with prodromal symptoms and occurrence of similar acute onset arthritis in the neighbourhood or a proven chikungunya outbreak in an area should raise the suspicion of chikungunya fever. Chikungunya joint pain requires stronger analgesics (nonsteroidal anti-inflammatory drugs (NSAIDs)) in acute stage, which could result in fatal bleeding inpatients co-infected with dengue. Furuya-Kanamori *et al*. in 2016 published a meta-analysis about dengue-chikungunya co-infection (*20*). They searched three biomedical databases (PubMed, Scopus and Web of Science) right from their inception until May 2015, for studies reporting co-infection of chikungunya and dengue viruses from the same patient.

In addition to that, data from WHO, CDC and Health map alerts were also extracted, in order to create up-to-date global distribution maps for both the diseases. The meta-analysis greatly emphasises on the likelihood of misdiagnosis of chikungunya infections in

Table 7. Dengue and chikungunya coinfection

S.N	Author	Title	Journal	Year	Place	Finding
1	Halstead SB, *et al*., 1969 (*19*)	Dengue d chikungunya virus infection in man in Thailand, 1962-1964. II Observations on disease in outpatients	American journal of tropical medicine and hygiene	1969	Thailand	Ten fold risk of progression of dengue to severe dengue in cases misdiagnosed as Chikungunya
2	Furuya-Kanamori L, *et al*., 2016 (*20*)	Co-distribution and co-infection of chikungunya and dengue viruses	BMC Infectious Dis-eases	2016	Africa and south-east Asian countries	Widespread geographical distribution of coinfec-tion
3	Kaur M, *et al*., 2018 (*21*)	Coinfection of chikungunya and dengue viruses: a sero-logical survey from North Western region of Punjab, India	J Lab Physicians	2018	India	9.54% coinfection. Arthralgia and thrombocytopenia significantly higher in co-infected cases
4	Mukherjee S, *et al*., 2017 (*22*)	Evidence of dengue and chikungunya virus co-infection and circulation of multiple dengue serotypes in a recent Indian outbreak	Eur J Clin Microbiol Infect Dis	2017	Kolkata, India	23% coinfection
5	Ramachandran VG, *et al*., 2016 (*23*)	Chikungunya: a reemerging infection spreading during 2010 dengue fever outbreak in National Capital Region of India	Virus Disease	2016	Delhi, India	9.91 % positivity for Chikungunya IgM among suspected dengue sera negative for dengue IgM
6	Kaur N, *et al*., 2017 (*24*)	Chikungunya outbreak in Delhi, India, 2016: report on coinfection status and comorbid conditions in patients	New Microbes New Infect	2016	Delhi, India	25.33% Coinfection
7	Edwards T, *et al*., 2016 (*25*)	Co-infections with Chikungunya and Dengue Viruses, Guatemala, 2015	Emerg Infect Dis.	2016	Guatemala	32% coinfection
8	Londhey V, *et al*., 2016 (*26*)	Dengue and Chikungunya Virus Co-infections: The Inside Story	JAPI	2016	Maharashtra, India	10% coinfection detected by PCR

the background of dengue transmission and vice versa (*20*). Misdiagnosis of dengue fever as chikungunya or missing a dengue infection when co-infection exists carries the risks of delayed or disrupted dengue-specific intensive supportive treatment, having a consequent ten-fold likelihood of progression from dengue fever to severe disease. It is also associated with the risks of inappropriate prescription of arthralgia alleviating non-steroidal anti-inflammatory drugs, usually used to treat chikungunya patients, which could result in severe bleeding in patients with thrombocytopenia or severe dengue. The other potentially more likely scenario where chikungunya infection could be misdiagnosed as dengue or even missed in a co-infected-individual would result in masking of the true geographical extent of CHIKV and the population at risk of infection. A similar scenario resulted in the unsolved issue, when the increased fatality rate reported in chikungunya diagnosed patients in post 2004 epidemic resulted from a mutated CHIKV. Whether it was otherwise attributable to deaths due to a dengue-like illness resulting from increased awareness of chikungunya during the outbreak is still a matter of debate.

Management of both viral disease is supportive treatment and use of safer antipyretic/analgesic like acetaminophen to avoid potential risk of complications associated with usage of NSAIDs. The prevalence of coinfection in India varies depending on geographical location as per published studies. A list of studies on dengue and chikungunya co-infection is depicted in Table 7. Mukherjee *et al*. reported 23% from Kolkata in 2017, Ramachandra and Kaur *et al*. reported 9.91% and 25.33% respectively in the year 2016 from Delhi by PCR based assay from Maharashtra in the same year (*21-23*). There are few other studies which suggest similar incidences. The vast difference in prevalence rates may be a result of cross reactivity or could be a result of varying rates of co-circulation of the viruses in specific geographical areas which depends on many host as well as environmental factors.

9. Scrub typhus

The onset of scrub typhus could be either insidious with headache, anorexia, and malaise, or abrupt with fever and chills. Some important clinical and laboratory findings consistent with scrub typhus include thrombocytopenia, normal or low leukocyte counts, mild to moderate elevations of hepatic aminotransferases. These features are seen as well in cases of dengue fever and hence pose

Table 8. Dengue and scrub typhus coinfection

S.N	Author	Title	Journal	Year	Place	Finding
1	Shelke YP, 2017 (*27*)	Spectrum of infections in acute febrile illness in central India	Indian J Med Microbiol	2017	India	47% prevalence of scrub typhus in acute undifferentiated febrile illness (AUFI) cases
2	Behera B, *et al*., 2019 (*28*)	Clinico-epidemiological analysis of scrub typhus in hospitalised patients pre-senting with acute undifferentiated febrile illness: A hospital-based study from Eastern India	Indian J Med Microbiol	2019	Odissa, India	26.3% scrub typhus prevalence among AUFI cases
3	Basheer A, *et al*., 2016 (*29*)	Clinical and Laboratory Characteristics of Dengue-Orientiatsutsugamushi co-Infection from a Tertiary Care Center in South India	Mediterr J He-matolInfec Dis	2016	India	6 cases of scrub-dengue coinfection from 2010 to 2014

a difficulty in differentiating dengue from scrub typhus. Rash is seen in almost half of the patients with scrub typhus, which is characteristically non-pruritic, macular or maculopapular rash. The rash typically begins on the abdomen and spreads to involve the extremities and the face. Petechial rash may rarely develop. The case-fatality rate in untreated classic cases is about 7-30%. Some patients may develop a localized necrotic skin lesion, the eschar, at the site of the bite of the infected chigger. The eschar may precede the onset of systemic symptoms, and may be found in multiple sites (*24-26*).

Treatment of scrub typhus includes a course of doxycycline or azithromycin for a period of 3-5 days. As dengue has no specific treatment, and scrub typhus responds dramatically to appropriate antibiotics, offering treatment for scrub typhus in suspected cases of co-infection timely can be of great value. Three studies from India are shown in Table 8. In a study from central India, the prevalence was found to be 47% among acute undifferentiated febrile illnesses and an additional cases were found positive by enzyme linked immunosorbent assay (ELISA) among those negative by an initial screening rapid diagnostic test kit (*27*). Another recent study from Odissa, India had reported 26.3% prevalence of scrub typhus among acute febrile illness cases (*28*). Clinical features like regional tender lymphadenopathy, eschars at hidden body parts (axilla, back *etc*.), early hepatic enzymes and creatinine elevation, near normal leukocyte counts, early drop in the platelet counts and hypoalbuminemia in a patient of dengue fever should create suspicion in the clinician and should order additional investigations including a sensitive test for scrub typhus, either IgM detection or PCR if available.

Timely detection and appropriate management of co-infection with O. tsutsugamushi with antibiotic has significant implications as it is likely to reduce the duration of hospital stay of the patient and the cost of therapy. In a study from South India by Basheer *et al*., six cases of dengue co-infected with scrub typhus was reported over a four years period from January 2010 to July 2014. In this study, they observed that co-infection in most cases was characterized by a lower nadir platelet count as compared to scrub typhus, and was associated with a lesser time to nadir platelet count and they had a longer duration of hospital stay as compared to those with either isolated dengue or scrub typhus (*29*).

10. Leptospirosis

There has been increased reports of dengue and leptospirosis coinfection from different parts of India especially the south Indian states and Maharashtra. Every year during rainfall and floods, these states witness a sharp spike in cases of these infections particularly because of stagnant water which acts as breeding ground for mosquitoes and increased rat population feeding on garbage brought to localities by flood water thereby transmitting leptospira in their urine. For the same reasons coinfections are also common during the same time. Clinical features of mild cases of dengue and leptospirosis can be similar. However, severe cases of these two infections have some striking differences which makes diagnosis easier. Dengue usually presents with fever, retro-orbital pain, headache and varying degrees of myalgia.

Myalgia is very pronounced in leptospirosis. Conjunctival haemorrhage and jaundice is very common in leptospirosis compared to dengue. Liver enzymes are moderately elevated, usually above 500 IU/mL whereas in dengue there is mild to moderate transaminitis. Lung and renal involvement is very common in severe cases of leptospirosis known as Weils's syndrome. Severe dengue usually presents with bleeding manifestations and plasma leakage compared to leptospirosis. Various studies across world are shown in Table 9. In a study published from Malaysia in 2018, myalgia, arthralgia, diarrhoea and jaundice were significantly associated with coinfection compared to mono infections (*30*). In a study published from south India in 2018 the prevalence of dengue and leptospirosis coinfection was found to be 3.4% (*31*). In another pilot study published from Malaysia, shock at presentation and male gender were significant predictors of coinfection in multiple logistic regression analysis (*32*).

Table 9. Dengue and leptospirosis coinfection

S.N	Author	Title	Journal	Year	Place	Outcome /Conclusion
1	Hishamshah M, *et al*., 2018 (*30*)	Demographic, clin-ical and laboratory features of lepto-spirosis and dengue co-infection in Malaysia.	J Med Microbiology	2018	Malaygia	Arthralgia, myalgia, diarrhoea, jaundice more in coinfection ($p < 0.05$)
2	Sachu A, *et al*., 2018 (*31*)	Prevalence of dengue and lepto-spirosis co-infection in a tertiary care hospi-tal in south India.	Iran J Microbiology	2018	India	Prevalence of dengue and leptospirosis coinfection was 3.4%
3	Suppiah J, *et al*., 2017 (*32*)	Clinical predictors of dengue fever co-infected with leptospirosis among patients admitted for dengue fever - a pilot study	J Biomed Sci	2017	Malaysia	Shock and male gender are significant predictors of coinfection ($p < 0.03$)

Table 10. Dengue and Zika co-infection

S.N	Author	Title	Journal	Year	Place	Outcome /Conclusion
1	Siqueira C, *et al*., 2020 (*33*)	Six cases of Zika/dengue coinfec-tion in a Brazilian cohort, 2015-2019	Viruses	2020	Brazil	Early rash, conjunctival hy-peremia, joint swelling and low grade fever favours Zika virus infection
2	Vogels CBF, *et al*., 2019 (*34*)	Arbovirus coinfection and co-transmission: A neglected public health concern?	PLoS Biology	2019	USA	Co-transmission in vectors is proportional to co-transmission in population which can con-tribute to huge number of co-infected cases compared to vectors with sequential trans-mission
3	Joob Bet *et al*., 2020 (*35*)	Clinical relevance of Zika symptoms in the context of a Zika Dengue epidemic	J Infect Public Health	2020	Cuba	Arthralgia, asthenia, diarrhoea favoured Zika virus infection during dengue zika epidemic (OR- 1.38, 1.33, 1.54 respectively)

Diagnosis of leptospirosis includes detection of IgM antibody by ELISA which is highly sensitive and specific and becomes positive as early as 2 days into illness. Management of dengue is symptomatic whereas leptospirosis needs immediate administration of either penicillin of ceftriaxone or doxycycline in order to prevent complications.

11. Zika virus

Zika virus causes a self-limiting illness in most cases which is indistinguishable from mild cases of dengue. Coinfection in the population has public health implications. The implications are especially grave in pregnancy because of its potential to cause severe congenital malformations. Table 10 shows studies on dengue-Zika coinfection. In a report of six cases from Brazil in 2020, low grade fever, early rash within first day of illness, conjunctival hyperaemia and joint swelling favoured Zika virus disease (*33*).

Vogels *et al*. reported that co-transmission of both viruses among vector population is directly proportional to transmission among human population (*34*). In a study from Cuba, arthralgia of small joints, asthenia and diarrhoea favoured a diagnosis of Zika virus disease during co-circulation of both the arboviral diseases (*35*). As far as management is concerned, there is no specific antiviral for both the disease. Coinfection if presents with severe dengue predominant features, the management would be similar to severe dengue.

12. Coronavirus disease-19 (COVID-19)

The course of illness in dengue and COVID-19 coinfection is similar to mono-infected patients. Of concern, is the management consideration especially because treatment of one infection adversely affects the outcome of the other. We have our first Indian national guideline on the management of COVID-19 with seasonal infections (*36*). Steroid is the cornerstone of therapy in moderate and severe COVID-19 cases whereas there is no concrete evidence for use in dengue infected patients and might also lead to severe disease. Anticoagulation is widely used to prevent complications related to microvascular thrombosis in COVID-19. But anticoagulation in dengue can be life threatening especially in settings of thrombocytopenia.

So in areas where both the diseases are co-circulating, clinical discretion is of paramount importance. Hydration in initial phase of both the illness is of paramount importance and with proven distinct benefit except for fluid restriction indicated because of some existing co-

morbidity. While COVID-19 requires good amount of fluid through the illness, same is not true for severe dengue management in second half of illness because of reabsorption of fluid leaked into interstitium. Nevertheless, data on this coinfection is still evolving.

13. Conclusion

The incidence of dengue has risen dramatically in recent times with about half of the world population at risk of this infection. The vaccines available have variable efficacy and are not in widespread use in tropical countries. Although the percentage of case fatality in severe dengue is low, the absolute numbers would still be very high especially in countries like India. The severity of dengue infection rises proportionately in presence of coinfections which are co-circulated during dengue season. The management of dengue is mainly conservative with intravenous fluids and platelet transfusion but the coinfections prevalent in tropical and subtropical climates are treatable which has direct implications on positive outcome especially if recognised early with prompt initiation of specific therapy. This review provides a comprehensive knowledge on management of dengue fever with coinfections.

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