



Opinions

Yellow Fever

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Yellow Fever represents a major arbovirolosis, endemic in about 40 countries in sub-Saharan Africa and South America.[1] Although the disease is mild in some cases, the clinical presentation often shows an acute picture with fever, nausea, vomiting, severe hepatitis, bleeding, and renal failure. The case fatality rate in these cases ranges from 20–60%, depending on the intensive care received by the patients. There are no antiviral drugs approved to treat this virus so far, and prevention through vaccination is the only weapon currently available to prevent outbreaks.[2] Several epidemiological factors are involved in this unexpected and rapid viral spread in our country over the last three years, increasing the chance of disease reurbanization in the country, with no confirmed urban cases since 1942. In about 18 months (2017–2018), 1833 laboratory confirmed cases with 578 deaths were reported in the Southeast region, where several epizootic diseases in nonhuman primates also occurred with near 100% lethality in these animals.[1,2,4,6] The virus circulated through Atlantic rain forest fragments near peri-urban areas of the country's largest metropolises, such as Rio de Janeiro, São Paulo and Belo Horizonte, leading to an exponential increase in the number of cases diagnosed in these Brazilian capitals. The most feasible hypothesis to explain the burst of cases in this region is human behavior combined with ecological changes that have led to a significant increase in the density of mosquitoes and nonhuman primates and their consequent close contact with people.[4–6] The negligence of early detection of wild epizootic diseases and the delayed response by public authorities to initiate immunization of the highly susceptible local population, especially in rural areas, resulted in an increased incidence of this viral infection in recent years. On the other hand, the considerable increase of yellow fever cases allowed a very wide knowledge of the various aspects of this disease previously unnoticed, but this time in the light of the previously nonexistent technological means and we have been able to advance a lot in this period to analyze its pathophysiology, immunological aspects, anatomopathology, diagnosis, clinical management, and testing potential antiviral drugs capable of shortening or aborting the progression of severe disease. A key aspect from this experi-

ence was that yellow fever is not an exclusive liver disease, but a systemic infection that affects multiple body organs or systems with huge difficulties to manage during its acute phase.[3]

The similarity between the genomes of the yellow fever virus and the hepatitis C virus, both of the family *Flaviviridae*, has brought light the possibility that recent approved drugs for the treatment of hepatitis C (the new DAAs, direct action drugs) could be used for the treatment of yellow fever infection. A previous example of this approach is the treatment of chronic hepatitis B with antiretrovirals initially used to treat HIV infection, since both viruses have the presence of reverse transcriptase, target of action of these drugs (nucleoside and nucleotide analogs).[7,8]

No drug to date, as already mentioned, has been approved for the treatment of yellow fever, including ribavirin, which shows *in vitro* action against the virus but lacks clinical studies that prove their effectiveness in humans. In this volume of the *Annals of Hepatology*, Araújo Mendes *et al.*, in an elegant study, tested the *in vitro* sensitivity of the amarilic virus to 3 drugs used to treat hepatitis C, sofosbuvir, ledipasvir and daclatasvir, observing good viral inhibition with sofosbuvir and daclatasvir, with no synergistic effect between them. They have shown efficacy in humans by compassionately treating 2 severe cases of the disease with sofosbuvir at the standard dose of 400 mg orally for 7 days and a progressive decrease in serum viral load has been observed during treatment with reflections on the clinical picture, leading to the progressive improvement of clinical and laboratory parameters and discharge after a few days of hospitalization. The decrease in viral load in both patients was about 3 log in 7 days, a little less when compared to the decrease in viral load in chronic hepatitis C patients treated with these drugs.[7,8]

This study undoubtedly represents a breakthrough in the medical treatment of yellow fever and for the first time demonstrates the activity of a drug on this old pathogen, which has decimated entire populations in the past. Progressively decreasing viral load throughout treatment may increase the chances of greater success in liver transplantation in severe cases, reducing postoperative complications (pancreatic, respiratory), still dependent on viral activity. Of course, larger studies with more cases are needed, as the authors suggest, before we can put sofosbuvir or another similar drug into the therapeutic arsenal for first-line use in yellow fever.

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Furthermore, this experiment opens a future perspective for the use of these medications in other arboviruses prevalent in our country, such as dengue and Zika, both viruses of the family *Flaviviridae*, which continue to cause epidemics in various regions of the country.

While we await new results from larger studies, our only weapon against yellow fever is prevention. The 17DD vaccine is highly immunogenic, safe and has been used for over 80 years. It is a powerful weapon to prevent future epidemics in the coming years and to reduce the possibility of reurbanization of the disease, since our urban centers are almost infested with *Aedes aegypti*, a vector of urban yellow fever.[9]

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