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EDITORIAL

What every Hepatologist should Know about Swine Flu?

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As world is witnessing ever fastest growing pandemic, physicians with various specialties should adopt themselves to the new situation [1]. Global death toll of swine flu by November 15, 2009, has raised to 6750. Many of those who died or were hospitalized suffered from comorbid conditions which increased either the severity or the risk of acquiring the disease [2]. Swine flu may change the course of many chronic diseases. Thus, all physicians in different disciplines should realize and consider the impact of the current pandemic on their daily practice.

As the new pandemic flu virus 2009 (H1N1) has been circulating only in the past nine months, there is still not much evidence on the interaction of this pandemic with chronic diseases. However, presumably, much of this interaction is expected to be similar to other circulating influenza type A viruses. But there are clear differences with the current pandemic , for example, near one-third of severe cases had no underlying conditions and their median age was much lower than the usual seasonal flu [3].

Hepatologists caring for both acute and chronic liver diseases anywhere in the world would probably see much about this interaction in upcoming months and even years. In this review, we tried to somehow classify our current knowledge on possible interactions between swine flu and various liver diseases. Much of the described effects are from the older evidence mostly related to influenza type A, and as was mentioned before, with expansion of the current pandemic and growing our knowledge about the nature of this new virus, these suggestions might be changed later on.

Liver damage by flu virus

Liver damage with influenza virus has been shown in animal models. Indeed, the mouse/influenza B virus is a well-established model for Reye's syndrome with a histological picture resembling human disease including microvesicular steatosis and minimal inflammation [4]. The primary infected cells in these animals are hepatocytes with minimal infection of the Kuppfer cells [5]. The liver parenchyma infection in mouse model is abortive or non-permissive characterized by the absence of viral replication in the liver and brain and absence of complete viral particles on electron microscopy, despite the presence of viral antigens within the hepatocytes and minimal inflammation in biopsied specimens [6].

At least, in animal models the liver damage could be seen even in the absence of virus isolation from the liver. Circulating cytokines and chemokines may contribute to liver damage. Derangement of lipid metabolism secondary to depressed mitochondrial enzyme activities and mitochondrial structural damage is probably a critical step in hepatic damage in flu infection [7]. Polakos *et al.* have recently reported the so called collateral damage of liver with influenza virus. They found that in the absence of viral antigen in the liver, hepatocytes could be damaged by viral specific $CD8^+$ T cells generated outside of liver for example in the lungs. In their series of 15 volunteers infected with H1N1 influenza virus, four patients developed liver enzyme elevation up to three times the upper limit of normal. Interestingly, this enzyme raise occurred when the fever was stopped indicating that the process is not related to direct viral replication [8].

Till 1980's, the most common hepatic manifestation of flu in children was considered to be Reye's syndrome [9]. Realizing the association of this dreadful complication of influenza-like illness (ILI) and aspirin ingestion, lead to a sharp decline in the incidence of this syndrome [10]. The importance of this association in the current pandemic, however, could not be overemphasized. Pediatric patients on chronic aspirin treatment such as those with rheumatologic diseases are at increased risk of this syndrome during the pandemic [11]. These patients probably need to be prioritized for flu vaccination and should discontinue their aspirin intake upon development of ILI.

In rare instances, flu virus may cause acute hepatic failure. The probability of causing such a complication may differ between subtypes of influenza virus [12]. Nevertheless, so far we do not have any data on the incidence of this complication with the new pandemic H1N1 virus. Reported death with the new virus was not accompanied with liver failure, so probably this complication is not common with this new virus.

Interaction of flu and chronic liver disease

Flu may increase the risk of decompensation in cirrhotic patients [13]. This could be attributed to direct hepatic damage by the flu virus or due to cytokines/chemokines-induced damage during systemic infection [14]. Risk of both acquiring the disease and developing severe form of the disease may be increased in these patients. In the meantime, concomitant pleural effusion, decreased lung compliance, hepatopulmonary syndrome and portopulmnary hypertension may also contribute to make the disease more severe [15].

This disease may have a higher mortality rate in immunosuppressed patients. Example of such patients are those with chronic liver disease, especially those suffering from autoimmune liver disease and liver transplant recipients who use immunosuppressive drugs.

Corticosteroids in doses higher than 10 mg per day or a cumulative dose of more than 700 mg predisposes the patient to a variety of infections including influenza [16]. Systemic corticosteroids may also increase the risk of hospitalization and death among patients with flu [17]. Corticosteroids in hepatology clinics are used usually in combination with immunosuppressants which may potentiate its detrimental effects on flu infection. Disease flare up has not been reported in rheumatologic patients receiving steroids, after acquiring flu. However, data on patients with liver disease taking steroids is not clear.

It is not known whether the risk of infection among patients receiving immunosuppressive drugs is higher but infection in these patients usually has a longer duration with more virus shedding and more chance of antiviral resistance [17].

In pediatric patients receiving solid organ transplantation including liver, the influenza virus infection is more severe, has higher hospitalization rate, has more need for mechanical ventilation and more chance of death [18]. Apalsch *et al.* reported that the risk factors for death among pediatric solid transplant recipients with flu are younger age of recipient (<6 month), early post-transplant period (<1 month) and increased dose of immunosuppressive agents [19].

The disease course in adults is more variable. A report from Sweden indicated that the course of influenza A in renal and bone marrow transplant recipients was usually mild and self-limited, although occasional severe cases also occurred [20]. This variability may be related to the amount of immunosuppresion and the time from transplantation.

Infection, itself, provokes rejection in kidney transplant patients but this observation has not been proven for liver transplantation [21]. Most of these reports came from the time when cyclosporine and other potent immunosuppressives were not available. Presence of such association has not been proved with the current immunosuppressive armamentarium.

Obesity and diabetes mellitus are two of the most common risk factors for fatality in the new pandemic flu in those aged 20 years and older [22]. In a recent series from California, USA, the rate of obesity was 50% in hospitalized patients with the new H1N1 pandemic influenza (2009); a quarter of which being morbid obese. In one-third of hospitalized patients, obesity was the only risk factor [23]. The association of obesity with non-alcoholic steatohepatitis (NASH) nowadays, has brought many of obese patients under follow-up of hepatologists. The higher complication rate of the new pandemic flu should alert hepatologists when taking care for these patients and any signs of ILI should be taken seriously and appropriate referral should be done in a timely manner.

Treatment of swine flu in patients with chronic liver disease

Available treatments for swine flu include neuraminidase inhibitors (*e.g.*, oseltamivir and zanamivir). Whether these drugs need dose adjustment in patients with hepatic failure is not

known. There are case reports of prolonged virus shedding and development of viral resistance in immunocompromised hosts receiving these antiviral agents [24].

Flu vaccine in chronic liver disease patients

There is concern about the effectiveness of vaccines in immunosuppressed patients. A diminished antibody response has been reported in liver transplant recipients after receiving influenza vaccine [25]. This lower antibody response depends on the type of immunosuppressant drug with much lower antibody response in those receiving mycophenolate mofetil or cyclosporine compared to drugs such as azathioprine. The lowest response has been reported with mycophenolate mofetil [26]. The current data did not show any difference between tacrolimus and either of cyclosporine or sirulimus. Previous recommendation advised yearly seasonal flu vaccination for all of solid organ transplant recipients six months after transplantation [27]. This recommendation was based on this assumption that in most cases of solid organ transplantation, by this time, the dose of immunosuppressive drugs has been reduced and stabilized so that there would probably be a higher antibody response. There is a theoretical concern that vaccination in these patients may evoke a T cell response leading to rejection [28]. The association of flu shot and rejection has not been shown in liver transplantation but there are contradictory reports on subclinical rejection in heart transplant patients receiving flu vaccine [29]. Based on these assumptions, delaying vaccination for six months was proposed in past. Currently, this recommendation may need some modifications, but there are no solid evidence indicating the exact timing of vaccination in this special group of patients. In post-liver transplantation patients, only 68% of flu vaccine recipients developed protective levels of antibody with a single shot of the vaccine. A second dose, inoculated one month later, increased the rate of antibody response to 80% [30]. Therefore, it is quite reasonable to schedule these patients to receive two shots from the beginning.

Vaccination of patients in waiting list for liver transplantation and probably all patients with chronic liver disease, especially those who are on immunosuppressive drugs or with cirrhosis, should also be prioritized.

As infection could spread from medical staff caring for these patients to them, even from asymptomatic or minimally symptomatic personnel, vaccination of these staff should also be done.

Antibody response to flu vaccine may be lower in patients on chronic steroid therapy depending on the dose, duration of the treatment, the underlying disease and use of immunosuppressant drugs [31].

No harmful event has been reported with use of live attenuated flu vaccine in patients on immunosuppressive and or corticosteroid therapy. Nonetheless, current data do not support the use of live attenuated vaccine, especially in transplant patients and those on immunosuppressive drugs; it is safer to use inactivated viral vaccines in these particular group of patients [32].

Data on the safety and efficacy of live attenuated flu vaccine in cirrhotic patients is not conclusive but the effect is probably not much different from healthy individuals, as long as the patient is not on immunosuppressive drugs or malnourished.

Antibody response in these patients depends on other factors including age, with least response in those less than one month old or older than 65 years [33].

Conclusions

As the current pandemic of new H1N1 virus is progressing, hepatologists should realize and consider the potential effects of this infection on patients with chronic liver disease. These patients, especially those on immunosuppressive agents and transplantation recipients should be prioritized for vaccination, preferably with an inactivated vaccine. The course of flu in these patients may be more severe. Obese patients with NASH should receive particular attention in this regard. Deterioration of hepatic function in patients with stable liver disease might be caused by flu. These patients may benefit from early diagnosis and treatment.

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