EMJ HEPATOLOGY

European Edition — Vol. 8.1 June 2020 emjreviews.com

+ TARGETING RAISED VON WILLEBRAND FACTOR LEVELS IN LIVER DISEASES: OPENING UP NEWER THERAPEUTIC AVENUES

+ INTERVIEWS

Prof Markus Peck-Radosavljevic and Prof Ashwani Singal speak about the impact COVID-19 is having on their clinical practice and patients.

+ ARTICLES

Topics include cholangioscopy, liver disorders in inflammatory bowel disease, and more

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"We hope that our continuous offering of quality content, including EMJ Hepatology 8.1, will serve as a home for trailblazing research and stimulate ground-breaking studies in the future"

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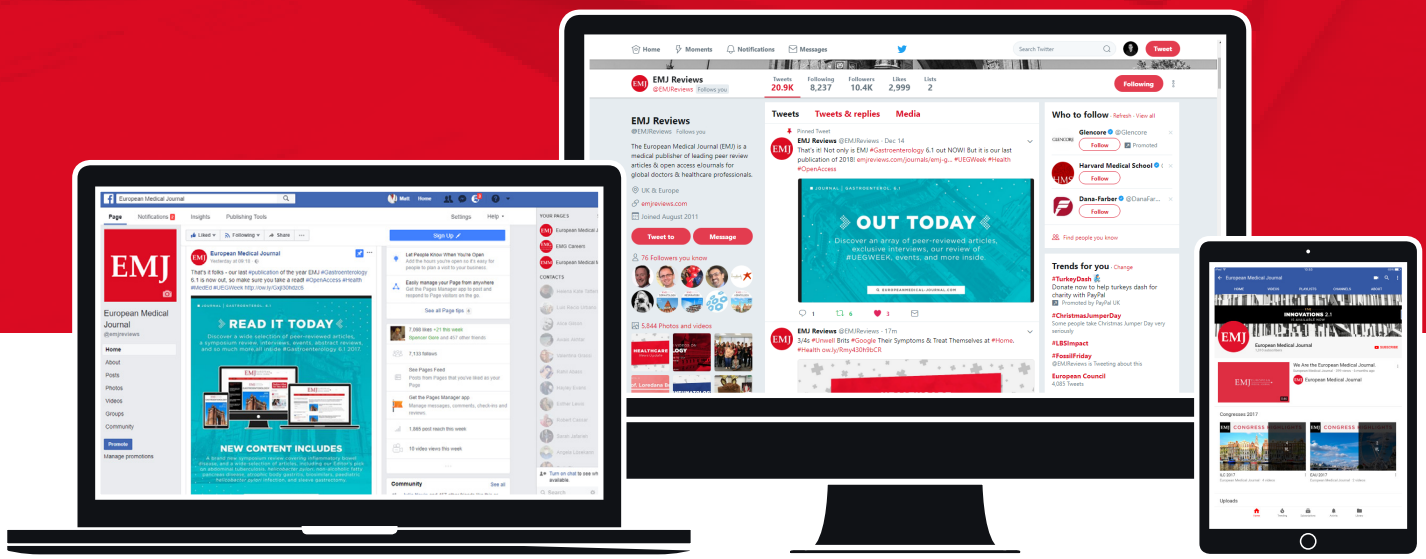

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This Publication

EMJ Hepatology is published once a year. For subscription details please visit: www.emjreviews.com

ISSN 2053-4221

Front cover and contents photograph: London, United Kingdom © Preve Beatrice / 123rf.com

EMJ Hepatol. 8.1

Welcome

Respected readers and friends,

I am delighted to welcome you once again to a new edition of *EMJ Hepatology*, a collection of the finest up-to-date articles of hepatic disorders. With all that is happening around us, dissemination of scientific endeavours could not be more crucial. At EMJ, our ambition is to become the go to place for healthcare professionals and therefore we are working hard to cater to your needs and ensure that access to research continues to be available now more than ever. We hope that our continuous offering of quality content, including *EMJ Hepatology 8.1*, will serve as a home for trailblazing research and stimulate ground-breaking studies in the future.

With all that is happening around us, dissemination of scientific endeavours could not be more crucial.

Ordinarily, the journal would feature our independent review of the International Liver Congress (ILC) which was due to be held in April but has now been postponed to late August 2020. Yet, we are tremendously pleased to inform you that we will be releasing the congress review later in the year as a supplement to this journal.

Make sure to give our interviews with Prof Markus Peck-Radosavljevic and Prof Ashwani Singal a read. Both present insightful information about the impact of COVID-19 on clinical practice and the risk it may pose to patients with hepatic disorders. Within these pages you will also find a fantastic collection of quality papers spanning from cholangioscopy and its role in primary sclerosing cholangitis to liver disorders in inflammatory bowel disease, which are sure to keep you engaged.

On behalf of EMG-Health, I would like to acknowledge all collaborators and contributors of this edition and extend a special thank you to our valued readers for your continued support. We hope that you enjoy the pages ahead and we look forward to connecting with you at Digital ILC 2020.

Spencer Gore

Chief Executive Officer, EMG-Health

Foreword

Dear Colleagues,

Usually at this time of the year, *EMJ Hepatology* would be reporting on the latest news from the International Liver Congress (ILC), EASL's flagship annual meeting, which was due to happen in London, UK, at the beginning of June. For reasons of the SARS-CoV-2 pandemic, ILC has been postponed to August.

Nevertheless, I am happy to present interesting topics in *EMJ Hepatology 8.1* that go beyond the omnipresent topics of non-alcoholic fatty liver disease and liver cancer. Remarkable progress has been made in our understanding and management of primary sclerosing cholangitis. One of the most feared complications is the premature development of cholangiocarcinoma, which is notoriously hard to detect early. Cholangioscopy has become a much more widely used technique, complementing radiologic imaging and endoscopic retrograde cholangiopancreatography in the differential diagnosis of strictures in primary sclerosing cholangitis. The importance of elevated von Willebrand factor (vWF) levels in advanced stage cirrhosis has been pioneered by my own group in Vienna and we could show it serves as a non-invasive marker of portal hypertension as well as a prognostic factor. Over time, it has become clear that vWF is one of the relevant haemostatic factors in portal hypertension and acute-on-chronic liver failure and can also be linked to disease progression and complications. An interesting review looks into the therapeutic potential of lowering vWF. Also, infection and TIPS remain an unholy alliance: hepatologists should be aware of the potential negative impact of prior infection on the further course including hepatic encephalopathy in patients undergoing TIPS-implantation.

An epidemiologic study into the prevalence of hepatitis B virus infection in the United Arab Emirates (UAE) completes the compilation of topics. Here, more work needs to be done: despite the low-to-moderate prevalence of hepatitis B virus infection and effective vaccination programmes in place, the epidemiology usually only covers the native UAE-population and not the thousands of migrant workers from poorer countries nearby, which have a much higher rate of infection and are not accounted for.

I hope you will be interested in the topics presented.

Kind regards,

Professor Markus Peck-Radosavljevic
Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

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Editorial Board Interviews

We spoke to the respected hepatologists Prof Markus Peck-Radosavljevic and Prof Ashwani Singal to find out about their clinical interests and the risk COVID-19 may pose to those with hepatic disorders.

Prof Markus Peck-Radosavljevic

Professor of Medicine and Chairman at the Department of Gastroenterology and Hepatology, Endocrinology, and Nephrology, Klinikum Klagenfurt, Klagenfurt, Austria

Q1 Following your medical training in Austria, Canada, and the USA, what have you learnt about adapting to novel working and training environments?

Each of these working environments have their strengths and weaknesses and each of them seem to make sense in the context of the respective medical system they are placed in. Legal and administrative principles differ between countries and organisational aspects, even between institutions, but the patients and their diseases remain very much the same. In my experience, the working environment is usually very helpful when you start a new appointment, which helps a lot in adapting to the different working environments. As long as you are willing to adapt to new circumstances, transitioning is usually rather smooth.

Q2 What motivated you to largely centre your research on liver disease and portal hypertension?

Within the gastrointestinal department in Vienna, Austria, I was looking for areas with an unmet clinical need as well as areas that were not already occupied by other researchers in my department. In liver disease in the early 1990s, there was a large unmet clinical need, and portal hypertension stood out as such an area with both a clinical need and good opportunities for research projects.

Q3 Can you provide a brief summary of the findings highlighted in your most recent paper: 'Impact of *HSD17B13 rs72613567* genotype on hepatic decompensation and mortality in patients with portal hypertension?'

"Legal and administrative principles differ between countries and organisational aspects, even between institutions, but the patients and their diseases remain very much the same"

We investigated the cohort of patients with portal hypertension from the Vienna Portal Hypertension Study group with regard to the recently published *HSD17B13* gene variant that had been shown to be protective for fibrosis progression in patients with alcoholic liver disease/nonalcoholic steatohepatitis. Despite the fact that we could find some circumstantial evidence for a potentially protective role in alcoholic liver disease/nonalcoholic steatohepatitis patients, for example, patients with at least one protective allele had a lower model for end-stage liver disease (MELD) score, trend towards less portal pressure gradient, and were older at presentation, we could not find a protective role for the gene variant in the overall cohort. This could have been because of a less favourable effect of the polymorphism on decompensation and mortality in the subgroup with hepatitis C virus (HCV)-associated advanced chronic liver disease.

Q4

Could you tell us about the current status of clinical trials in HCV infection in patients undergoing haemodialysis and with HIV–HCV coinfection?

The question about how to treat HCV is mostly solved with regard to the highly effective drugs we have today. This is also true for indications like patients on haemodialysis and with HIV–HCV coinfection. Since coinfection is at least partly linked to intravenous drug use, most research in this area is dedicated to getting treatment to all individuals in need and optimising care delivery in order to eradicate HCV infection.

Q5

Will your ongoing work trialling antivirals in HCV infection be put on pause as clinicians are dedicating their time to the COVID-19 pandemic?

I think this is highly dependent on the individual clinical setting and how the area is affected by COVID-19 cases. Here in Austria, because of the early lockdown and the measures taken, we are not overwhelmed with treating COVID-19 patients and can manage our HCV and liver disease patients as they need it.

Q6

It has been proposed that COVID-19 causes direct liver injury via viral hepatitis, what are your thoughts on this hypothesis?

Many viral infections can cause a hepatitis-like picture and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be able to do that as well. But we have not seen any serious liver damage caused by SARS-CoV-2 ourselves nor in the literature and I think the liver is not the reason why the world is in lockdown right now. COVID-19 could well be a threat to patients with advanced-stage liver disease, in particular decompensated patients, for whom any acute infection can be life-threatening.

Q7

The literature also suggests that patients with long-term liver transplant and metabolic comorbidities may be more at risk of hospitalisation with COVID-19. How can these patients be protected effectively?

These patients can be protected the same way as everybody else is protected: through focussing on measures of hygiene and social distancing. Since these patients might have more hospital visits, one way of protecting them is switching to remote online consultations and reducing the number of in-person visits to the absolute minimum.

Prof Ashwani Singal

Associate Professor of Medicine, University of South Dakota Sanford School of Medicine, Vermillion, South Dakota, USA, and Transplant Hepatologist and Chief of Clinical Research Affairs, Avera University Hospital and Transplant Institute, Sioux Falls, South Dakota, USA

Q1 Your various specialities include alcoholic and nonalcoholic liver diseases, acute kidney injury in cirrhosis, and simultaneous liver–kidney transplantation. What ignited your interest in hepatology and motivated you to acuire skills in these areas?

An algorithmic approach, evidence-based decisions, and the cognitive aspects of hepatology attracted me to establish a career in this discipline. Further, the ability to change the lives of people with liver disease using liver transplantation stimulated me further to obtain specialty training in transplant hepatology from the Mayo Clinic in Minnesota, USA. To be specific, the lack of specific therapies, magnitude of disease burden, yet the ability to prevent progression to the advanced spectrum with control of risk factors developed my interest in alcohol and nonalcohol-related fatty liver diseases. Prevalence of renal dysfunction in cirrhosis and an unmet clinical need for biomarkers and models for allocation of simultaneous liver–kidney transplantation provide opportunities to contribute to this rapidly evolving field of acute kidney injury in patients with cirrhosis.

Q2 Regarding your specific interest in hepatic porphyria, could you tell us more about this group of disorders and why you believe they merit wider attention?

Porphyria is a group of metabolic disorders with eight different porphyrias, each due to a specific enzymatic defect in the haem synthesis pathway, with characteristic biochemical and clinical phenotypes. Understanding the pathophysiological basis provides the basis for specific treatment of each individual porphyria. The rarity of the condition and lack of awareness result in delay in diagnosis, rationalising the need for wider attention to these disorders by healthcare providers.

Q3 Could you enlighten us on the overall mission of the Avera Transplant Institute of which you are the Chief of Clinical Research Affairs?

Compassion, hospitality, and stewardship are three pillars of providing excellent patient care at Avera and make a difference in the lives of people. Avera is known for its excellent patient care through experienced nurses, advanced practice providers, physician hospitalists, and specialists, and I am proud to be a part of it. With a need and ambition of the health ministry at Avera for establishing footprints in research, I was recruited to the Avera Transplant Institute and division of transplant hepatology as Chief of Clinical Research to establish research, apart from furthering care to patients with liver disease in pre, peri, and posttransplant settings.

Q4 In 2018, you published clinical guidelines on alcoholic liver disease. Could you summarise the key take-home messages of these recommendations?

The clinical guidelines on alcohol-associated liver disease (ALD) for the American College of Gastroenterology (ACG) provide evidence based guidance to practising physicians on diagnosis, medical treatment, and liver transplantation aspect of ALD. The main take-home messages from this document are: i) several host and environmental factors predispose an individual with daily harmful alcohol use (>3 drinks/day in males or >2 drinks/day in females) to develop advanced spectrum of fibrosis, cirrhosis, and alcoholic hepatitis (AH); ii) abstinence and treatment of alcohol use disorder is the most effective strategy to treat patients with ALD and AH; iii) corticosteroids are the only available and first-line therapy for patients with severe AH and pentoxifylline is not effective; and iv) liver transplantation should be considered for select patients with severe AH

who are either unresponsive to or ineligible for corticosteroid therapy.

Q5

What drove you to take on the position of Chair of the Alcohol-Associated Liver Disease special interest group of the American Association for the Study of Liver Diseases (AASLD), and what do you hope to achieve during your term?

Considering the increasing disease burden, especially in the young population 20–39 years of age, lack of effective therapies, frequent presentation with advanced spectrum disorders, and scarce use of an integrated approach with addiction specialists in management drove me to contribute to the field of ALD like many others. Taking up the role of Chair of the Alcohol-Associated Liver Disease special interest group of the AASLD provides me with better access and opportunities to contribute my bit and add a drop to the ocean of ongoing efforts, knowledge, and awareness, all of which are very important toward the ultimate goal of global outreach and controlling this preventable liver disease.

Q6

In light of the recent COVID-19 pandemic, do you believe the virus poses a threat to patients with hepatic diseases, and if so, what measures would you recommend they take to remain safe?

Cirrhosis, risk factors like alcohol use and diabetes, and use of immunosuppressive medications for transplant recipients and autoimmune disease make these patients susceptible to acquiring, or developing complications of COVID-19. Besides, measures like social distancing, wearing masks, frequent hand washing, it is prudent to avoid in person patient visits to clinics, and limit liver transplantation to urgent cases. Further, keeping a low threshold to test for COVID-19 for transplant donors and recipients, and widespread effective use of personal protective equipment for healthcare personnel are critical to protect patients.

Q7

How has COVID-19 directly or indirectly impacted your daily clinical practice, and what actions have been taken to adapt to the current situation?

The COVID-19 pandemic has significantly impacted my daily practice, like several other providers and centres. The spectrum of impact includes, but is not limited to, thinning the volume of patients in clinics and hospitals, obtaining training outside my usual expertise as a basis for preparing for the surge, and providing care to potential COVID-19 patients. Actions taken include social distancing; use of virtual platforms for patient care, education, meetings, and community service; diligent use of personal protective equipment during direct patient encounters for urgent patients; and avoiding domestic and international travel. These are critical to adopt for the current situation and to reduce the impact.

"Compassion, hospitality, and stewardship are three pillars of providing excellent patient care at Avera and make a difference in the lives of people"

Targeting Raised von Willebrand Factor Levels in Liver Diseases: Opening Up Newer Therapeutic Avenues

EDITOR'S PICK

Goel and colleagues give an interesting overview of what could potentially develop into a way of treating advanced-stage cirrhotics: targeting the coagulation cascade in cirrhosis, which arguably plays an essential part in disease progression through thrombotic obliteration of the liver sinusioids as well as its impact on the bloodflow. Over time, it has become clear that von Willebrand factor is one of the relevant haemostatic factors in portal hypertension and ACLF and can also be pathophysiologically linked to disease progression and complications in cirrhosis, which makes it a likely target for future therapeutic intervention. This interesting review explores the therapeutic potential of lowering von Willebrand factor.

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Disclosure: The authors have declared no conflicts of interest.

Received: 25.11.19

Accepted: 19.12.19

Keywords: Liver failure, therapeutic plasma exchange, von Willebrand factor (VWF) reduction.

Citation: EMJ Hepatol. 2020;DOI/10.33590/hepatol/20-00051

Abstract

Raised levels of the blood coagulation protein von Willebrand factor (VWF) are now recognised to be important in patients with liver disease. The markedly raised plasma VWF levels in patients with acute liver failure and acute-on-chronic liver failure may contribute to the pathogenesis of liver failure, and of multi-organ failure, by impeding microcirculatory perfusion in the liver and the other affected vital organs. In this review, the authors present a brief introduction to VWF biology, discuss the ability of raised plasma VWF levels to accurately predict survival in different syndromes of liver diseases, speculate why plasma VWF levels are raised in liver failure syndromes, and examine the therapeutic potential of VWF-lowering therapies in these scenarios.

INTRODUCTION

The most commonly inherited bleeding disorder, von Willebrand disease, is caused by the deficiency of von Willebrand factor (VWF). In contrast to von Willebrand disease, the opposite scenario of raised VWF levels in circulation is attracting increasing attention in patients with liver diseases. The VWF protein has binding sites for platelets as well as factor VIII and collagen, thus it has important roles in both primary and secondary haemostasis.

While VWF deficiency is associated with bleeding tendency, raised VWF levels are a minor risk factor for thrombotic events such as cerebrovascular accidents and coronary artery disease.[1,2] Recent reports have documented mild increases of plasma VWF levels in patients with cirrhosis, as well as a marked increase of plasma VWF levels in patients with acute and acute-on-chronic liver failure (ACLF). The raised plasma VWF levels are relatively accurate in predicting survival in patients with liver disease (cirrhosis, ACLF, and in acute liver injury and failure).

AN INTRODUCTION TO VON WILLEBRAND FACTOR BIOLOGY FOR THE HEPATOLOGIST/ GASTROENTEROLOGIST

von Willebrand Factor Synthesis, Storage, and Secretion

VWF is a large, adhesive glycoprotein synthesised by endothelial cells and megakaryocytes. The VWF protein is stored in Weibel–Palade bodies in endothelial cells and in α-granules of platelets. Secretagogues, such as vascular endothelial growth factor (VEGF), histamine, thrombin, oestrogen, and desmopressin, and inhibitors, such as nitric oxide and dopamine, influence VWF secretion via endothelial cells and platelets.[3]

The different forms, or multimers, of VWF exist as low, intermediate, high, and ultra-large-molecular-weight forms. In endothelial cells and platelets, VWF is stored as ultra-large multimers. As the secreted VWF rapidly undergoes proteolysis, the size of ultra-large VWF multimers is reduced; therefore, typically the ultra-large multimers of VWF are not found in plasma. Constitutively secreted forms of VWF are shorter and are usually high-molecular-weight forms. Circulating plasma has high (large), intermediate, and low sized VWF multimers. The size of VWF multimers determines its haemostatic function. Of the different sized VWF multimers in circulation, the high-molecular-weight fraction has the most potent haemostatic function.[4]

Some of the endothelial cell-derived VWF multimers remain bound onto the endothelial cell surface. The globular form of VWF is stretched out under the high shear stress of normal blood flow (such as in arterioles) to a string-like form. In these stretched-out, string-like forms of VWF, the site for cleavage of VWF by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin Type 1 motif, member 13) is exposed.

Three types of VWF are recognised in the human body: soluble plasma VWF, basement membrane VWF (i.e., extracellular matrix VWF), and cellular VWF. VWF is the largest known protein in human plasma. The high-molecular-weight-forms of VWF have molecular weights of up to 10,000 kDa.[4]

von Willebrand Factor Function

VWF is an important blood coagulation protein. The three main haemostatic functions of VWF are to mediate platelet–platelet interactions, platelet–subendothelial collagen interactions in the vessel wall, and to be a carrier of factor VIII in circulating blood. Recently, nonhaemostatic functions of VWF have also been proposed, such as roles in angiogenesis, smooth muscle cell proliferation, tumour cell metastasis, and immune cell regulation.[3]

VWF protein has separate sites, or domains, for binding to platelets and collagen. Collagen located in the subendothelial space is exposed when a vessel wall is injured. VWF binds to collagen, thus exposed. VWF, bound to the collagen, localises factor VIII (VWF functions as a factor VIII carrier). The platelet-binding domain of the VWF protein is exposed when VWF is unfolded and stretched out by the shear

stress of arterial circulation. Thus, platelets are recruited to the site of vascular injury.

As described above, the VWF molecule has a vital role both in primary haemostasis (platelet plug formation), as well as in secondary haemostasis (in the coagulation cascade). The binding activity of VWF to collagen is used to assay VWF activity; this is called VWF collagen binding activity. The binding activity of VWF to platelets can also be used to assay VWF activity, as measured by the ristocetin cofactor activity assay.

HOW TO ASSAY VON WILLEBRAND FACTOR LEVELS IN PLASMA

The assays for VWF have been mostly developed and tested with the aim of diagnosing VWF deficiency (i.e., to diagnose and to accurately subtype von Willebrand disease).[5]

Plasma samples for assays of VWF require several specific precautions to be undertaken during sample collection and processing. A clean venepuncture is advised, with minimal venous stasis, and a 19–21-gauge needle. The VWF assays are performed on platelet-poor plasma; for example, the blood sample is collected using 0.109 M citrate anticoagulant and centrifuged at 2,500 g for 15 mins, and separated plasma is used for VWF assays. In patients with liver disease, it is important to obtain a baseline blood sample for VWF assays prior to administration of any VWF-lowering treatments, such as N-acetylcysteine, fresh frozen plasma, or therapeutic plasma exchange.

VWF antigen is measured using an ELISA kit. Activity of VWF is assayed as collagen binding activity[6] and as ristocetin cofactor activity,[7] which reflects its binding affinity for collagen and platelets, respectively. The multimeric structure of VWF may be determined by agarose gel electrophoresis, followed by Western blotting.[8]

It has been suggested by Favaloro[9] that VWF activity in a collagen binding assay reflects the presence of high-molecular-weight VWF multimers.

RAISED PLASMA VON WILLEBRAND FACTOR LEVELS AND MULTI-ORGAN FAILURE IN CRITICALLY ILL PATIENTS

Thrombo-Inflammation

The close relationship between inflammation and thrombosis, especially in primary haemostasis, has recently been the subject of active research. 'Thrombo-inflammation', secondary to the co-ordinated activation of the immune system (such as complement components, or innate immune cells) and primary haemostasis (such as platelets and endothelial cells), is the body's primary response to a variety of external, potentially harmful stimuli.[10] This response is needed for tissue repair after initial damage. The complement components, specifically the lectin and alternative pathways, form the major interface between inflammation and primary haemostasis.[11] If not controlled, these responses may lead to widespread thrombotic microangiopathies and inflammatory complications. Thrombotic microangiopathy accompanies sepsis syndrome and has been termed thrombocytopenia-associated multi-organ failure.[12]

Endothelial Activation in Inflammatory Conditions/Sepsis

In inflammatory conditions, endothelial activation leads to a progressive rise in plasma VWF, especially the ultra-large VWF multimer subset. This is accompanied by a parallel steady decrease in the cleaving protease ADAMTS13, leading to VWF–ADAMTS13 imbalance, which has been shown to contribute to and correlate with the severity of inflammation and organ failure in sepsis.[13,14]

In a randomised controlled trial involving children with sepsis, reversing the VWF–ADAMTS13 imbalance by therapeutic plasma exchange reversed organ dysfunction in patients with thrombocytopenia-associated multi-organ failure. All seven children who died of thrombocytopenia-associated multi-organ failure had reduced plasma ADAMTS13 levels and VWF-rich microvascular thrombi at autopsy.[15]

The imbalance of high VWF and low ADAMTS13, and its correlation with disease severity, has been studied in a variety of critical illnesses, including sepsis,[16] acute pancreatitis,[17] severe malaria,[18] dengue fever,[19,20] sickle cell disease,[21] alcoholic hepatitis,[22] and complications such as acute lung injury[23] and disseminated intravascular coagulation.[24]

Plasma von Willebrand Factor Levels as a Prognostic Marker in Critical Illnesses

Multiple studies have explored the role of plasma VWF levels in predicting short-term prognosis in critical illnesses. For example, Hyseni et al.[25] found measurement of active VWF plasma levels useful as an independent predictor of short-term outcome in patients with sepsis and systemic inflammatory response syndrome.[25]

Dynamic changes in plasma VWF levels predicted multiple organ dysfunction and death in patients with scrub typhus,[26] and acute lung injury and death in patients with acute pancreatitis.[27]

The imbalance of high VWF and low ADAMTS13 in sepsis/inflammatory conditions can be a predisposition to platelet microthrombi and an impedance to vital organ microcirculation, leading to multi-organ failure and death in critically ill patients. As multi-organ failure is seen in critically ill patients with a severe grade of ACLF or with acute liver failure, it is possible that raised plasma VWF levels may contribute to disease pathogenesis in these patients.

RAISED PLASMA VON WILLEBRAND FACTOR LEVELS PREDICT SURVIVAL IN PATIENTS WITH CIRRHOSIS, ACUTE-ON-CHRONIC LIVER FAILURE, AND ACUTE HEPATOTOXICITY

VWF was previously recognised as an endothelial activation marker in patients with cirrhosis.[28,29] Recent studies document raised plasma VWF levels as a prognostic marker of outcome in patients with acute and chronic liver disease. It is more relevant in liver disease because ADAMTS13 is produced in liver stellate cells. The level of plasma ADAMTS13 has been shown to decrease with increasing severity of liver disease.[30,31] This leads to an exaggerated imbalance of primary haemostasis that favours clotting. This imbalance is probably maximised in the presinusoidal portal vein radicles (because ADAMTS13 is secreted from the stellate cells), which, in turn, explains its occurrence in pure vasculopathy in idiopathic noncirrhotic portal hypertension. This progressive imbalance may also play a part in cirrhosis disease deterioration by contributing to portal micro-occlusions and parenchymal extinction.

In patients with idiopathic noncirrhotic intrahepatic portal hypertension due to chronic portal microangiopathy, deficiency of ADAMTS13 is noted despite preserved hepatocellular function.[32-35] In patients with noncirrhotic portal hypertension, low plasma ADAMTS13 levels are also associated with vascular complications such as portal vein thrombosis,[36] pulmonary hypertension,[37] and hepatopulmonary syndrome.[38]

Plasma von Willebrand Factor Levels Predict Survival in Cirrhosis

In a recent systematic review of five studies on plasma VWF levels in patients with cirrhosis (N=715 patients), Eidelberg et al.[39] found that baseline plasma VWF antigen level was an independent predictor of medium-term mortality in patients (median: 25.6; range: 23.6–33.0 months), with an area under the curve of 0.74 (95% confidence interval: 0.70–0.79) and an optimal cut-off median (318%; range: 216–390%).[39] Newer reports continue to corroborate these findings.[40]

Model for end-stage liver disease (MELD) scores, although a good predictor of hepatocellular dysfunction, may not adequately predict portal hypertensive complications, for which a vascular/endothelial marker may be more efficient. A combination of MELD score and VWF antigen levels appears to be a better predictor of survival in patients with cirrhosis. While plasma VWF antigen level was an independent predictor of 3-month mortality in patients listed for liver transplant comparable to MELD-Na, a composite score (VWF antigen and MELD-Na) improved prediction of 3-month waiting list mortality.[41]

Plasma von Willebrand Factor Levels Predict Survival in Acute Hepatotoxicity

Acute liver failure is often associated with increased release of endotoxins and cytokines, which may lead to a decrease in ADAMTS13 activity and a concomitant rise in VWF levels.[42]

A mechanistic link between VWF, platelet accumulation in the liver, and liver repair has been suggested in experimental models of acute liver injury.[43] In an animal study, low-dose dimethylnitrosamine activated hepatic stellate cells, and influenced the levels of ADAMTS13.[44]

High plasma levels of VWF and low ADAMTS13 were shown in 50 patients with acute liver injury and acute liver failure. Low baseline ADAMTS13 levels predicted transplant-free survival in these patients. Plasma VWF antigen levels did not predict survival in these patients. However, this study included patients with nine different aetiologies of liver disease. Additionally, the majority of these patients had blood samples drawn for a VWF assay after they had received N-acetylcysteine, as part of their acute liver failure management (N-acetylcysteine may reduce VWF levels).[45]

In contrast to the above-mentioned study, plasma VWF levels accurately predicted inpatient survival in patients with acute hepatotoxicity caused by a single aetiology (yellow phosphorus contained in rodenticides). In a recent report of 24 patients with rodenticide-induced hepatotoxicity, of whom 20 had acute liver injury, three had acute liver failure and one had uncomplicated acute hepatitis. Plasma VWF antigen levels were raised to a median of 423% (range: 146–890%) in patients with acute liver injury and to a median of 448% (range: 414–555%) in patients with acute liver failure. Normal plasma VWF antigen levels were 50–150%. The raised plasma VWF levels predicted survival more accurately than the MELD and sequential organ failure assessment (SOFA score) in these patients.[46]

Plasma von Willebrand Factor Levels Predict Survival in Acute-on-Chronic Liver Failure

Plasma VWF levels are noted to be consistently higher in patients with acute-on-chronic liver failure (ACLF).[47,48] Prasanna et al.,[49] in a study of 50 ACLF patients, showed that plasma VWF levels were 5–7-fold elevated, which correlated independently with organ failure and in-hospital survival. Similarly, in patients with cirrhosis and superimposed inflammation, VWF was high and predicted transplant-free survival.[50]

WHY ARE PLASMA VON WILLEBRAND FACTOR LEVELS INCREASED IN PATIENTS WITH LIVER FAILURE?

Plasma VWF levels are increased 2–3-fold in patients with chronic liver diseases (cirrhosis patients in the outpatient setting[39] and patients with noncirrhotic portal hypertension),[34,35] 4.0–4.5-fold in patients with acute hepatic dysfunction (acute liver injury and acute liver failure),[46] and 5–7-fold in patients with ACLF.[39,49] This raises many questions on the reason this occurs; is it because of increased VWF production/secretion, reduced VWF clearance from the circulation, or both? Increased VWF secretion from endothelial cells may reflect endothelial activation. The highest levels of plasma VWF noted in ACLF may reflect acute-on-chronic endothelial activation.[51]

The Liver is an Important Site of von Willebrand Factor Clearance

Is VWF clearance affected in patients with liver failure? The mechanisms of VWF clearance seem to be linked to adequate liver function. When radiolabelled VWF was injected intravenously into VWF-deficient mice to study biodistribution of VWF, the bulk of VWF protein was noted to be taken up by the liver. When expressed in relative terms, the liver and spleen were equally efficient in VWF uptake.[52]

Mechanisms of von Willebrand Factor Clearance

Clearance of VWF is performed by macrophages, endothelial cells, and hepatocytes via C-type

lectin domain family-4 (CLEC4M) receptors,[52] galactose-type lectin receptors,[53] low density lipoprotein receptor related protein-1 (LRP-1),[54] and Ashwell–Morell receptor.[54]

The sugar moieties in the VWF glycoprotein seem to influence VWF clearance.[55] The glycosylation profile of VWF affects plasma VWF levels.[56] VWF protein contains 10 sites for O-linked and 12 sites for N-linked glycosylation. Some of the N-linked sugars contain ABO blood group determinants, which are absent on the O-linked sugars. ABO blood groups appear to influence plasma VWF levels: mean VWF levels are approximately 25% lower in individuals with blood group O compared to non-O individuals; these levels are even further reduced in individuals with the Bombay blood group (who do not express ABO antigens).[57]

Desialylation of VWF is yet another effect on VWF glycosylation, which leads to its rapid clearance by hepatocytes. Sialylation is important to prevent premature clearance by receptors which recognise non-sialylated terminal galactose residues, such as the Ashwell–Morell receptor expressed on hepatocytes. The purified normal factor VIII/VWF protein possesses both procoagulant activity and ristocetin-induced platelet-aggregating activity, and contains 154±15 nmol of sialic acid/mg of protein and 28±3 mol of sialic acid/mol of 200,000 molecular weight subunits. Desialylation of this protein was associated with reduction in ristocetin-induced platelet aggregating activity, while procoagulant activity, measured by partial thromboplastin time, remained unchanged. Desialylated factor VIII/VWF protein is rapidly cleared in the liver.[58]

Cleavage of VWF by ADAMTS13[59] and by plasmin[60] is another mechanism of VWF clearance. Globular forms of VWF are resistant to cleavage by ADAMTS13 and by plasmin in static conditions, though they are readily cleaved under shear stress.

More than 90% of tissue-resident macrophages in the body are located in the liver, known as Kupffer cells. The Kupffer cells are located in hepatic sinusoids and adhere to the hepatic sinusoidal endothelial cells. Kupffer cell population is severely decreased in the initial 24 hours of injury in mouse models of acute liver failure (induced by paracetamol) and chronic liver injury (induced by carbon tetrachloride).[61] The cells that synthesise ADAMTS13 (hepatic stellate cells) are located in the perisinusoidal space in the liver.

Hepatic Sinusoidal Endothelium: A 'von Willebrand Factor-Free' Zone

VWF is heterogeneously expressed in endothelial cells throughout the vascular tree, with higher expression in veins compared with arteries and arterioles. However, immunostaining and messenger RNA expression studies show that VWF is not expressed on the hepatic sinusoidal endothelial cells in a healthy liver.[62] Of note, ADAMTS is produced by hepatic stellate cells.[63] Tissue-resident macrophages (>90% are located in hepatic sinusoidal lining) are involved in VWF clearance. Thus, in the healthy liver, hepatic sinusoidal endothelium appears to be a 'VWF-free' zone, and an important site for removing VWF from the circulation. It is perhaps unsurprising that VWF levels are raised in different forms of liver disease.

ROLE OF VON WILLEBRAND FACTOR IN PROGRESSION OF LIVER DISEASE

The role of VWF in causing progression of acute liver injury was studied in a mouse model using genetic and antibody-mediated strategies to achieve VWF reduction. Paracetamol overdose-induced acute liver injury in this model was associated with VWF deposition in the liver, raised plasma VWF levels, and impaired VWF clearance. Administration of VWF to VWF-deficient mice led to a delay in the repair of paracetamol-induced liver injury (associated with platelet deposits and increased necrosis in the liver). Interventions to reduce VWF led to reduction in platelet deposition, less necrosis, and accelerated repair of the liver, even in mice with established liver injury. Thus, this experimental model provides clear evidence that VWF contributes to progression of acute liver injury caused by the hepatotoxin paracetamol.[43]

Table 1: Ability of raised plasma von Willebrand factor antigen levels at baseline to predict death in different types of liver diseases in select studies.

Type of liver disease	Baseline plasma VWF antigen level*	Time period when prediction of death was studied	AUROC (95% CI) for plasma VWF antigen level to predict survival	Reference
Cirrhosis†	Median: 318% Range: 216–390%	Median: 25.6 months Range: 23.6–33.0 months	0.74 (0.70–0.79)	Eidelberg et al.,[39] 2019
Acute-on-chronic liver failure	712%	8 days	0.63 (0.47–0.80)	Prasanna et al.,[49] 2016
Acute liver injury/ acute liver failure‡	486%	7 days	0.92 (0.80–1.00)	Sardar et al.,[46] 2019

(Normal plasma VWF antigen levels are 50–150%).

*Optimal cut-off level of plasma VWF antigen level.

†Meta-analysis of five studies of patients with cirrhosis (N=715 patients).

‡Of the 24 patients with acute hepatotoxicity caused by a single agent (rodenticide), 20 patients had acute liver injury, three had acute liver failure, and one had uncomplicated acute hepatitis.

AUROC: the area under the receiver operating characteristic; CI: confidence interval; VWF: von Willebrand factor.

VON WILLEBRAND FACTOR REDUCTION: A POTENTIAL NEW THERAPEUTIC OPTION IN LIVER FAILURE SYNDROMES

In view of the emerging evidence of the deleterious effects of raised plasma VWF levels in liver diseases (Table 1), the potential of treatments to reduce VWF needs to be explored in patients with liver diseases. Currently, there are limited data on the role of VWF reduction to treat patients with liver diseases. The beneficial effects of some of the treatments currently in use to treat patients with liver diseases may be due to the VWF-lowering effects of these treatments.

N-acetylcysteine is used to treat acute liver failure as a result of paracetamol overdose and other causes. Glutathione repletion is a recognised mechanism to explain how N-acetylcysteine exerts its benefits in these patients. N-acetylcysteine has been used for many years to treat chronic obstructive pulmonary disease by reducing levels of mucins (the main protein component of mucus). Chen et al.[64] explored whether N-acetylcysteine has a similar effect in reducing VWF multimers, which polymerise in a manner similar to mucin multimers. They found that N-acetylcysteine reduced the size and activity of VWF in human plasma and mice. N-acetylcysteine reduces the disulfide bonds linking VWF dimers.[64]

Fresh frozen plasma infusions provide ADAMTS13 supplementation, which, in turn, reduces plasma VWF levels (ADAMTS13 causes proteolysis of VWF). Infusions of fresh frozen plasma have been used to treat a patient with noncirrhotic portal hypertension and portopulmonary hypertension, who also had severe ADAMTS13 deficiency.[37]

Therapeutic plasma exchange dramatically increases survival rate in patients with thrombotic thrombocytopenia purpura (TTP).[65] ADAMTS13 deficiency linked to a genetic trait (congenital TTP or Upshaw–Schulman syndrome) or due to anti-ADAMTS13 antibodies (in haemolytic uraemic syndrome after *Escherichia coli* diarrhoea), is associated with ultra-large-molecular-weight forms of VWF in the circulation. VWF reduction in therapeutic plasma exchange occurs as a result of two mechanisms: the removal of the ultra-large VWF multimers during plasmapheresis, and ADAMTS13 supplementation by infusion of fresh frozen plasma or cryosupernatant from healthy donors to replace the plasma removed from the patient.

Preliminary reports in acute hepatotoxicity (acute liver injury and acute liver failure) because of yellow phosphorus (rodenticide) poisoning suggest that therapeutic plasma exchange is the most potent of these VWF-reducing treatments. In a small number of patients, institution of VWF-reducing treatment, as per a management protocol tailored to the degree of liver dysfunction, improved survival in patients with acute liver injury and acute liver failure, without liver transplantation.[46]

Fresh frozen plasma contains VWF; however, the question is, is it safe to transfuse or exchange plasma in patients with acute liver injury or failure, who already have raised plasma VWF levels? Plasma exchange appears to improve survival in patients with acute liver failure[46,66] and acute liver injury.[46] It is likely that in acute liver failure patients, the plasma removed during plasma exchange has high VWF content, and is replaced by plasma obtained from healthy donors (with normal VWF content). Transfusion of fresh frozen plasma to supplement ADAMTS13, as a means to reduce VWF, appeared beneficial in a single patient with ADAMTS13 deficiency and portopulmonary hypertension,[37] as well as in acute liver injury.[46] Further studies are needed to explore the risks and benefits of plasma exchange and transfusions as a VWF-lowering strategy in patients with liver failure.

It is important to obtain blood samples for assays for VWF or for ADAMTS13 prior to initiation of any of these VWF-lowering treatments.

CONCLUSION

Recent reports document raised plasma VWF levels as predictors of poor survival in different syndromes of liver disease. These clinical observations suggest that the markedly raised plasma VWF levels in syndromes of acute liver failure and ACLF may contribute to the pathogenesis of liver failure and multi-organ failure by impeding microcirculatory perfusion in the liver and other affected vital organs. Experimental evidence now confirms that VWF contributes to progression of acute liver injury. VWF-reducing treatments may offer a new therapeutic avenue in liver failure syndromes. Of the different VWF-lowering treatments available, therapeutic plasma exchange appears to be the most efficacious. Current understanding of the dynamics of VWF metabolism in liver failure is rudimentary. There are scarce data on treatments targeting VWF in patients with liver diseases. Further studies are needed to apply these insights to better treatments for patients with liver disease.

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Liver Disorders in Inflammatory Bowel Disease

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Disclosure: The authors have declared no conflicts of interest.

Received: 19.02.2020

Accepted: 18.03.2020

Keywords: Extraintestinal manifestations, hepatotoxicity, inflammatory bowel disease (IBD), primary sclerosing cholangitis (PSC).

Citation: EMJ Hepatol. 2020;8[1]:26-32.

Abstract

Abnormal liver tests are frequent in patients with inflammatory bowel disease. These may occur at the time of diagnosis or throughout the course of the disease. There are multiple aetiologies, such as concomitant diseases and extraintestinal manifestations of the same disease, primary sclerosing cholangitis being the most characteristic. Other aetiologies include adverse reactions to the drugs used in the treatment of these patients. This review will evaluate the different causes of liver test abnormalities.

INTRODUCTION

Hepatobiliary diseases constitute some of the most common extraintestinal problems of inflammatory bowel diseases (IBD) reported in ulcerative colitis (UC) and Crohn's disease (CD). Approximately 50% of patients with IBD will present a transient elevation of liver tests during long-term follow up.[1] Non-alcoholic fatty liver disease (NAFLD) is the most common cause of impaired liver tests. Primary sclerosing cholangitis (PSC) is a liver disease more specifically associated with IBD, mainly UC.[2,3] Other related diseases are autoimmune hepatitis, primary biliary cholangitis (PBC), choledocholithiasis, hepatic amyloidosis, portal vein thrombosis, and drug-induced liver injury (DILI), among others.[4] Clinicians must carry out a complete evaluation to determine the aetiology of abnormal liver tests, the possible association with a disease related to IBD, and their clinical relevance. The main objective of this review was to describe the main hepatobiliary manifestations related to IBD.

Liver Function Test Alteration

The transient or persistent elevation of liver tests is frequent in IBD. In a recent study of 306 patients with IBD, 19.6% presented with abnormal liver test results.[5] In up to 60.0% of the patients the alterations were mild and spontaneously returned to normal values. The most frequent cause of transient alteration in liver tests is secondary to DILI (34.1%), while fatty liver is the most frequent cause of persistent transaminase alteration and even chronic liver disease (65.4%).[1]

PRIMARY SCLEROSING CHOLANGITIS

PSC is characterised by chronic inflammation that affects the intra and/or extrahepatic bile ducts. PSC can cause segmental stenosis, saccular dilatations, different degrees of fibrosis, and in advanced stages, even liver cirrhosis.[6]

Epidemiology

The incidence of PSC is estimated at 0.9 and 0.5 per 100,000 inhabitants per year for North America and Europe, respectively.[7] It usually occurs in men, with a median age of diagnosis of 41 years.[8] Approximately 50–80% of patients with PSC have concomitant IBD, most often UC. Nevertheless, only 5% of patients with IBD develop PSC. Incidence varies if the diagnosis is radiologic or histopathologic. In a study that included 255 patients with IBD that underwent abdominal surgery and liver biopsy, 12.8% presented findings compatible with PSC. Of these, only 24.1% had alterations of liver function tests.[9] In another study of 756 patients with IBD, 24 patients (7.5%) had PSC-compatible lesions in the magnetic resonance cholangiography (MRCP). Only seven (2.2%) of these had a previous PSC diagnosis by clinical findings and/or impaired liver tests. These data suggest that the prevalence may be underestimated, since up to two-thirds of the patients may be asymptomatic.[10]

Clinical Findings, Diagnosis, and Complications

Patients can be asymptomatic or present multiple symptoms that can be intermittent, such as fatigue, pruritus, fever, night sweats, and pain in the upper right quadrant. The laboratory finding of a cholestatic pattern (elevation of alkaline phosphatase and γ-glutamyl transferase) is characteristic. The study of choice is MRCP, given it is a non-invasive exam with high sensitivity and specificity.[11,12] Typical findings of PSC include multifocal segmental stenosis with saccular dilations, which produce a classic appearance known as 'string beads'. The European Crohn's and Colitis Organisation (ECCO) consensus recommends restricting the use of endoscopic retrograde cholangiopancreatography only in cases of need for intervention as an indication for dilatation due to imaging and/or diagnostic cytological findings.[13]

Liver biopsy is reserved in cases of diagnostic doubt or if small duct PSC is suspected. Characteristic findings are obliterating fibrosis of small bile ducts with concentric periductal fibrosis in an 'onion skin' pattern. Causes of secondary sclerosing cholangitis must be excluded, such as infection, immunodeficiency, ischaemia, pancreatic disease, or diseases related to IgG4. The presence of PSC associated with IBD correlates with a specific IBD phenotype.[14,15] Loftus et al.[16] described a series of 71 patients with IBD. Evidence of backwash ileitis was found in 51% of the PSC-IBD patients compared with 7% in the control group (IBD only). Rectum preservation was found in 52% and 6% of patients, respectively.[16] PSC associated with UC mainly presents as extensive colitis beyond the splenic flexion in 90% of cases. There is greater involvement of the right colon, with rectum preservation, frequent reflux ileitis, and increased risk of colorectal carcinoma (CRC), which persists after liver transplantation.[5,16] When PSC associates with CD, the course of the IBD tends to be more benign. The predominant phenotype is the inflammatory type of colon, which may or may not have terminal ileum involvement. Stenosing and fistulising phenotypes are less frequent.[14,17] The combination of PSC with IBD is associated with complications such as cholangitis, cholecystolithiasis, osteoporosis, fat-soluble vitamin deficiency, and steatorrhoea.[18,19] These patients also have an increased risk of developing malignancies, mainly cholangiocarcinoma (CCA) and CRC.[10]

Primary Sclerosing Cholangitis and Colon Cancer

Patients with IBD have a significantly increased risk of developing CRC, mainly because of the pro-neoplastic effect secondary to chronic intestinal inflammation. The risk is greater if there is an association with PSC.[20] In 77 patients with PSC-IBD, CRC was detected in 7.8% versus 2.3% (p=0.016) in the control group (UC without PSC).[13] Interestingly, in PSC-UC, all colorectal tumours were located proximal to the splenic flexion. In UC without PSC, tumour location was predominantly in the left colon (100% versus 40%).

Additional risk factors for the development of CRC include the duration of the disease and the extent of IBD (pancolitis). In a comparative study, 46 of 273 patients with PSC (223 with UC and 50 with CD), it was established that patients with UC had a 56% higher risk of developing CRC compared to CD.[21]

Primary Sclerosing Cholangitis and Cholangiocarcinoma

The possibility of developing CCA in patients with PSC is 10%. The risk is 400–1,400 times higher than that of the general population,[12,22] and is even higher if PSC associates with IBD.[23] CCA is mainly associated with intra and extrahepatic PSC, with some cases reported in small duct PSC.[24,25] Over half of patients with PSC and CCA are diagnosed at an advanced stage, in part because of the challenges of achieving an early diagnosis. Therefore, the diagnosis of CCA in patients with PSC requires a high index of suspicion and active surveillance.[12]

Treatment

No therapy has been shown to prevent liver transplantation, CCA, or death.[8] The use of ursodeoxycholic acid (15–20 mg/kg/day) is associated with an improvement in the cholestatic pattern. It has not been demonstrated to prevent the progression of the disease: the reason why the American Academy for the Study of Liver Disease (AASLD) does not recommend it.[24]

Liver transplantation is the only therapy that can cure PSC. Patients with PSC and end-stage liver disease or disabling symptoms (intractable pruritus or repeated cholangitis) should be considered for liver transplantation.[13,17]

Follow-Up

Due to the higher risk of colorectal cancer, ECCO guidelines[12] recommend surveillance colonoscopy in patients with PSC and IBD at diagnosis and every 1 to 2 years after that. Chromoendoscopy with targeted biopsies is the surveillance strategy of choice. In patients with PSC without evidence of IBD, colonoscopy is recommended every 5 years. Screening PSC patients for CCA is a rational approach due to their increased risk of this neoplasia. Ultrasound imaging assessment of the biliary tree (sensitivity: 57%; specificity: 94%) or MRI/MRCP (sensitivity: 89%; specificity: 75%) in combination with CA 19-9 every 6–12 months, seems to be the right approach. Experts recommend MRI for CCA surveillance, as it has higher sensitivity than ultrasound. ERCP should not be considered for surveillance.[26,27]

OTHER HEPATIC MANIFESTATIONS IN PATIENTS WITH INTESTINAL BOWEL DISEASE

Non-Alcoholic Fatty Liver Disease

NAFLD is a chronic liver disorder, characterised by the presence of steatosis in >5% of hepatocytes. Current data suggest an increase in the prevalence of NAFLD in patients with IBD and is now one of the most frequent hepatic manifestations in IBD. The prevalence of NAFLD is 6.7–35.5% in patients with UC and 7.8–9.5% in CD.[28] The range of incidence depends on the diagnostic method used. A controlled study analysed 928 IBD patients, 7.2% had NAFLD diagnosed with abdominal imaging. BMI and prevalence of metabolic syndrome were greater in NAFLD than patients without NAFLD. Risk factors for NAFLD in IBD included small bowel surgery (odds ratio [OR]: 3.7; 95% confidence interval [CI]: 1.5–9.3; p=0.005), hypertension (OR: 3.5; 95% CI: 1.5–8.1; p=0.004), obesity (OR: 2.1; 95% CI: 1.05–4.00; p=0.035), and steroid use (OR:3.7; 95% CI: 1.5–9.3; p=0.005).[29]

In addition to metabolic syndrome, the pathogenesis of NAFLD in the population with IBD may be more complex and involve specific risk factors for the disease, such as chronic inflammation, drug-induced hepatotoxicity, steroid exposure, malnutrition, and intestinal dysbiosis.[30] Nonspecific guidelines for the evaluation of NAFLD in IBD have been established. Ultrasound is commonly used for the screening and evaluation in patients suspected of NAFLD. Non-invasive serum biomarker scores, such as the Fibrosis-4 calculator and NAFLD fibrosis score, have been validated for the assessment of fibrosis. There is also more information about using transient elastography (TE), which may assess the presence of advanced fibrosis.[31] A specific treatment for the IBD population has not been evaluated. The current approach to NAFLD therapy is lifestyle and diet modification with the objective of a weight reduction of at least 7%, which has been associated with a biochemical and histological improvement in patients with NAFLD. Pharmacological therapy should be evaluated case-by-case.

Drug-Induced Liver Injury

Drugs used in the treatment of IBD have accounted for some cases of DILI. These may be transient elevations of liver enzymes up to sporadic cases of clinically significant liver injury.[32,33] Aminosalicylates report an estimate incidence of 3.2 cases per million prescriptions of DILI, including mild transaminase elevations, cholestatic pattern, and hypersensitivity reactions.[34] The hepatoxic effects of thiopurines, azathioprine and 6-mercaptopurine, are primarily mediated by the metabolite 6-methylmercaptopurine.[35] In adult patients with IBD starting thiopurines, the American Gastroenterological Association (AGA) have suggested routine thiopurine methyltransferase testing and monitoring of thiopurine metabolite to guide thiopurine dosing if IBD is active.[35] Different patterns of hepatocellular, cholestatic, and mixed liver injury have been identified, characteristically being a more acute DILI. Long-term evolution can even lead to liver cirrhosis with portal hypertension secondary to vascular compromise (sinusoidal dilation, sinusoidal obstruction syndrome), and regenerative nodular hyperplasia.[36] Methotrexate may cause acute liver test disturbances and prolonged use at cumulative doses greater than 1.5 g may develop macrovesicular steatosis and progressive fibrosis towards cirrhosis. Risk factors for fibrosis with methotrexate use include alcohol consumption, obesity, diabetes, and previous liver disease.[37]

Anti-TNF have been associated with four types of liver test alterations: 1) infusion hepatitis, which appears after two to five infusions, for which the alteration is usually transient and generally asymptomatic; 2) cholestatic, which can occur later; 3) *de novo* autoimmune hepatitis, with a hepatocellular pattern and the presence of antinuclear antibodies and other autoantibodies; and 4) reactivation of chronic hepatitis B, being necessary to test it before starting biological therapy.[5,38] Vedolizumab is a gut-specific anti-integrin that binds α4-β7 to MAdCAM1. In a systematic review it was shown that liver test alterations were not significant compared to placebo.[39] Small molecules are an effective treatment in moderate-to-severe, immune-refractory or anti-TNF-failing UC. No significant alterations in liver tests have been reported regarding these.[39] Table 1 shows the different hepatic damage patterns associated with drugs used in the treatment of IBD patients.

Primary Biliary Cholangitis

PBC is a chronic cholestatic nonsuppurative destructive cholangitis. Most patients are asymptomatic or have nonspecific symptoms such as fatigue or pruritus and it is not usually associated with IBD. Liberal et al.[40] described a series of six patients with PBC-IBD where the majority were women without differences between UC or CD.[40]

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic liver disease characterised by alteration of transaminases, hypergammaglobulinaemia, and periportal hepatitis in liver biopsy. The prevalence in patients with IBD is low. It has been reported mainly in children with UC reaching up to 0.77%. In patients with PSC, the prevalence is higher, where the overlap of AIH was observed in 10% of cases.[41,42] The response to the treatment of AIH is not affected by the presence of IBD.

Table 1: Hepatic damage patterns associated with drugs for intestinal bowel disease.

Patterns	Associated Drug
Hepatocellular	Sulfasalazine, mesalamine, thiopurines, methotrexate, anti-TNF
Cholestatic	Sulfasalazine, mesalamine, anti-TNF
Granulomatous hepatitis	Sulfasalazine, thiopurines
Vascular lesions (sinusoidal dilatation, peliosis hepatis, veno-occlusive disease)	Thiopurines
Nodular regenerative hyperplasia	Thiopurines
Hepatic steatosis	Methotrexate, corticosteroids
De novo autoimmune hepatitis	Anti-TNF
Reactivation of chronic hepatitis B	Anti-TNF

Pyogenic Liver Abscess

Patients with IBD have a higher risk of pyogenic liver abscess than the general population. In a cohort study, the incidence was higher in IBD patients (6.72 IBD versus 4.06 per 10,000 person-year in non-IBD).[43] The abscesses are often multiple in number and are located more frequently in the right hepatic lobe. Clinically they present with abdominal pain, jaundice, fever, diarrhoea, and in some cases, hepatomegaly. They are mainly associated with CD due to transmural inflammation and may be secondary to direct extension of intra-abdominal abscess, pylephlebitis, or secondary to fistulising disease. Additional risk factors are diabetes and bile duct manipulation.[44] Treatment does not differ from management in other clinical contexts. A guided antibiotic therapy should be administered according to cultures or drainage results, size, and evolution.[30]

Hepatic Amyloidosis

Secondary hepatic amyloidosis is a rare complication that has been reported in 0.90% of patients with CD. It is mainly described in cases of severe CD with infectious complications and intestinal resection, and in 0.07% of patients with UC.[45] Chronic inflammatory activity in the intestine contributes to the deposition of amyloid in the vessels and sinusoids of almost any organ, including the liver, which leads to asymptomatic hepatomegaly. The treatment is to decrease IBD activity.

Granulomatous Hepatitis

Granulomatous hepatitis is a rare complication of IBD, with a prevalence of less than 1%, which is more frequent if associated with CD. It can be induced by drugs used in IBD treatment, such as mesalamine and sulfasalazine, and also with other concomitant autoimmune pathologies such as PBC and AIH. The presence of non-calcified granulomas characterises it, occasionally with multinucleated cells, which are located both in the portal space and the lobules. Patients are usually asymptomatic, so suspicion should arise in the presence of a cholestatic pattern.[46]

Portal Vein Thrombosis

Patients with IBD have a known risk of increased thromboembolic disease, and the portal vein is a common place of thrombosis. Major risks have been described in the postoperative period of IBD and during exacerbations, although it may occur in patients in remission. In a Spanish retrospective study, 40% of patients who presented thrombotic episodes also had a proven prothrombotic genetic factor, the most frequent being hyperhomocysteinaemia.[47] Therefore, the ECCO guidelines recommend an appropriate evaluation for both the underlying acquired prothrombotic conditions (related to IBD) and for hereditary thrombophilia.[12] Treatment with anticoagulants is recommended according to general guidelines.

CONCLUSION

Elevation of liver enzymes is frequent in patients with IBD. Causes are varied and alterations range from slight increases to progressive severe diseases with poor prognosis. Therefore, in patients with IBD, liver tests should be routinely monitored, and a full diagnostic workup performed if they are altered (Figure 1). Differential diagnosis should always include DILI.

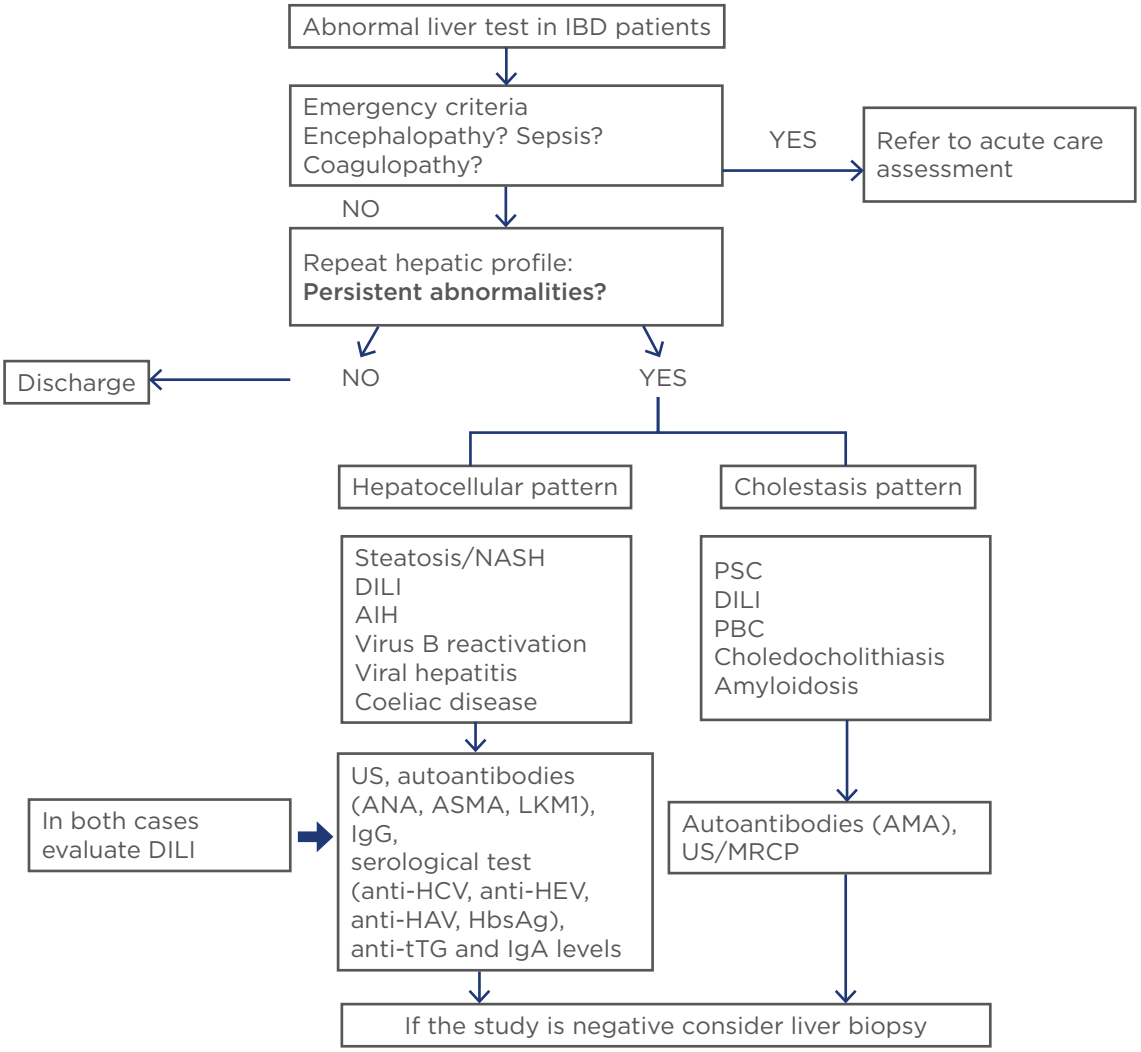

Figure 1: What should we do with abnormal liver test in inflammatory bowel disease? A stepwise approach for patients with abnormal liver test in IBD.

AIH: autoimmune hepatitis; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibody; LKM1: liver kidney microsome antibody; AMA: antimitochondrial antibody; PBC: primary biliary cholangitis; DILI: drug-induced liver injury; HAV: hepatitis A virus; HCV: hepatitis C virus; HEV: hepatitis E virus; IBD: inflammatory bowel disease; MRCP: magnetic resonance cholangiography; NASH: non-alcoholic steatohepatitis; PSC: primary sclerosing cholangitis; tTG: tissue transglutaminase; US: ultrasound.

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Rethink Your Transjugular Intrahepatic Portosystemic Shunt (TIPS): Pre-TIPS Infection Predicts Post-TIPS Infection and Post-TIPS Portosystemic Encephalopathy

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Disclosure: Ester Little has received research grants from Intercept Pharmaceuticals. Other authors have not declared any conflicts of interests.

Acknowledgements: The authors are forever thankful to the Interventional Radiology team at Banner – University Medical Center Phoenix who performed the TIPS procedure during the years of the study: Dr Kevin Hirsh, Dr David Wood, Dr Steven Chen, and Dr Cole Mendenhall.

Received: 16.12.19

Accepted: 23.03.20

Keywords: Ascites, cirrhosis, infection, portal hypertension, portal systemic encephalopathy, transjugular intrahepatic portosystemic shunt (TIPS).

Citation: EMJ Hepatol. 2020;8[1]:34-41.

Abstract

Objective: Transjugular intrahepatic portosystemic shunt (TIPS) is used for decompression of elevated portal pressure; however, there are potential complications. The aim of this study was to compare the risk of complications of TIPS in those who had an episode of infection within 6 months prior to TIPS to those without an infection prior.

Methods: A retrospective chart review was performed on patients who underwent TIPS at a single transplant centre over 8 years. They were divided into two groups: patients without infection during the 6 months prior to TIPS (n=349) and those with an infection prior (bacterial/fungal) (n=53). The Wilcoxon rank-sum test was used to compare continuous variables while chi-squared analysis and Fisher's exact test was used for categorical variables. Multiple logistic regression was used to ascertain the association between pre-TIPS infection status and likelihood of post-TIPS infection.

Results: In the group of patients who had an infection before TIPS, 26.4% (n=14) had an episode of infection after the procedure, while in the group without infection prior, 16.2% (n=55) had an infection after the procedure (p=0.047; odds ratio: 2.08). In the pre-TIPS infection group, 54.7% (n=29) had an episode of portosystemic encephalopathy post-TIPS versus 39.6% (n=134) in the group without infection before TIPS (p=0.046; odds ratio: 1.93).

Conclusion: Pre-TIPS infection within 6 months of TIPS procedure is a risk factor for post-TIPS portosystemic encephalopathy and infection. Further studies are needed to determine the potential benefit of antibiotic prophylaxis in patients who had an infection in the 6 months preceding TIPS placement.

INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is widely used for the decompression of elevated portal pressure. Several studies have demonstrated that TIPS is very effective for secondary prevention of oesophageal variceal bleeding and treatment of refractory ascites, Budd–Chiari syndrome, hepatic hydrothorax, ectopic varices, and more recently, portal vein thrombosis.[1-4]

Complications of the TIPS procedure include portosystemic encephalopathy (PSE), infection, bleeding, respiratory complications, and liver failure.[5-7] The model of end stage liver disease (MELD), and later its modification to include serum sodium in the calculation (MELD-Na), has been proven to be the best model to predict mortality after TIPS placement.[3,8-13]

Other factors have been identified as predictors for specific complications of TIPS. Increased age, prior episodes of PSE, and a higher Child–Pugh class have been identified as predictors of post-TIPS portosystemic hepatic encephalopathy.[14] TIPS inserted for control of acute variceal bleeding and use of overlapping shunts at stent insertion have been shown to be risk factors for infection of the TIPS shunt ('tipsitis') and for post-TIPS unexplained sustained bacteraemia.[15]

Patients with cirrhosis have an increased risk of infections in general including infection of the ascitic fluid, particularly spontaneous bacterial peritonitis.[16-20] Similar to the known risk factors that predict certain complications of TIPS, there are known predisposing factors that can predict the probability of spontaneous bacterial peritonitis in patients with ascites, such as low serum sodium levels, Child–Pugh Stage C, and elevated ascitic polymorphonuclear cell counts.[21] However, there are insufficient data about whether an infection (bacterial or fungal) prior to the insertion of the TIPS can affect the rate of complications after the procedure. The aim of the study was to compare the rate of complications of TIPS in patients who had an episode of infection within 6 months prior to TIPS and those without a history of infection preceding the procedure.

METHODS

A retrospective chart review was performed on all patients who underwent TIPS procedure at the Banner – University Medical Center Phoenix between January 2010 and April 2018. The study was approved by the local Institutional Review Board (IRB). All patients had a polytetrafluoroethylene covered Viatorr© stent (WL Gore, Flagstaff, Arizona, USA). Patients' clinical characteristics, including demographics, laboratory tests before and after the procedure, cause of portal hypertension, and the indication for TIPS placement, were collected. Data on episodes of infection (bacterial or fungal) in the 6 months prior to TIPS, complications of the procedure, and outcomes post-TIPS were also collected. The information was derived from the patients' electronic medical records. The laboratory tests conducted closest to the day of the procedure were utilised for the tables and the MELD-Na score calculations.

Prior to the TIPS procedure, and in addition to routine clinical history, physical exam, and laboratory tests, all patients had an ECG to make sure the ejection fraction was normal. In addition, all patients had a CT or MRI to evaluate the anatomy of the liver and its vascular structures, as well as to exclude the possibility of liver cancer. Upon discharge after TIPS insertion, the patients were instructed to return to the radiology department for a Doppler ultrasound to check for TIPS patency 1–2 weeks after discharge. If any possible complications of the procedure were identified at that point, the patients were either admitted to the hospital or referred to the hepatology clinic for an appointment.

During the study period, there were 402 patients who underwent TIPS and were divided into two groups: those who had no infection during the 6 months prior to TIPS (n=349), and those

who did have an episode of infection (bacterial or fungal) during the 6 months preceding the procedure (n=53).

The diagnosis of infection, both prior to and after TIPS, was based on clinical data, laboratory tests, and imaging results that when combined prompted the admitting doctors to start antibiotic therapy. Patient demographic and baseline clinical characteristics in those with and without infection 6 months prior to the TIPS procedure were reported as means, standard deviations for continuous variables, and frequencies and percentages for categorical variables. The 6-month period was chosen arbitrarily as a period that would capture infections that could possibly interfere with the outcome of the TIPS procedure. The Wilcoxon rank-sum test was used to compare continuous variables between the groups, while chi-squared analysis and Fisher's exact test were used to compare the categorical variables. Logistic regression was implemented to ascertain the odds of clinical outcomes relative to pre-TIPS infection status with patients with no infection as a reference group. All models were adjusted for age, sex, race, pre-TIPS and post-TIPS lab values, dialysis, and pre-TIPS PSE statuses. All p values were two-sided and $p<0.05$ was considered statistically significant. All analyses were conducted using STATA version 14© (STATA Corp; College Station, Texas, USA).

RESULTS

The group of patients that had an infection during the 6 months prior to TIPS was referred to as Group A, and the group of patients that did not have an infection during the 6 months prior to TIPS was referred to as Group B.

The two groups were similar in the distribution of age, sex, and ethnicity. The mean age in years for Group A was 56.9 and for Group B was 57.7 (p=0.67). Group A consisted of 60.4% males and Group B was 61.4% males (p=0.88). In Group A, 84.3% of the patients were Caucasian (27.0% Hispanic), 3.9% were African American, and 11.8% were American Indian or Alaska Native. In Group B, 88.1% were Caucasian (27.7% Hispanic), 0.6% were African American, 3.0% were Asian American, and 10.3% were American Indian or Alaska Native. There was no statistically significant difference between ethnicity or race between the two groups (p=0.2).

The aetiology of liver disease was also very similar in the two groups. Hepatitis C, alcoholic liver disease, and nonalcoholic fatty liver disease were the most common aetiologies of portal hypertension in both groups. In Group A, the aetiology of liver disease was hepatitis C in 33.3% of the patients, 31.9% had alcoholic liver disease, 20.3% had nonalcoholic fatty liver disease, 4.4% had autoimmune hepatitis, 2.9% had primary biliary cholangitis, 1.5% had haemochromatosis, and 13.0% had other causes of liver disease, with some patients having more than one aetiology. The aetiology of the liver disease in Group B was 31.6% hepatitis C, 39.9% alcoholic liver disease, 19.2% nonalcoholic fatty liver disease, 3.1% autoimmune hepatitis, 2.5% primary biliary cholangitis, 1.2% haemochromatosis, 0.6% α-1-antitrypsin deficiency, 0.6% hepatitis B, 0.3% hepatocellular carcinoma, and 13.6% had other causes of liver disease. Some patients also had more than one aetiology. The only statistically significant difference in aetiology between the two groups was for alcoholic liver disease, which was more common in Group B, patients who did not have an infection in the 6 months prior to TIPS (p=0.019).

The indications for TIPS placement were also comparable between the two groups (Table 1), except for patients requiring TIPS for both ascites and hepatic hydrothorax, which was more frequently seen in patients in Group A (11.3% of the patients in Group A and 4.5% of patients in Group B [p=0.045]).

Table 2 shows the laboratory tests, results, and the MELD-Na of the two groups before and after TIPS. Prior to TIPS, the patients in Group A had a statistically significant higher MELD-Na score, with a lower serum sodium and higher international normalised ratio, creatinine, and total bilirubin. However, the difference in serum albumin and the percentage of patients who required haemodialysis were not significantly different amongst the two groups. In the post-TIPS laboratory tests, the MELD-Na and creatinine remained higher in Group A. The serum sodium, total bilirubin, and albumin were different between the groups, but the differences were not statistically significant. However, the percentage of patients requiring dialysis post-TIPS was significantly higher in Group A.

Table 3 depicts the rate of complications of TIPS in the two groups. Before TIPS, PSE was seen in 52.8% of the patients in Group A and in 32.1% of the patients in Group B. After TIPS, 54.7% (n=29) of patients in Group A and 39.6% (n=134) of patients in Group B had PSE (p=0.046; odds ratio [OR]: 1.93). Of the patients in Group A, 26.4% (n=14) had an infection post-TIPS, whereas 16.2% (n=55) of patients in Group B had an infection post-TIPS (p=0.047; OR: 2.08). Except for PSE and infection, there were no statistically significant differences between the two groups for other complications of TIPS including hospitalisation within 90 days, acute kidney injury requiring haemodialysis, procedural haemorrhage, gastrointestinal haemorrhage, respiratory complications, or death.

DISCUSSION

The TIPS procedure is the leading portosystemic shunt performed in the USA. With 4.5 million adults in the USA diagnosed with liver disease, many of whom will develop cirrhosis and its complications, it is crucial to better delineate the complications of the procedure and potential risk factors associated with those complications.[22,23] While there are known risk factors for some specific complications of TIPS, there are limited data about if and how an infection pre-TIPS affects patients post-TIPS. This is an important factor to consider because infection, whether bacterial or fungal, is a potentially modifiable risk factor.

Prior to the data collection, the authors hypothesised that an episode of infection (fungal or bacterial) pre-TIPS placement would cause an increase in the number of infections after the procedure, and that an episode of infection prior to the procedure had the potential to increase the rate of other complications of TIPS. These results confirmed the hypothesis that infection pre-TIPS increased the risk of infection post-TIPS, with post-TIPS infection seen in 26% of the patients in Group A, compared with 16% of the patients in Group B. This difference was statistically significant. Logistic regression was used to ascertain the odds of clinical outcomes relative to pre-TIPS infection status, with patients with no infection as the reference group.

Table 1: Indications for TIPS in patients with versus those without infection in the 6 months prior to TIPS placement.

Variables	Group A n=66	Group B n=387	p value
Indications n (%)			
Acute variceal bleeding	22 (42.0)	123 (35.0)	0.37
Ascites	21 (40.0)	122 (35.0)	0.5
Hydrothorax	3 (6.0)	15 (4.0)	0.71
Ascites and hydrothorax	6 (11.0)	16 (5.0)	0.045
Oesophageal variceal bleeding not responsive to banding	2 (3.0)	15 (4.0)	1
Non-bleeding gastric varix	4 (8.0)	25 (7.0)	1
Portal vein thrombus	7 (13.0)	64 (18.0)	0.36
Budd–Chiari	1 (2.0)	6 (2.0)	1
Hepatorenal	0 (0.0)	1 (0.3)	1

p values were calculated using the Wilcoxon rank-sum test to compare continuous variables. Chi-squared and Fisher's exact were used to compare categorical variables. The number of patients listed in the table is greater than the total number of patients enrolled in the study because patients may have had multiple indications for TIPS.

Group A: patients that had an infection during the 6 months prior to TIPS.

Group B: patients that did not have an infection during the 6 months prior to TIPS.

TIPS: transjugular intrahepatic portosystemic shunt.

Table 2: Laboratory values pre-TIPS and post-TIPS in patients with versus those without infection in the 6 months prior to TIPS placement.

Variables	Group A n=53	Group B n=349	p value
Pre-TIPS			
Haemoglobin (mean, SD)	9.33 (+/-2.31)	10.00 (+/-2.39)	0.03
INR (mean, SD)	1.87 (+/-0.83)	1.57 (+/-0.81)	<0.001
Dialysis (yes, %)	4 (+/-7.55)	11 (+/-3.20)	0.12
Creatinine (mean, SD)	1.44 (+/-0.89)	1.19 (+/-0.98)	0.003
Albumin (mean, SD)	2.65 (+/-0.74)	2.73 (+/-0.72)	0.44
Total bilirubin (mean, SD)	4.03 (+/-6.29)	2.56 (+/-3.55)	0.006
Sodium (mean, SD)	135.8 (+/-5.63)	137.7 (+/-5.53)	0.026
MELD-Na (mean, SD)	21.8 (+/-9.70)	16.8 (+/-6.99)	<0.001
Post-TIPS			
Haemoglobin (mean, SD)	9.25 (+/-1.70)	9.85 (+/-1.97)	0.02
INR (mean, SD)	1.96 (+/-0.70)	1.71 (+/-0.59)	0.004
Dialysis (yes, %)	6 (+/-11.80)	11 (+/-3.24)	0.015
Creatinine (mean, SD)	1.29 (+/-0.75)	1.12 (+/-1.00)	0.005
Albumin (mean, SD)	2.49 (+/-0.61)	2.60 (+/-0.66)	0.18
Total bilirubin (mean, SD)	4.69 (+/-5.56)	3.75 (+/-4.66)	0.27
Sodium (mean, SD)	138.2 (+/-5.46)	139.3 (+/-5.57)	0.21
MELD-Na (mean, SD)	22.4 (+/-8.80)	18.7 (+/-6.81)	0.006

p values were calculated using the Wilcoxon rank-sum test to compare continuous variables. Chi-squared and Fisher's exact were used to compare categorical variables.

Group A: patients that had an infection during the 6 months prior to TIPS.

Group B: patients that did not have an infection during the 6 months prior to TIPS.

INR: international normalised ratio; MELD-Na: model of end stage liver disease-sodium; SD: standard deviation; TIPS: transjugular intrahepatic portosystemic shunt.

An episode of infection within 6 months of TIPS placement was a predictor of post-procedure infection (p=0.047; OR: 2.08).

In 2016, Deng et al.[24] looked at risk factors associated with early infection following TIPS procedure. The authors identified cholangiolithiasis, Child–Pugh Class C, and hepatitis C virus infection to be correlated with fever post-TIPS. This finding was statistically significant. There was no correlation between infection and factors such as age, sex, and diabetes. Episodes of infection before TIPS as possible predictors of post-TIPS infection were not included.[24]

In a more recent publication, Vozzo et al.[25] looked at 30-day readmission after TIPS placement and found that 36% of the patients were readmitted to the hospital. In their study, the authors identified the most common reasons for admission as hepatic encephalopathy (48%), infection (15%), bleeding (11%), and fluid overload (7%). The percentage of patients who were readmitted because of infection were similar to that of the patients in this present study who had no episodes of infection in the 6 months prior to TIPS placement. However, in the study by Vozzo et al.,[25] the authors did not comment on whether or not the patients readmitted because of infection had previously had an episode of infection prior to TIPS placement.

Table 3: Complication of TIPS procedure in patients with versus those without infection in the 6 months prior to TIPS placement.

Outcomes	Group A n=53	Group B n=349	OR (95% CI)	p value
Hospitalisation within 90 days (yes, %)	31 (62.0)	181 (53.4)	1.43 (0.74–2.99)	0.25
PSE (yes, %)	29 (54.7)	134 (39.6)	1.93 (1.01–3.70)	0.046
Post-TIPS infection (yes, %)	14 (26.4)	55 (16.2)	2.08 (1.01–4.29)	0.047
AKI Req HD (yes, %)	5 (9.4)	27 (8.0)	0.17 (0.02–1.38)	0.09
Procedural haemorrhage (yes, %)	0 (0.0)	13 (3.9)	N/A	
Gastrointestinal haemorrhage (yes, %)	8 (15.1)	33 (9.8)	2.32 (0.71–7.55)	0.15
Respiratory complication (yes, %)	11 (20.8)	67 (22.6)	0.26 (0.05–1.32)	0.1
Other (yes, %)	6 (11.5)	58 (17.2)	0.79 (0.22–2.81)	0.71
Death (yes, %)	17 (32.1)	82 (24.2)	1.08 (0.51–2.31)	0.83

Odds ratios and 95% confidence intervals were calculated using multiple logistic regression adjusting for pre-TIPS and post-TIPS lab values, dialysis, and PSE Pre-TIPS.

Group A: patients that had an infection during the 6 months prior to TIPS.

Group B: patients that did not have an infection during the 6 months prior to TIPS.

AKI Req HD: acute kidney injury requiring haemodialysis; PSE: portosystemic encephalopathy; TIPS: transjugular intrahepatic portosystemic shunt.

In a study from Allaire et al.[26] presented at the European Association for the Study of Liver (EASL) meeting in 2019, the authors reported the survival and risk factors of mortality after emergency TIPS for uncontrolled acute variceal bleeding in patients with cirrhosis and portal hypertension.

In this specific subset of patients, sepsis was the cause of mortality in 8% of the 73 patients included. Moreover, despite the fact that all patients received antibiotic prophylaxis (as part of the standard of care treatment of cirrhotic patients hospitalised for acute variceal bleeding), 42% of patients developed an in-hospital infection, including multi-drug resistant bacteria (23%). The authors did not mention whether any of the patients who developed infection post-TIPS placement had previously had an episode of infection prior to the procedure.[26]

While none of the aforementioned studies stated whether an episode of infection in the months prior to TIPS placement increased the risk of infection post-TIPS procedure, they all documented infection as a common and serious complication seen in patients who had TIPS.

The MELD-Na (and some of the tests used to calculate the MELD-Na) score was higher in the group of patients who had an infection before the TIPS. This indicates that the group of patients who had an episode of bacterial or fungal infection before TIPS had more advanced liver disease. Therefore, the fact that the MELD-Na score in this group remained higher after the TIPS placement was not surprising. Similarly, the fact that there was a higher percentage of patients in Group A who had PSE prior to TIPS was also expected, given the fact that infection is one of the well-known triggers of PSE.[27]

Whether the higher MELD-Na or the previous infection determined the higher number of infections post-TIPS cannot be entirely determined because patients with a higher MELD score, by

definition, have more advanced stages of the liver disease, and are therefore more likely to develop any of the complications of cirrhosis, including infection. However, this fact does not weaken the value of the results; in fact, it is likely that both a high MELD score and a history of infection in the 6 months prior to TIPS increase the risk of infection after the procedure. An episode of PSE pre-TIPS as a predictor of post-TIPS PSE has also been previously described.[14,25]

Conversely to what was hypothesised by the authors, despite the higher frequency of post-TIPS infection and post-TIPS PSE in Group A, the frequency of other complications of TIPS procedure, particularly hospitalisation, the need for TIPS revision, the need for liver transplant, or death, was not affected. Since this was a retrospective chart review study, this finding cannot be attributed to any specific measure intentionally taken. However, these results may be used as an alert. When deciding on TIPS placement in a patient who had an infection in the 6 months preceding the procedure, closer attention must be paid to early signs and symptoms of infection post-TIPS.

This study has some limitations: it lacks detailed information about which types of infection the patients had, the duration of the episodes, whether or not there were any infections by multi-drug resistant organisms, and the exact time from infection to TIPS placement. In addition, information in regard to hospitalisations and other comorbidities that could have increased the risk of infection is also missing.

Despite these limitations, these results offer valuable information for the clinician treating patients with portal hypertension. The finding that an episode of infection in the 6 months preceding TIPS is related to post-TIPS infection, to the authors' knowledge, has not been previously described. This observation brings important considerations when treating this patient population. The first is the possibility of, whenever feasible, delaying the TIPS placement until possible infections have been ruled-out, and when present, treated. Secondly, while use of antibiotics must always be judiciously evaluated, further studies are warranted to consider the possible benefit of antibiotic prophylaxis to prevent post-TIPS infection in patients with a history of infection in the 6 months preceding TIPS placement, particularly those with a higher MELD-Na score. In addition, given the fact that an episode of infection prior to TIPS increases the risk of both PSE and infection post-TIPS, these results also highlight the importance of educating patients and care givers about the further increase in the risk of PSE post-TIPS in those with a history of infection prior to TIPS placement.

Finally, while no episodes of infection of the TIPS shunt itself (tipsitis) were diagnosed during the study period, pre-TIPS infection is a possible risk factor of tipsitis. This is particularly important to consider in those patients who are not candidates for liver transplant because treatment options for tipsitis are limited to orthotopic liver transplantation or lifetime antibiotics, as an infected TIPS shunt cannot be removed.[5,15]

CONCLUSION

Comparing patients with an episode of infection in the 6 months prior to TIPS placement (Group A) and those with no infection in the 6 months preceding TIPS (Group B), a statistically significant increased frequency of post-TIPS infection in patients in Group A compared to Group B was found (26.4% versus 16.2%). Using regression analysis, pre-TIPS infection was a predictor of post-TIPS infection (p=0.047; OR: 2.08). It was also discovered that there was an increased frequency of post-TIPS PSE in Group A versus Group B. In Group A, 54.7% (n=29) of the patients had an episode of PSE post-TIPS versus 39.6% (n=134) in Group B (p=0.046; OR: 1.93). This finding was not surprising, given the well-known fact that infection is a trigger of PSE. However, it underscores the importance of educating patients and care givers about the further increased risk of PSE after TIPS placement. While these findings did not correlate with the frequency of other complications of TIPS procedure, namely hospitalisation within 90 days, acute kidney injury requiring haemodialysis, procedural haemorrhage, gastrointestinal haemorrhage, respiratory complications, or death, these results serve as an alert to the possibility of other complications of TIPS in this specific population. In addition, the results pave the path for further studies to determine the potential benefit of antibiotic prophylaxis in patients who had an episode of infection in the 6 months preceding TIPS placement.

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Cholangioscopy and its Role in Primary Sclerosing Cholangitis

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: Dr Fung reviewed the literature for relevant original studies and other content, designed and formatted the figures, and drafted the manuscript. Dr Tejaswi and Dr Tabibian assisted with image acquisition. Dr Fejleh, Dr Tejaswi, and Dr Tabibian critically reviewed the manuscript. All authors provided critical input and approved the final version of the manuscript. This work was completed in part through the United States National Institutes of Health (NIH) grants T32 DK007198 and UL1 TR000135.

Received: 31.01.20

Accepted: 19.03.20

Keywords: Biliary stricture, cholangiocarcinoma (CCA), cholangioscopy-guided biopsy, cholangioscopy-guided lithotripsy, dominant stricture, peroral cholangioscopy (POC), single-operator cholangioscopy (SOC).

Citation: EMJ Hepatol. 2020;8[1]:42-53.

Abstract

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterised by chronic inflammation and fibro-obliteration of the intrahepatic and/or extrahepatic bile ducts. It is associated with numerous hepatobiliary complications including an increased risk of malignancy (in particular, cholangiocarcinoma) and biliary tract stone formation. The evaluation of biliary strictures in patients with PSC is especially challenging, with imaging and endoscopic methods having only modest sensitivity for the diagnosis of cholangiocarcinoma, and treatment of biliary strictures poses a similarly significant clinical challenge. In recent years, peroral cholangioscopy has evolved technologically and increased in popularity as an endoscopic tool that can provide direct intraductal visualisation and facilitate therapeutic manipulation of the biliary tract. However, the indications for and effectiveness of its use in patients with PSC remain uncertain, with only a few studies performed on this small but important subset of patients. In this review, the authors discuss the available data regarding the use of peroral cholangioscopy in patients with PSC, with a focus on its use in the evaluation and management of biliary strictures and stones.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, idiopathic, cholestatic liver disease characterised by intrahepatic and/or extrahepatic bile duct strictures and destruction.[1,2] It is usually diagnosed based on a combination of persistent cholestatic liver test abnormalities and cholangiography via endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography showing characteristic multifocal strictures and proximal ductal dilation.[3-5] PSC is also associated with many hepatobiliary complications, including an especially high risk of developing cholangiocarcinoma (CCA), estimated to be 400–1,500 times higher than in the general population.[6-9] As a result, accurate diagnosis of biliary strictures in patients with PSC is of particularly high importance. In fact, the most common indication for endoscopic intervention in patients with PSC is to evaluate and treat 'dominant strictures' seen on either initial workup for PSC or routine surveillance in patients with an established diagnosis of PSC.[3,10]

For decades, ERCP, which relies on the use of fluoroscopy to image the biliary tree, has been the primary tool for evaluation of indeterminate strictures and other pancreaticobiliary pathology in patients with and without PSC. Other imaging modalities, such as CT and magnetic resonance cholangiopancreatography are often inadequate due to insufficient resolution, artefact, and/or the inability to acquire tissue specimen. During ERCP, intraductal brushings are often performed for cytology in order to make a diagnosis; however, the sensitivity of brushings for biliary pathology is low and limited by the poor cellular yield. This stems from the desmoplastic nature of many biliary tract neoplasms (particularly in the setting of PSC) and the inability to directly visualise a lesion while brushing, among other factors.[11,12] Other endoscopic modalities, such as endoscopic ultrasound and probe-based confocal laser endomicroscopy, have been used as ancillary means of evaluating indeterminate biliary strictures; however, these modalities have their respective limitations and have generally not seen wide uptake in clinical practice.[4]

Over the years, another diagnostic and therapeutic method, cholangiopancreatoscopy, has been developed and refined, allowing for direct visualisation of and therapeutic manipulation within the pancreaticobiliary ducts. This technique was first described as early as 1941 in the surgery literature as an intraoperative method to exclude choledocholithiasis after cholecystectomy.[13] Two decades later, a percutaneous, transhepatic approach was introduced, though this was limited by its invasiveness.[14] Although the percutaneous approach is still used today, the technique has largely been replaced by a peroral approach developed in the 1970s, allowing visualisation of the biliary duct system through peroral endoscopy. Today, there are multiple peroral cholangioscopy (POC) techniques available, each with a different set of advantages and disadvantages. This review discusses the use of POC in patients with PSC, with a focus on its use in the evaluation of biliary strictures and management of biliary stones.

TYPES OF CHOLANGIOSCOPY

'Mother-Baby' Dual Operator Peroral Cholangioscopy

The original peroral cholangioscope, developed in the 1970s, required two operators and is therefore frequently referred to as dual operator POC or 'mother-baby' POC. In this technique, two components are required: a 'mother' duodenoscope and a 'baby' cholangioscope, with one operator controlling the mother duodenoscope and one operator controlling the baby cholangioscope. To evaluate the biliary tree, the cholangioscope is threaded through the working channel of the duodenoscope which serves as a delivery mechanism. The first prototypes were limited by a lack of working channels, irrigation, and tip deflection. However, subsequent prototypes have addressed many of these problems.[15] Two mother-baby POC scope systems are available today for clinical use in the USA; however, both are infrequently used due to the inconvenience of requiring two endoscopists, the fragility of the cholangioscope, and the high cost of repairs.[16]

Single-Operator Peroral Cholangioscopy

In 2005, a single-operator cholangioscopy (SOC) system called the SpyGlass™ Direct Visualization System (Boston Scientific Corp, Natick, Massachusetts, USA) was developed, making POC significantly more feasible and less complex, overcoming many of the shortcomings of previous methods. In this first-generation SOC system (now referred to as SpyGlass Legacy), a 10 French gauge, 230 cm long multichannel disposable access and delivery catheter (SpyScope™) is inserted through the standard working channel of a therapeutic duodenoscope and introduced into the biliary tree with guidewire assistance after traditional ERCP-based biliary access.[17] A reusable fibre optic probe (SpyGlass Direct Visualization Probe) is then advanced through a 0.9 mm diameter channel within the SpyScope catheter, providing 6,000-pixel images with four-way tip manoeuvrability and a 30˚ view in each direction. The access and delivery catheter also features two 0.6 mm irrigation channels and a 1.2 mm working channel through which disposable 3 French gauge biliary biopsy forceps (SpyBite™) or a probe for electrohydraulic or laser-assisted lithotripsy can be inserted. The light source, video monitor, and irrigation pump are all separate components. Although the SpyGlass Legacy made POC feasible in everyday practice, there were still limitations including poor fibreoptic probe durability (rated for 8–10 uses, though lasting only 3–4 times in real life use before having to be replaced), poor image quality and field of view, a small therapeutic channel, as well as an elaborate set up with multiple separate components.[18]

In 2015, Boston Scientific released a second-generation SOC system called the SpyGlass DS Direct Visualization System, with the goal of addressing many of the shortcomings of the previous version. Notably, this new system provides better image quality (with four-times the resolution), a 60% wider field of view, improved manoeuvrability of the catheter tip, and an easier setup (reducing set-up time) compared with the previous generation system (with an integrated light source and processor). The new system also has dedicated irrigation and aspiration connections to clear the field of view and, if desired, obtain specimens.[19] In 2018, a third-generation access and delivery catheter was introduced, called the SpyScope DS II Access & Delivery Catheter. This catheter is advertised to have even higher resolution (2.5-times that of the SpyScope DS), adjusted lighting to reduce light flare, as well as a new SpyGlass Retrieval Basket and SpyGlass Retrieval Snare for the removal of biliary stones and foreign bodies, respectively.[20] There is also a newer and larger forceps, SpyBite Max, which is scheduled to be launched in the USA in 2020 and designed to facilitate acquisition of larger tissue samples.

Direct Peroral Cholangioscopy

In response to the drawbacks of mother-baby scopes, techniques using ultra-slim upper endoscopes (e.g., endoscopes originally designed for use in paediatric and transnasal applications) have been developed. In this technique, an ultra-slim upper endoscope with an external diameter ranging from 5 to 6 mm is advanced freehand or assisted by a guidewire or a balloon catheter to cannulate the biliary papilla.[21,22] Only one operator is required, and many of the newer generation ultra-slim endoscopes provide high-definition images that can be used with narrow-band imaging (NBI) allowing detailed examination of the biliary tree (Figure 1).[23] However, this technique is not without limitations. Cannulation of the bile duct and maintaining access and positioning within the common bile duct can be difficult; thus, specialised accessories and stabilisation techniques (e.g., balloon catheter, overtube balloon, guide probe of Kautz, etc.) have been developed to stabilise the endoscope.[24–27] Another limitation is that the larger outer diameter of these endoscopes requires the bile duct to be dilated (limiting its use in most cases of PSC), and endoscopic sphincterotomy or sphincteroplasty with endoscopic papillary large balloon dilation pretreatment is almost always required, (which is associated with additional risks).[28]

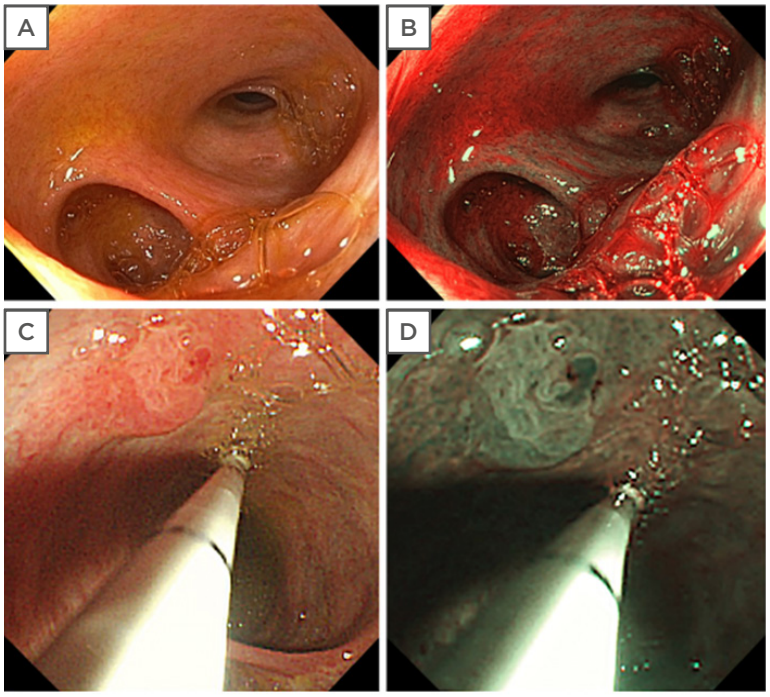

Figure 1: Narrow band imaging (NBI) assists with visualising mucosal features of the biliary tree. Noninflamed, nondysplastic biliary mucosa seen under conventional white light **(A)** and NBI **(B)**. Cholangioscopic evaluation of a perihilar bile duct stricture and lesion with white light **(C)** and NBI **(D)**.
Figure 1D adapted from Tabibian et al.[4]

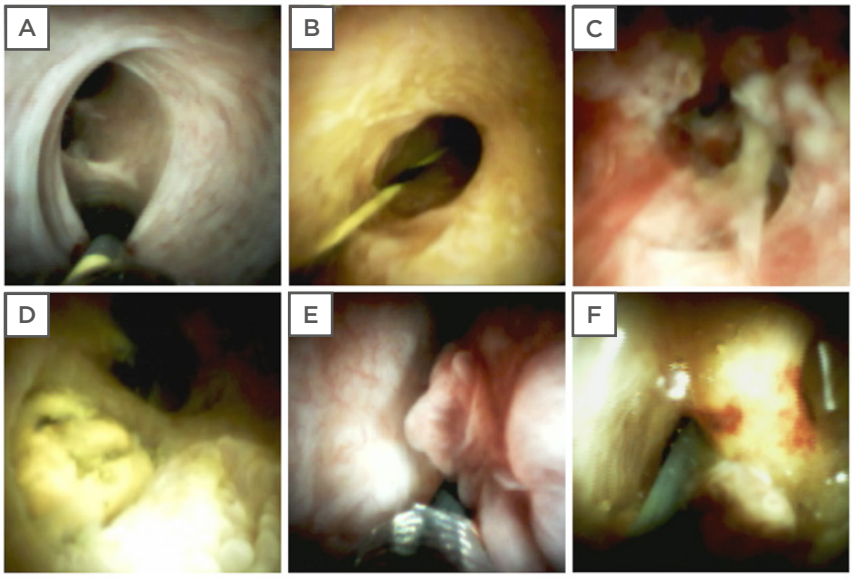

Figure 2: Applications and shortcomings of cholangioscopy illustrated with the SpyGlass™ DS Direct Visualization System.

(A) Cholangioscopy facilitates subselective ductal guidewire cannulation when conventional fluoroscopically-guided means are unsuccessful. **(B)** Visualisation of a benign biliary stricture in PSC. **(C)** Papillary fronds and abnormal vascularity of a perihilar bile duct suggestive of and subsequently proven to be CCA in a patient with PSC. **(D)** Biliary stone cholangioscopically identified at the cystic duct insertion which was subsequently managed with electrohydraulic lithotripsy. **(E)** Villous appearing biliary mucosa with papillary frond-like projections may mimic CCA; in this case, repeated SpyBite™ sampling, intraductal brushings, and additional testing over 2 years of follow-up ruled out malignancy. **(F)** Abnormal intraductal erythema that can be misinterpreted as a sign of dysplasia or malignancy but was in fact caused by reactive changes related to a newly removed plastic biliary stent.

CCA: cholangiocarcinoma; PSC: primary sclerosing cholangitis.

Percutaneous Transhepatic Cholangioscopy

Similar to direct POC, percutaneous transhepatic cholangioscopy provides direct visualisation of the biliary tree for diagnostic and therapeutic interventions. However, this technique requires significant preprocedural planning. In this technique, serial dilation of a tract is performed with subsequent tract maturation (and additional interval tract dilation) over the course of 1 week while an external biliary drainage catheter is left in place.[29] Once adequate drainage is obtained and a mature tract is established, the drainage catheter can be removed over a stiff guidewire and a cholangioscope can be replaced for diagnostic and therapeutic interventions.[29] This technique has several strengths. Once a percutaneous tract is established, multiple subsequent sessions can be performed. Furthermore, by using a shorter cholangioscope (which can increase manoeuvrability), areas that are difficult or impossible to reach via POC can sometimes be reached with percutaneous transhepatic cholangioscopy. Percutaneous transhepatic biliary biopsy can also be performed with high diagnostic accuracy.[30–32] However, this procedure is time-consuming and has a notable risk of adverse events, including haemobilia, cholangitis, bacteraemia, bile duct injury, and tumour seeding via the sinus tract.[33] As such, POC has largely replaced the use of percutaneous transhepatic cholangioscopy.[34] However, for patients who are not able to tolerate a peroral endoscopic procedure (e.g., those with altered oropharyngeal or gastrointestinal anatomy), percutaneous transhepatic cholangioscopy remains a viable option. Further discussion of this technique, so far not described in the context of underlying PSC, is beyond the scope of this review but can be found elsewhere.[35]

THE NEED FOR ENDOSCOPIC BILIARY INTERVENTION IN PRIMARY SCLEROSING CHOLANGITIS

Because of the chronic, progressive, and variable nature of PSC, its high risk for biliary complications, and the often incomplete evaluation with imaging modalities alone, endoscopy plays a large diagnostic and therapeutic role in the management of patients with this disease. Indications for biliary endoscopy include the evaluation of dominant strictures, treatment of biliary strictures, treatment of biliary stones, intraductal foreign body retrieval (e.g., retained stent), and palliation of associated CCA. For the purposes of this concise review, and considering clinical relevance as well as available literature, the following sections focus on the evaluation of dominant strictures and treatment of biliary stones (Figure 2).

Dominant Strictures

Patients with PSC have a high propensity to develop dominant strictures, with an estimated prevalence of 36–57%.[36–38] These strictures are defined as a stenosis of ≤1.5 mm diameter in the common bile duct or ≤1.0 mm diameter in the hepatic duct within 2.0 cm of the hepatic ductal confluence and are associated with poorer long-term outcomes.[3,36,39] In a 25-year longitudinal study of 128 patients with PSC, the mean survival of patients with dominant strictures was almost one-half of those without dominant strictures (13.7 versus 23.0 years).[40] This significant difference in survival is thought to be attributable to a combination of factors, including: 1) a high proportion of dominant strictures contain CCA;[6,7] 2) the lack of identifiable predictors for identifying CCA in patients with PSC;[7,9] 3) the lack of specific symptoms in early stages;[2] and 4) the aggressiveness of CCA, with one study finding 80% of patients dying after a median period of 1 year.[6] For these reasons, accurate and early differentiation between benign and malignant strictures is important for patients with PSC. Dominant strictures also frequently require therapeutic endoscopic interventions. Endoscopic balloon dilation is commonly performed for benign biliary strictures, while stent placement can be considered for strictures refractory to balloon dilation or for malignant strictures (i.e., CCA).[2] A recent study has found that scheduled endoscopic dilation of dominant strictures is associated with a longer median liver-transplantation-free survival time compared with on-demand endoscopic treatment (17.9 versus 15.2 years), reinforcing the importance of early intervention.[41]

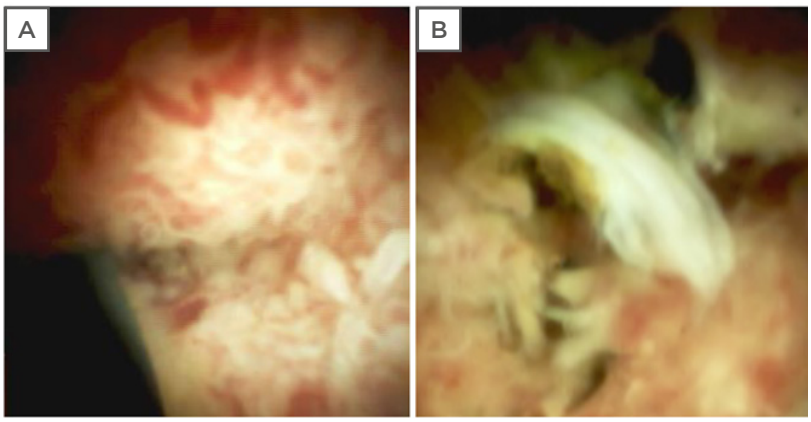

Figure 3: Identification of cholangiocarcinoma using cholangioscopy.

(A) Cholangiocarcinoma appearing as a mass growing into the lumen with associated tumour vessels in a patient without primary sclerosing cholangitis. **(B)** Cholangiocarcinoma appearing as an irregular growth with exudates, mucosal erythema, and luminal narrowing, without apparent classic tumour vessels in a patient with primary sclerosing cholangitis.

A classification system of extrahepatic PSC phenotypes called the Edmonton Classification has also been proposed as a way to describe and help providers with the management of dominant strictures in PSC.[42]

Biliary Stone Disease

Patients with PSC appear to have a high incidence of biliary stones frequently requiring endoscopic biliary intervention. Two retrospective studies of patients with PSC found that over 51% and 56% of patients with PSC who underwent ERCP and cholangioscopy, respectively, had a stone.[43,44] Furthermore, one of the studies found that one-third of stones were missed on cholangiography.[44] Unlike the general population in whom extrahepatic bile duct stones are relatively common and intrahepatic bile duct stones are rare, patients with PSC appear to develop stones in both locations with relatively high frequency,[45] thus making stone extraction with conventional ERCP more difficult in many cases (particularly for intrahepatic stones).

CHOLANGIOSCOPY IN PRIMARY SCLEROSING CHOLANGITIS

Evaluation of Indeterminate Strictures

Over the years, endoscopists have found that POC can be helpful in the evaluation of indeterminate strictures.[46-49] Summarised here are the various aspects of POC as reported in the published literature. However, the available literature must be interpreted with caution, as many studies have considerable limitations (e.g., false-negative classification, lack of comparisons to a gold standard such as pathology, limited duration of follow-up, etc.) and/or only a small proportion of their respective samples comprised patients with PSC.

Cholangioscopic Visual Assessment

Visual assessment of a stricture using POC has previously been suggested as a sensitive method for diagnosing malignancy in patients without PSC.[50] For patients with PSC, the use of visual assessment is more unclear. Due to the very nature of the disease, patients with PSC often have significant inflammation and fibrosis of the bile ducts (Figure 3), limiting the ability to transverse and adequately access biliary strictures.[51] Visual assessment in patients

with PSC is also more difficult than in patients without PSC, as it is more difficult to evaluate strictures arising in a background of ductal inflammation and scarring (which itself can mimic changes of CCA) as compared to normal biliary epithelium (where CCA is generally a focal problem without the added diagnostic and therapeutic challenges of a diffusely diseased biliary tree).[52] A prospective study with 47 patients with PSC found that visual assessment during POC was unable to distinguish between benign and malignant strictures.[53] However, it should be noted that the vast majority of studies have been performed with the previous generation of POC, which was limited by a suboptimal image quality; current generation digital SOC (i.e., SpyGlass DS) offers superior views, which may aid in both visual diagnosis and targeting biopsies. A prospective trial is currently underway with the aim of evaluating the performance of SpyGlass DS in the diagnosis and early detection of CCA in patients with PSC.[54]

The utility of cholangioscopic assessment in PSC may also vary based on the specific type of CCA. One study reported that PSC has two distinct pathways of carcinogenesis, one of which has been classified as the intestinal type (a subtype that is unique to PSC and is not reported to occur in the absence of PSC), and the other is called the classical type.[55] The intestinal type is predominantly seen in the hilum or secondary biliary radicles, making them well within reach of the cholangioscope. These tumours also have a distinct morphology, characterised by intraductal papillary growths with associated mucinous nodules, a pattern that is seen in cases of intraductal papillary neoplasms of the bile ducts, and can be recognised by experienced cholangioscopists. Furthermore, this type of CCA has a distinct immunohistochemical pattern that can help differentiate it from active inflammation, allowing one to overcome interobserver (both endoscopist and pathologist) variability and reduce uncertainty in the diagnosis of CCA in the setting of active inflammation or reactive mucosal changes secondary to previous stenting or balloon dilation of strictures. Future studies can determine if this type of cancer or premalignant changes can be identified based on visual assessment and immunohistochemical staining of SOC-directed biopsies. The second type of CCA described in PSC is the classical nonintestinal type that is more invasive and more difficult to detect by cholangioscopy, and therefore has a worse prognosis than intestinal type CCA. This too requires further research with the improved generation of cholangioscopes and larger biopsy forceps.

Cholangioscopically-Guided Biopsies

A systematic review and meta-analysis of 15 studies found the sensitivity and specificity of cholangioscopy-directed biopsies in all-comers (i.e., not limited to patients with PSC) to be 71.9% (95% confidence interval [CI]: 66.1–77.1%) and 99.1% (95% CI: 96.9–99.9%), respectively, with a positive and negative likelihood ratio of 18.1 (95% CI: 9.1-35.8) and 0.3 (95% CI: 0.2-0.4), respectively.[46] Summary receiver operating characteristic curves showed an area under the curve of 0.98, concluding that cholangioscopy-directed biopsies can be useful in the evaluation of indeterminate biliary strictures. Other systematic reviews have found similarly positive results.[47–49] However, the majority of these studies have not evaluated the effectiveness of POC in patients with PSC, a subset of patients with a particularly high rate of malignancy, a high rate of biliary stones, and particularly difficult biliary anatomy (caused by the prevalence of strictures making passage of the cholangioscope into the bile duct particularly challenging).[56] The following section describes the limited available data on the use of POC in patients with PSC.

In 2006, Awadallah et al.[44] published the first series of patients with PSC undergoing POC for the evaluation of dominant strictures and cholangioscopy-directed stone therapy. In this series of 41 patients, the authors found that POC-guided biopsies appeared to be helpful in excluding biliary malignancy (and provided a high rate of adequate tissue samples), but the study was limited by the small number of patients with a diagnosis of CCA (n=1). Over the past decade, additional studies have been performed, showing promising results. A study by Tischendorf et al.[57] found that POC was superior to ERCP for detecting malignancy in terms of its specificity (93% versus 51%), accuracy (93% versus 55%), positive predictive

value (79% versus 29%), negative predictive value (97% versus 84%), and a trend towards better sensitivity (92% versus 66%, though this was not statistically significant). Another study supporting the use of POC in patients with PSC found that in 21 patients who underwent POC prior to liver transplantation, POC during a second ERCP improved the sensitivity and specificity (100% and 97%, respectively) for detection of CCA or high-grade dysplasia after an initial ERCP with conventional brush cytology.[58] A systematic review with meta-analysis of ERCP-based modalities for the diagnosis of CCA in PSC found that SOC with targeted biopsies appeared to be the most accurate ERCP-based modality for diagnosing CCA in PSC, with a pooled sensitivity and specificity of 65% (95% CI: 35–87%) and 97% (95% CI: 87–99%), respectively, for the diagnosis of CCA.[59] Furthermore, Kalaitzakis et al.[56] found that sensitivity, specificity, and accuracy of POC for malignancy may be similar in patients with and without PSC (50% versus 55%, 100% versus 97%, and 88% versus 80%, respectively).

Other studies have found more modest outcomes for the use of POC.[60] In a retrospective cohort study of 92 patients, of which 36 patients had PSC, SOC-guided biopsy combined with cytology and fluorescent *in situ* hybridisation demonstrated statistically significant improvement in sensitivity compared to conventional brush cytology alone (71.4% versus 44.7%; p=0.03).[61] However, a similar improvement was not seen when restricting the analyses to the subset of patients with PSC (63.6% versus 50.0%; p=1). Moreover, a recent retrospective single-centre study of patients who underwent POC for indeterminate strictures (of which 40% had PSC) found that the diagnostic accuracy of POC was inferior to brush cytology and had low impact on patient management.[62] A prospective study of 30 patients undergoing POC with NBI found that NBI use lead to a 48% increase in suspicious lesions biopsied, but did not improve the dysplasia detection rate.[63] Additional studies, including studies with the soon-to-be launched SpyBite Max forceps, are needed to better characterise the performance characteristics of POC.

Considerations in and Limitations of Cholangioscopy in the Evaluation of Indeterminate Strictures

The utility of POC is also dependent on its success rate and ease of use. In a retrospective study of 165 patients undergoing SOC (of which 16 patients had PSC), it was reported that while POC appeared to be useful for the evaluation of indeterminate biliary lesions and difficult biliary stones in patients without PSC, the technique was associated with a lower procedure success rate (59% versus 92%) and lower rate of bile duct cannulation (82% versus 97%) in patients with PSC compared to patients without PSC, as alluded to earlier.[64] POC also increases procedure times, with one study finding the mean total procedure time of ERCP plus POC to be 45 minutes, of which 20 minutes was spent on POC.[52] While the increased procedure time and additional equipment increases costs, it remains unclear whether POC leads to cost savings in the long run; one study at two Belgian academic hospitals found the use of POC for stricture diagnosis to decrease the number of procedures by 31% and costs by 5% compared with the use of ERCP alone.[65] However, it should be noted that these studies report on the older legacy system, and set-up time for the newer SpyGlass DS system is significantly shorter.

Despite the aforementioned limitations and suggested modest sensitivity for malignancy, POC may also play other roles in patients with PSC. In a study on the impact of SOC on patient outcomes, SOC was noted to lead to changes in the management of nine out of 13 patients (69%) with PSC (despite having a moderate sensitivity), and helped to avoid unnecessary hepatobiliary resection in seven patients.[66] The use of POC also appears to facilitate obtaining greater quantities of tissue specimen[63,67] and can provide a more accurate diagnosis of inflammatory changes than brush cytology.[67]

Cholangioscopic Treatment of Biliary Stones

POC is now commonly used for the treatment of biliary stones. A recent systematic review and meta-analysis of 24 studies found the rate of stone clearance with POC to be 94.3% (95% CI: 90.2–97.5%), with 71.1% of patients achieving

stone clearance in a single session.[68] Another systematic review and meta-analysis of 33 studies found a similarly high stone clearance rate of 88% (95% CI: 85–91%), and the authors concluded that POC is a safe and effective method for the treatment of bile duct stones when conventional methods have failed.[47] However, the aforementioned studies are not specific to patients with PSC.

Data on the performance and outcomes of POC for the treatment of biliary stones in patients with PSC are limited. In a prospective study of 41 patients who underwent POC to evaluate dominant strictures or stones, 23 (56%) patients had stones, of which seven (30%) were missed with cholangiography and only detected by POC.[44] Seven of nine (78%) patients who underwent POC-directed lithotripsy had complete clearance while only three of eight (38%) patients who underwent conventional methods of stone extraction had complete clearance. In another prospective study of 32 patients (with and without PSC) who underwent POC-directed lithotripsy, four of eight (50%) patients with PSC had stones detected by POC that were missed by cholangiography, and six of eight (75%) patients with PSC had complete stone clearance (two had partial clearance).[69] Of the four patients with recurrent stones, three had PSC. Based on the limited data available, POC-directed lithotripsy appears to be helpful for patients with PSC (and possibly cost-effective),[65] though more data are needed before any definitive guidance can be provided.

Treatment of Biliary Strictures and Cholangiocarcinoma

In recent years, the use of POC has been described for the treatment of biliary strictures and malignancy (which, as previously stated, is more frequent in patients with PSC). However, data are primarily limited to case report descriptions, and there are no available studies evaluating its effectiveness specifically in patients with PSC. Nevertheless, discussed below are several recently described indications.

Biliary tract obstruction is traditionally treated with balloon dilation and/or stent placement via ERCP, with the former favoured for benign strictures and the latter for malignant strictures.[70] However, either of these approaches can sometimes be challenging because of the inability to pass a guidewire through the obstructed segment and into a target duct. Bokemeyer et al.[71] recently noted that POC appeared to be helpful in selective guidewire placement, especially across benign strictures.[71] In several reports, POC has also been shown to be helpful in the removal of intraductal foreign bodies (e.g., retained stents).[72–74] In addition, POC may play a role in radiofrequency ablation (RFA) of biliary malignancies. RFA is a technique that delivers thermal energy to induce local tissue necrosis, typically performed using ERCP guidance, and has been reported to potentially improve survival in patients with malignant strictures.[75] However, it is also associated with considerable adverse events (up to 62%), including significant bleeding, injury to adjacent vascular structures, and perforation, which may be more likely to occur when RFA is performed outside the tumour margin (which can sometimes be difficult to approximate with ERCP alone).[76] By improving localisation of the malignant stricture, POC can help increase the safety and efficacy of RFA.[77–79]

RISKS OF CHOLANGIOSCOPY

POC appears to be a relatively safe procedure with an adverse event rate similar to conventional ERCP alone. In a systematic review and meta-analysis consisting of 45 studies from 2000 to 2016, the pooled adverse event rate for all patients undergoing POC was 7% (95% CI: 6–9%), with an estimated severe adverse event rate of 1% (95% CI: 1–2%).[47] This is comparable to the adverse event rate for ERCP alone; a recent systematic survey estimated an ERCP adverse event rate of 6.85% (95% CI: 6.46–7.24%) and a severe adverse event rate of 1.67% (95% CI: 1.47–1.87%).[80] However, several individual studies have also reported significantly higher adverse event rates with the use of POC, the reasons for which are unclear.[81,82] The most common adverse events are cholangitis (4%), pancreatitis (2%), and perforation (1%) (Table 1).[47,56,71,81-86]

Table 1: Reported adverse events of peroral cholangioscopy.

	Occurrence rate (%)
Common	
Acute cholangitis	0.0–11.0[47,56,71,81-86]
Acute pancreatitis	2.0–8.9[47,56,71,81,82,84-86]
Bacteraemia	8.8[83]
Bleeding	0.0–3.3[71,81,82,84-86]
Abdominal pain	23.8[81]
Rare	
Perforation	0.4–1.0[47,82,84,85]
Cardiopulmonary or sedation-related	0.5[82]
Air embolism	<1.0
CO_2 embolism	<1.0

In addition, POC appears to increase the risk of cholangitis, but the risk may be significantly reduced with peri-procedural administration of antibiotic prophylaxis.[83,84] In the literature, there are also reports of air embolism (caused by the high solubility and reabsorption of air); thus, CO_2 insufflation can be used instead (though case reports of CO_2 emboli with uncontrolled gas insufflation can also be found in the literature).[87,88] Sufficiently large papillary access (e.g., by maximum-incision papillotomy or endoscopic papillary large balloon dilation) may also reduce the risks of air/gas embolism; however, this has not been proven.

While the adverse event rate for POC appears to be similar to conventional ERCP in pooled analyses, it remains controversial whether POC increases the risk of adverse events in patients with PSC. Because strictures often prevent adequate drainage of postcontrast injection as well as the higher frequency of biliary sphincterotomy, patients with PSC have a high risk of cholangitis post-ERCP.[89] However, whether POC increases the risk of cholangitis over conventional ERCP is unknown.

In a retrospective study of 92 patients (of which 36 patients had PSC) undergoing SOC, there was no difference in the rates of overall adverse events (14.0% versus 23.2%; p=0.27) or infection (3.0% versus 4.0%; p=0.83) in patients with and without PSC.[61] Furthermore, this study also found that post-ERCP abdominal pain occurred more frequently in patients without PSC compared to patients with PSC (12.0% versus 0.0%; p=0.02). A separate retrospective study of 341 patients (of which 12 patients had PSC) also found the rate of adverse events to be similar for patients with and without PSC.[90]

CONCLUSION

POC is an endoscopic technique which provides direct visualisation and the ability to perform therapeutic interventions within the biliary tree. In recent decades, it has been found to be a safe and effective method in the evaluation of indeterminate strictures and management of difficult to reach biliary stones. However, its usefulness in patients with PSC is unclear; additional studies on the use of this endoscopic technique in patients with PSC are needed.

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Hepatitis B Care Pathway in the United Arab Emirates: Current Situation, Gaps, and Actions

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Disclosure: Dr Al Zaabi, Dr Al Quraishi, Dr Al Rifai, Dr Abdelaziz, Dr Bassil, and Dr Taha have received fees for consultancy and expert testimony from Gilead Sciences. Dr Mansour, Dr Snehanshu, and Dr Kozma are full-time employees of Gilead Sciences.

Funding: This research was supported by funding from Gilead Sciences. All the authors had full access to the data and complete autonomy for data analysis, data interpretation, and manuscript writing.

Received: 25.03.19

Accepted: 07.06.19

Keywords: Diagnosis, epidemiology, hepatitis B, treatment, United Arab Emirates (UAE).

Citation: EMJ Hepatol. 2019; DOI/10.33590/emjhepatol/19-00061.

Abstract

Introduction: Hepatitis B virus (HBV) infection remains a worldwide public health problem. The last major review of the epidemiology and management of HBV in the Middle East was published in 2011. This paper aims to assess the current situation of the HBV care pathway in the United Arab Emirates (UAE), identify gaps in our knowledge and barriers therein, and recommend initiatives to be taken to improve the management of such patients.

Methods: A literature search was conducted in PubMed as well as through free internet searches. Interviews and group discussions were held with key opinion leaders and HBV experts.

Results: The national prevalence of HBV is estimated to be approximately 1.0–1.5%; however, prevalence is expected to be higher in those >25 years of age born before the introduction of the HBV vaccination programme. There is limited data on the burden of HBV-related hepatocellular carcinoma in the country.

Discussion: Awareness of various aspects of the disease is perceived to be low among the general population and medium among healthcare providers. There are several mandated national screening structures present; however, there are no country-specific HBV guidelines regarding diagnosis, linkage-to-care, treatment, and follow-up. Improvements have been made in the past 30 years in the UAE, evident through a decline in prevalence. The burden attributable to HBV complication and the coverage of screening and treatment remain unclear.

Conclusion: Key stakeholders in all areas of the HBV care pathway must reduce morbidity and mortality in the UAE population, and interventions should be supported by research.

INTRODUCTION

Chronic hepatitis B (CHB) is a worldwide public health problem.[1] As per the Global Burden of Disease Study, the number of hepatitis B virus (HBV) infections was estimated to be 468 million cases in 2016.[1] In the World Health Organization (WHO) Eastern Mediterranean Region, an estimated 3.3% of the general population is infected with HBV.[2]

The last updated review of the epidemiology, burden, and management of HBV in the Middle East was published in 2011.[3] The authors observed a trend from 'high-to-intermediate' to 'low-to-intermediate' endemicity.[3] Medical experts considered it imperative to assess whether this trend continued, as well as to assess the current situation in the 'HBV care pathway'.[3] The key stages and indicators to consider on the 'HBV care pathway' are:

- Epidemiology of the disease and the awareness of different stakeholders about various aspects of the disease.
- Screening for disease, as well as diagnosing patients presenting with symptoms, reporting of positives, and linking them to care.
- Appropriate evaluation of the disease and treatment initiation if needed.
- Compliance/adherence to treatment and periodic patient follow-up.

This paper aims to assess the current situation of the HBV care pathway in the United Arab Emirates (UAE), identify gaps and barriers therein, and recommend comprehensive initiatives to be undertaken to improve the overall situation.

METHODS

A pragmatic literature search was conducted in PubMed to identify evidence on HBV in the UAE using the key words "United Arab Emirates or UAE", "hepatitis B or HBV", "chronic hepatitis B or CHB", "hepatocellular carcinoma or HCC", "cirrhosis", "prevalence", "awareness", "epidemiology", "vaccination", "diagnosis", "screening", "treatment", "care pathway", and "adherence". The reference lists of those articles were scanned for any additional articles. In addition, free internet searches were conducted using similar key words to find reports, guidelines, conference abstracts, posters, and presentations. To provide context to the results from the literature review, as well as to collect diverse stakeholder perspectives on those areas for which either no or limited evidence was found in the literature, discussions were held with various healthcare professionals, including key opinion leaders and HBV experts. Different organisations are involved in healthcare provision in the various emirates; in Abu Dhabi, the Department of Health (DOH) (formerly known as Health Authority - Abu Dhabi [HAAD]) is the governing regulatory body and Abu Dhabi Health Services Company (SEHA) is a provider of health services; in Dubai, the Dubai Health Authority (DHA) is both the governing body and service provider; and in the Northern Emirates, the Ministry of Health (MoH) is active. Finally, inputs were taken from the UAE HBV Working Group which included hepatology experts practising in the UAE.[4]

RESULTS

Prevalence of Hepatitis B Virus Infection

HBV infection rates (HBV surface antigen [HbsAg]-positive) among women of child bearing age in the prevaccination era was 2.5%, based on a mathematical model estimating the HBV burden worldwide using global evidence.[5] Since the introduction of the vaccination in 1991, six studies have been conducted to estimate the prevalence of HBV in the UAE.[6-11] From the age of the subjects enrolled, it can be deduced that most of these studies included populations that have either not been vaccinated or are from the prevaccination era.

The most recent study among blood donors found a HBV prevalence of 0.23%.[7] With an estimated Emirati population of about 1.2 million in 2016, a prevalence of 0.23% would give an estimated 2,760 HBV cases in the country. Assuming 1.5% prevalence however, which was reported among pregnant women in 2000, would yield an estimate of 18,000 HBV cases in the country.[8] Medical experts agreed that the national prevalence is plausibly between 1.0% and 1.5% among the Emirati general population, so the number of HBV infections is estimated to range between 12,000 and 18,000 cases.[4]

A recent systematic review by Schweitzer et al.[12] pooled worldwide data published between 1965 and 2013; in the case of UAE, two studies were included in the review with a total of 1,859 people, which found a prevalence of 0.70%.[12] However, it is not clear which UAE studies were included in this review. In general, local prevalence studies conducted in the UAE concentrated more on at-risk populations, such as haemodialysis/end-stage renal disease patients, and continue to show higher prevalence rates than the general population. Furthermore, it would be expected that the prevalence in the older population (>25 years) will be higher because they were born in the prevaccination era, however none of the studies provide prevalence rates by age group.[6-11]

The UAE started the compulsory vaccination programme for HBV for all newborns in 1991;[13] all infants receive 4 doses of the vaccine at 0, 2, 4, and 6 months of age.[14,15] Moreover, all school students born before October 1991 were vaccinated by the year 2000.[14] One could deduce that at least all Emiratis <25 years of age would have received the first dose of vaccine at birth and hence should be protected from the disease. However, the vaccination of school students born before October 1991 was left to the compliance of students, parents, and schools. With respect to the age distribution of HBV cases, in 2015, 74% of the reported Emirati cases to DOH were >30 years of age (which is an increase from the 62% reported in 2013) and the 30–39 age group contributed the highest proportion (38%).[16] Looking at cases reported to DHA, which covers cases in Dubai, the highest number of cases was reported in the 25–34 age group in 2016 (41% of all cases among Emiratis).[17] The large numbers of cases in this age group could be a result of strict premarital screening interventions.

Focussing on high-risk groups, a study published in 2010 involving 994 healthcare workers found that 62% of all respondents had been immunised for hepatitis B.[18] However, a more recent prospective cohort study that involved 261 (61% female) Emirati medical students conducted between 1st July 2011 and 30th May 2012 found that all students were vaccinated: 40% at birth and the remaining 60% at school.[13]

No information was found concerning awareness regarding HBV in the community, although this was rated low for general awareness, prevalence of disease, origin, transmission, and high-risk groups by the UAE HBV Working Group.[4] This might be because no community awareness campaigns have been conducted recently, the last ones that focussed on HBV dating back to 2007 and 2008. Also, no studies were found assessing the awareness of general practitioners (GP), but medical experts rated this to be medium for general awareness, prevalence of disease, origin, transmission, and high-risk populations.[4]

Chronic Hepatitis B Virus Burden

People with CHB have a 15–40% lifetime risk of developing end-stage liver disease including cirrhosis, liver failure, and hepatocellular carcinoma (HCC), a primary malignancy of the liver.[19] Furthermore, it was found that the health-related quality of life in patients with CHB tends to be impaired in the later stages of liver disease.[20-23] In the Arab population, an estimated 6,447 deaths occurred from HBV-associated HCC in 2010, and from 1990 to 2010, the burden of HBV-associated HCC deaths increased at a much faster rate (137% increase) compared to the rest of the world (62% increase).[24] Khan G et al.[24] reported in 2015 that, in the UAE, the age-standardised death rate for HBV-associated HCC increased by approximately 10% between 1990 and 2010 to 3.2 per 100,000 males, and 1.2 per 100,000 females in 2010 (or 45 deaths among men and 6 among women). No specific reasons were given for the change in the UAE other than what was mentioned for Arab countries in general.

Although vaccines have been proven very effective in HBV prevention in adolescents and led to a decrease in prevalence, it takes decades to observe their effect in HCC reduction in adults.[20] No research studies were found on the awareness levels of patients or high-risk populations on the chronicity and consequences of HBV. Experts of the UAE HBV Working Group rated the awareness of GP about clinical sequelae of disease to be medium.[4] Genotype D HBV was found to be significantly associated with more advanced stages of liver disease.[25] One study, conducted in the UAE, included serum samples of 90 HBV DNA positive subjects and the results showed that genotypes D and A accounted for 77.8% and 17.8%, respectively.[26] Another study conducted among 88 HBsAg positive patients found that HBV genotype D was the most prevalent (79.5%) genotype, followed by genotypes A (18.2%) and C (2.3%). In this study, only 5.7% of patients were HBeAg positive.[27]

Presentation, Evaluation, and Diagnosis

There are a number of mandated screening structures (Figure 1) present in the country identifying patients through blood tests (HBsAg test, antibodies for blood donors).[28]

Per DOH and DHA regulations, HBV reporting is mandated for all healthcare practitioners and facilities licensed by the respective regulator.[29,30] Despite reporting being mandatory, gaps in the reporting are still seen. The typical HBV patient journey in the UAE is illustrated in Figure 2.[4]

Figure 3 shows the number of reported HBV cases over a 10-year period in Abu Dhabi and Dubai.[16,17] The number of cases reported to DOH (Abu Dhabi) for both Emiratis and expatriates has increased in the past few years (from 699 in 2013 to 1,121 in 2015). However, in the same period, the number of cases reported to DHA (Dubai) has decreased. Increasing numbers of cases in Abu Dhabi, despite the existence of a vaccination programme, might be attributable to a combination of various factors such as:

- Increased reach and effectiveness of mandated screening interventions.
- Double counting of previously diagnosed cases that were lost to follow-up.
- Double counting of cases attributable to the migration of people from Dubai to Abu Dhabi (and vice versa).
- Emiratis from the Northern Emirates increasingly approaching public hospitals in Abu Dhabi (and Dubai) for treatment.

It is unclear how many cases are diagnosed in the Northern Emirates because no publications could be found on HBV statistics from the MoH.

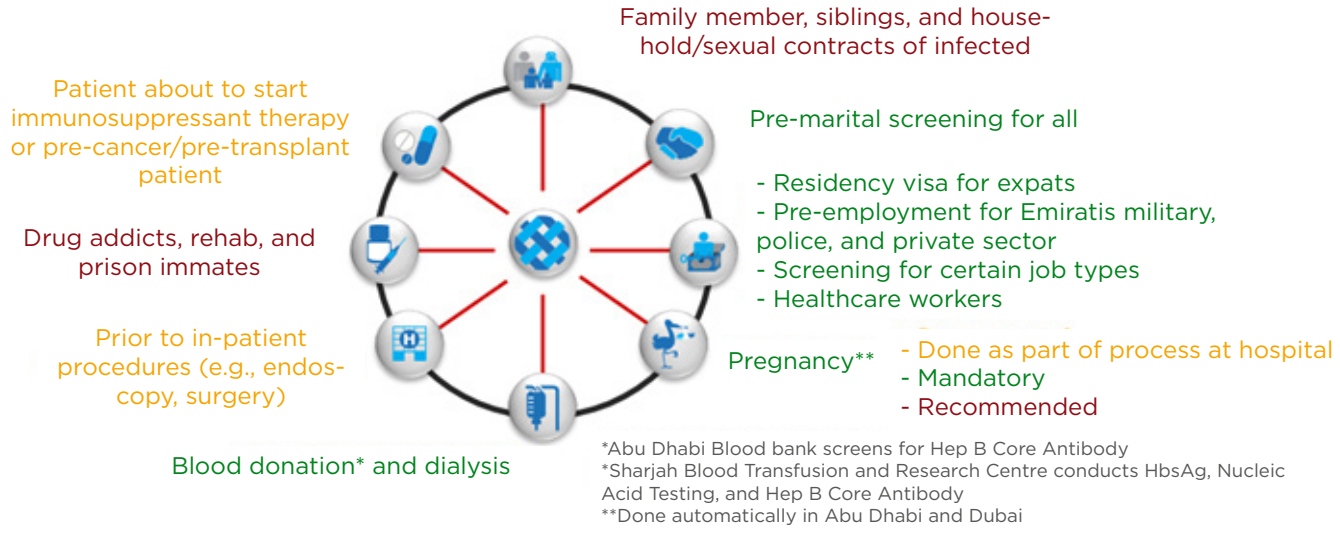

Figure 1: Potential hepatitis B virus screening points in United Arab Emirates.

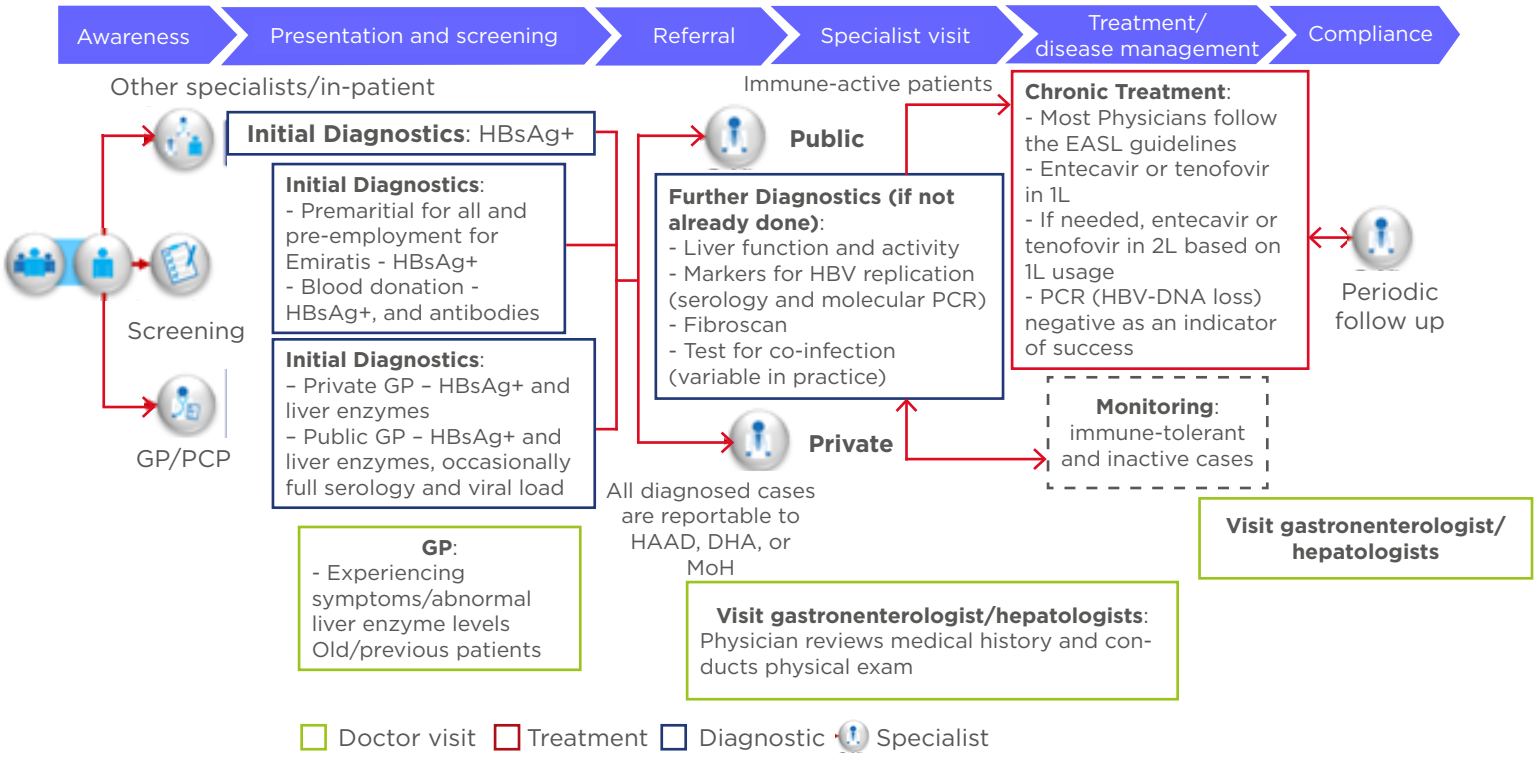

Figure 2: Hepatitis B virus patient journey in United Arab Emirates.

DHA: Dubai Health Authority; EASL: European Association for the Study of the Liver; GP/PCP: general practitioner/primary care providers; HAAD: Health Authority – Abu Dhabi; HBsAg+: hepatitis B surface antigen positive; HBV: hepatitis B virus; MoH: Ministry of Health; PCR: polymerase chain reaction.

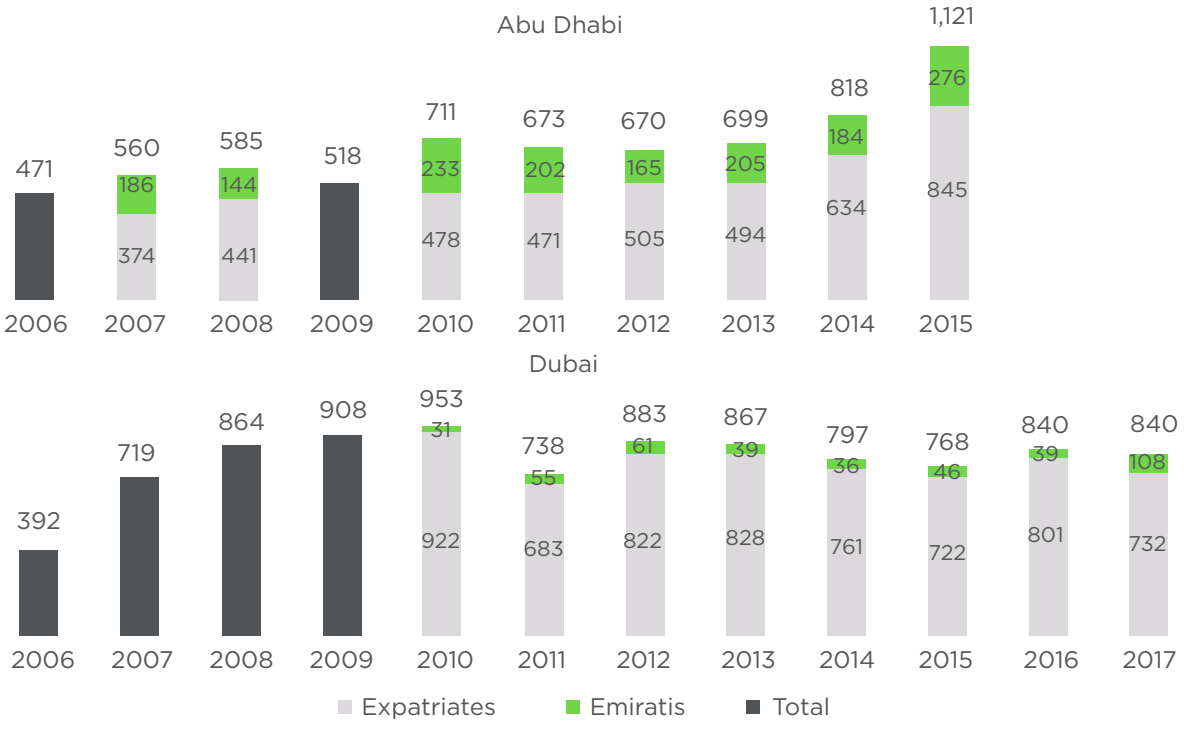

Figure 3: Cases of hepatitis B virus reported to Department of Health (2006–2015)[16] and Dubai Health Authority (2006–2017).[17]

In 2015 only, the total number of reported cases in Abu Dhabi and Dubai was 1,889, of which 322 (17.0%) were Emiratis and 1,567 (83%) were expatriates.

Knowing that approximately 60% of the Emirati population live in Abu Dhabi and Dubai and the remaining live in the Northern Emirates, it could be assumed that the total number of reported HBV cases among Emiratis across the country in 2015 is around 537.

When screened positive or diagnosed positive by a GP in a primary care facility based on symptoms, signs, and abnormal diagnostic tests, patients will be referred to a specialist for further diagnosis.

Treatment and Disease Management

Treatment is delivered to patients in the public sector (Emiratis only) and private sector (both Emiratis and expatriates). In the public sector, specialists/hepatologists and gastroenterologists receive the referrals in their outpatient or hospital-based clinics affiliated to DHA in Dubai, to SEHA in Abu Dhabi, and to MoH in the Northern Emirates. Private sector specialists are available in outpatient ambulatory centres or outpatient clinics in private hospitals. The predominant proportion of HBV care and treatment is delivered in the public sector as it contributes approximately 81% of the HBV prescription share, considering only nucleos(t)ide analogues (NA).[28] The majority of the treatment centres are concentrated in Dubai and Abu Dhabi.

Of the approximate 12,000–18,000 prevalent cases in the country, only 21–32% are estimated to be diagnosed (although this may well be an underestimation of the proportion that knows their status, as people could have been diagnosed in previous years).[4] Of the diagnosed cases, only 21% are currently on treatment with the majority in the public sector.[31] While only a minority of all patients need to be treated as per the current guidelines (approximately 25%),[27] the smaller number of treated patients in UAE could be attributed to breaks in the care continuum. It is assumed that some screened and/or diagnosed patients do not reach the specialists and are not linked to care, owing to the lack of a system for monitoring, tracking of patients, and/or proper longitudinal follow-up.

There is no local guideline for HBV; hence most specialists follow the European Association for the Study of the Liver (EASL) guideline.[4] However, experts indicate that there are minor variations in specialists' interpretation of phasing of the disease (HBV DNA levels and serum alanine aminotransferase upper limit of normal); therefore, subsequent variations in the timing of treatment initiation might exist.[4] The primary goal of HBV therapy is to improve survival and quality of life by preventing disease progression and death.[32] The recommended antiviral therapies for CHB treatment in the country are entecavir (ETV) and tenofovir disoproxil fumarate (TDF). Other treatments, such as pegylated interferon (Peg-IFN-alfa-2a), lamivudine (LAM), telbivudine, and adefovir, have also been approved but are prescribed to a much lesser extent.[31] While all drugs have market authorisation in the country, ETV, TDF, and LAM are available in public sector formularies and are provided free of charge to Emirati patients based on specialist prescription.[4] Physicians indicate that LAM usage is decreasing and that they prefer ETV over TDF; data show that ETV holds roughly 73% of the patient share for HBV treatment, considering only NA, followed by TDF (approximately 19%) and LAM (8%).[31] Physicians' low prescription of LAM emanates from their poor experience with it because patients developed resistance and had to be eventually shifted to TDF.[4] A systematic review found that resistance to LAM emerges in approximately 20% of patients after 1 year and in 70% of patients after 5 years of treatment.[33]

The main limitation of current antiviral therapy is that the long-term toxicity and health effects are unknown, in a context in which lifelong treatment might be needed.[4] Furthermore, disease progression is likely to occur when the suppressive effect of NA is removed; especially in cases of treatment cessation attributable to drug-related adverse events or drug resistance.[32,34] There is a significant unmet need for a treatment that can cure HBV. In the absence of such a curative therapy, there is an unmet need for new effective treatment options, with a higher barrier to resistance and with fewer treatment-related adverse events than the currently available treatment options.

Compliance and Adherence

It is recommended that all patients treated with NA should be followed with periodical assessments.[32] Nonadherence with recommended follow-up visits is a major barrier for completing treatment and is consequently associated with unfavourable clinical outcomes. Experts in the UAE rate the compliance and adherence to treatment among Emirati patients to be high: approximately 80–90% of the patients who start treatment remain compliant.[4]

RECOMMENDATIONS

The following recommendations are based on inputs from experts of the UAE HBV Working Group and evidence from the literature review.

There is a need for a nationally representative (including all Emirates) population-based prevalence study (using HBsAg and core antigen screening). Only then can an accurate overall disease prevalence be estimated; in addition, an epidemiology stratification should be made by citizenship status, age (especially the population 25+ years), and gender. Other suggested variables include sociodemographic characteristics, vaccination status, HBeAg status, and mode of transmission, all of which can inform prevention and treatment strategies. It is also advised to establish a national HBV registry, because current data originates from DOH and DHA separately (and reporting systems do not work optimally), with no data available from the MoH in the Northern Emirates. Furthermore, it would be prudent to initiate a broader liver registry, because currently there is limited data on the complications of HBV to inform treatment interventions.

Experts suggest that more research should be conducted on the status of the awareness regarding HBV in the general population and, specifically, in high-risk groups including the elderly, surgery patients (who are not always screened), and medical staff. Use of technology (e.g., social media) and public spaces (e.g., shopping centres) are suggested as key channels.

The WHO advocacy brief highlights that certain prevention and diagnosis targets should be achieved to reach HBV elimination.[35] It is important that GP and primary healthcare workers conduct screening of at-risk persons including family members and close contacts of infected Emirati patients and the older population (>40 years old) at high risk of exposure to HBV from the prevaccination era. Hence, with respect to healthcare staff, it is anticipated that establishing training programmes as well as tools and algorithms for GP and public health physicians, to assess high-risk patients visiting their clinics, will lead to improved rates of diagnosis and referral to specialists.

Linkage to care will be maintained only when a system is in place to follow patients through the successive phases of the care pathway. Follow-up of patients is needed along with increased patient awareness (through counselling) to improve treatment compliance and reduce morbidity and mortality. It is recommended that screening for HCC should be increased through simple measures such as the alpha-fetoprotein test and the abdominal ultrasound.

CONCLUSION

In conclusion, significant improvements have been made in the UAE over the past 30 years to reduce HBV prevalence. However, challenges regarding CHB management and long-term follow-up of the disease persist. Specific healthcare initiatives are needed to address these challenges, including the conduct of a population-based prevalence study, launch of educational and awareness campaigns, and improvement of screening and linkage to care. Continuous efforts must be made by all key stakeholders across the care pathway (hepatology specialists, GP, policy makers, and public health specialists) to reduce both morbidity and mortality of HBV in the UAE population.

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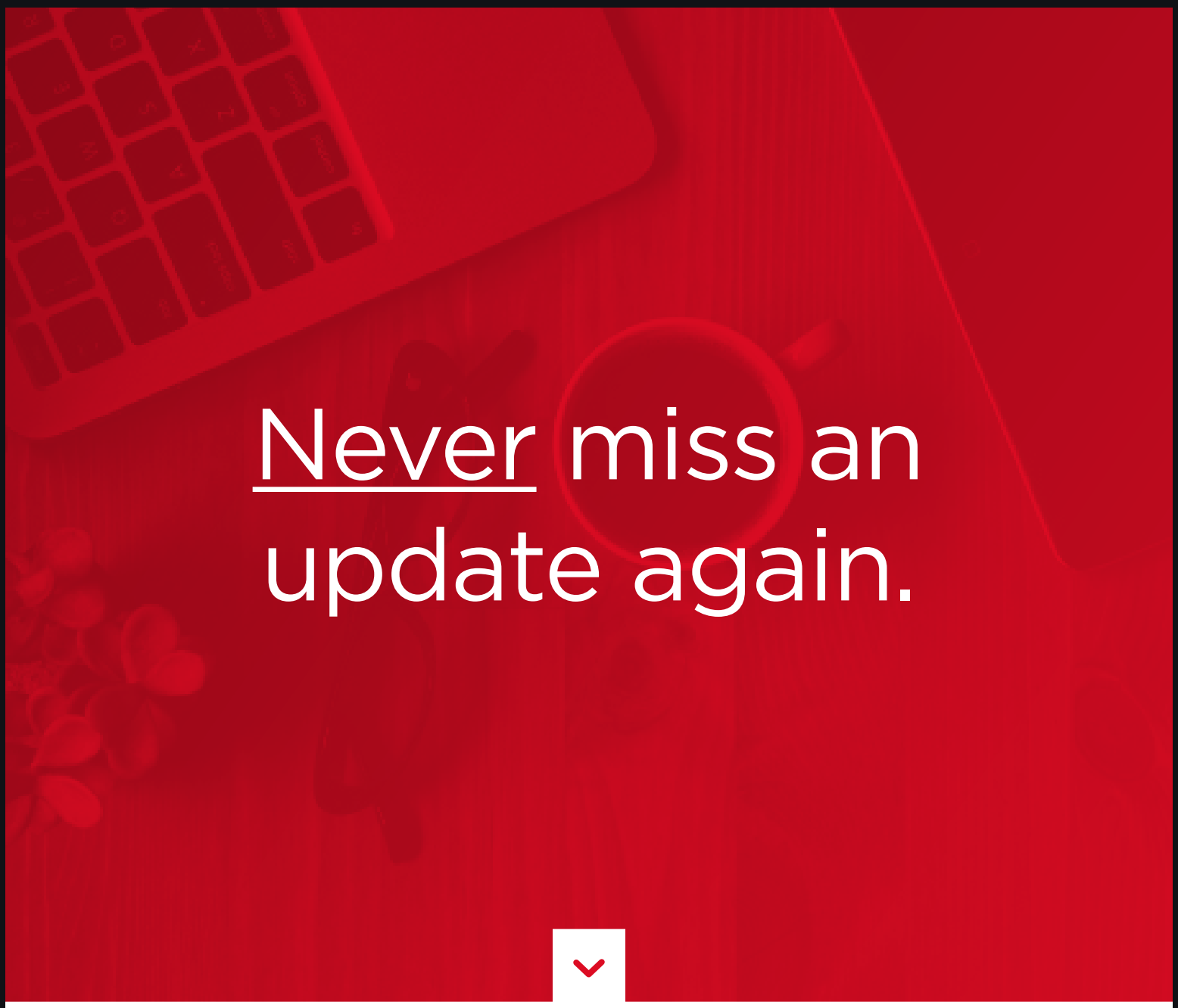

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