Ultrasound in Med. & Biol., Vol. 00, No. 00, pp. 1–12, 2018

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2018.06.002

● *Review*

NEW ULTRASOUND TECHNIQUES CHALLENGE THE DIAGNOSIS OF SINUSOIDAL OBSTRUCTION SYNDROME

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(*Received* 16 *March* 2018; *revised* 14 *May* 2018; *in final from* 4 *June* 2018)

Abstract—Sinusoidal obstruction syndrome, also known as veno-occlusive disease (SOS/VOD), is a potentially life-threatening complication that can develop after hematopoietic cell transplantation. Clinically, SOS/VOD is characterized by hepatomegaly, right upper quadrant pain, jaundice and ascites, most often occurring within the first 3 wk after hematopoietic cell transplantation. Early therapeutic intervention is pivotal for survival in SOS/VOD. Thus, a rapid and reliable diagnosis has to be made. Diagnosis of SOS/VOD is based on clinical criteria, such as the Seattle, Baltimore or recently issued European Society for Blood and Marrow Transplantation criteria, to which hemodynamic and/or ultrasound evidence of SOS were added for the first time. However, to rule out major differential diagnoses and to verify the diagnosis, a reliable imaging method is needed. Ultrasound techniques have been proposed in SOS/VOD. Nevertheless, the sensitivity and specificity of transabdominal ultrasound and Doppler techniques need to be improved. Innovative ultrasound methods such as a combination of Doppler ultrasound with shear wave elastography and contrast-enhanced ultrasound techniques should be evaluated for diagnosis and follow-up of SOS/VOD. The goals of this review are to discuss currently available ultrasound techniques and to identify areas for future studies in SOS/VOD. (E-mail: Christoph.dietrich@ckbm.de)

Key Words: **Sinusoidal obstruction syndrome, Diagnosis, Ultrasound, Elastography, Guideline.**

INTRODUCTION

Sinusoidal obstruction syndrome, also known as veno-occlusive disease (SOS/VOD), is a potentially life threatening complication that can develop after hematopoietic cell transplantation (HCT) and classically presents in the early post-transplantation period and, with a potentially late-onset SOS/VOD, after certain medications (*e.g.,* gemtuzumab ozogamicin or inotuzumab ozogamicin). The average incidence of SOS/VOD is approximately 10% in adults and 20% in children (Corbacioglu et al. 2018). Although SOS/VOD progressively resolves within a few weeks in some patients, the most severe forms (grade III) result in multi-organ dysfunction and are associated with a high mortality rate (>80%) (Mohty et al. 2015, 2016). Accurate and early diagnosis of SOS/VOD is clinically important to reduce the reported high fatality rate (Jones et al. 1987; McDonald et al. 1984). Jones et al. (1987) reported that only 1 of 25 patients with SOS/VOD and a serum bilirubin level >15 mg/dL survived, and Zager et al. (1989) reported that only 14% of SOS/VOD patients who required hemodialysis survived. Most patients with distinct SOS/VOD die of multi-organ failure within the second month after the transplant. Therefore, careful attention must be paid to allow early detection of

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SOS/VOD (or prevention), particularly because defibrotide has proven to be effective and is licensed for its treatment (Braden et al. 2002, Ignee et al. 2016; Imran et al. 2006; Mohty et al. 2016). The mortality could potentially be reduced (Richardson et al. 2016) by early diagnosis and treatment and, in high-risk pediatric patients, by a prophylactic approach. Here we describe the current and potential value of ultrasound techniques to diagnose SOS/VOD. All cited studies have obtained informed consent from each study participant and protocol approval by an ethics committee andinstitutional review board

SYMPTOMS AND CLINICAL EVALUATION

Sinusoidal obstruction syndrome/veno-occlusive disease is characterized by a marked, otherwise unexplained sudden increase in weight >2% (Seattle criteria) (McDonald et al. 1984) and 5% (Jones et al. 1987), respectively, resulting from fluid retention (>2% [5%] of the initial weight caused by hypotonic hyperhydration), right upper quadrant pain caused mainly by painful hepatomegaly ("capsule pain"), ascites (Baltimore criteria) (peripheral edema) and jaundice (increase in serum bilirubin >2 mg/dL caused by ductal plate injury).

Patients with a severe course of the disease often appear confused (hepatic encephalopathy), have spontaneous hemorrhages and develop hepatorenal syndrome (50%−80%). About 25% of patients with renal insufficiency will require hemodialysis (Corbacioglu et al. 2016; Mohty et al. 2015). Heart failure (≤60%) has been reported as well. Not all clinical features may be present, and the severity of signs and symptoms can vary (Corbacioglu et al. 2012; Mahgerefteh et al. 2011). Most patients develop symptoms within the first 3 wk after HCT (Carreras 2015; Richardson and Guinan 1999), although later presentations have been reported (Bearman 1995; McDonald et al. 1993; Pai et al. 2012; Platzbecker et al. 2009; Richardson and Guinan 1999; Richardson et al. 2017). SOS/VOD has also been described after the use of chemotherapeutic agents in non-transplant settings (*e.g.,* oxaliplatin), ingestion of alkaloid toxins, after high-dose radiation therapy and after liver transplantation (Coppell et al. 2010). Very late onset SOS/VOD has been reported after use of the new toxin-linked antibody inotuzumab-ozogamizin (Kantarjian et al. 2016).

The sensitivity of the reported symptoms is good, but the specificity is relatively low because a large number of patients with pre-existing hepatic diseases could worsen under HCT, and its accompanying therapy must be taken into account. In addition, other conditions such as infections and graft versus host disease (GVHD) may cause similar symptoms.

A system of subdividing SOS/VOD patients according to symptoms has been proposed: patients with minor symptoms (frequency of occurrence 10%−20%, no symptomatic therapy necessary); patients with moderate symptoms (50%−70%, symptomatic therapy necessary) and patients with a severe clinical picture (approximately 25%) that is detectable more than 100 d after HCT or a lethal outcome within the first 100 d after HCT (Mohty et al. 2016). Icterus occurs slightly later than the weight increase and hepatomegaly. On the sixth day, the average bilirubin level is 2 mg/dL and gradually increases to a maximum level between 12 and 18 mg/dL (Essell et al. 1992). The revised European Society for Blood and Marrow Transplantation (EBMT)) criteria divide VOD into four severity classes, which are explained in detail.

DIAGNOSIS

In general, SOS/VOD is diagnosed clinically. Daily clinical examination and weight monitoring are the easiest and most important tools used to diagnose SOS (Mohty et al. 2015).

Baltimore and Seattle criteria

Until recently, two slightly different definitions of SOS/VOD co-existed: that based on the Seattle criteria, reported by McDonald et al. (1984), and that based on the Baltimore criteria, reported by Jones et al. (1987). With minor clarifications and modifications (Corbacioglu et al. 2012; McDonald et al. 1993), the modified Seattle and the Baltimore criteria have been used in clinical practice, as well as in research studies and trials, in the past three decades. According to a recent meta-analysis, the incidence of SOS/VOD varies, according to the criteria used, between 17.3% (Seattle) and 9.6% (Baltimore) (Coppell et al. 2010). One of the major difficulties is that, unlike some other transplant-related complications, SOS/VOD is very dynamic in its manifestations, and the exact definition is hard to establish (Table 1). Before their diagnosis, the severe forms require overt clinical manifestations and serious organ damage, such as severe pulmonary or renal dysfunction and encephalopathy (Mohty et al. 2016).

Revised EBMT criteria for diagnosis of SOS/VOD

As indicated earlier, the Seattle and Baltimore criteria have been published and used since the 1980s. However, the HCT landscape has changed significantly over the past 30 y. Briefly, modern imaging techniques; the use of unrelated, mismatch or haploidentical donors; reduced-intensity conditioning; and the observation of late-onset SOS/VOD (beyond day 21) led the EBMT to reconsider and to consent to a revision of the diagnosis criteria for SOS/VOD. The updated EBMT criteria for diagnosis of SOS/VOD in adult patients includes the changes described below.