·标准与讨论·

造血干细胞移植后肝窦隙阻塞综合征诊断与治疗中国专家共识(2022年版)

中华医学会血液学分会
通信作者:黄晓军,北京大学人民医院,北京大学血液病研究所,国家血液系统疾病临床医学研究中心,造血干细胞移植治疗血液病北京市重点实验室,北京 100044,Email:xjhrm@medmail.com.cn;吴德沛,苏州大学附属第一医院血液科,江苏省血液研究所,国家血液系统疾病临床医学研究中心,苏州 215006,Email:wudepei@suda.edu.cn
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Chinese expert consensus on the diagnosis and management of sinusoidal obstruction syndrome after hematopoietic stem cell transplantation (2022)

Chinese Society of Hematology, Chinese Medical Association
Corresponding author: Huang Xiaojun, Peking University People's Hospital, Peking University Institute of Hematology, National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing 100044, China; Wu Depei, The First Affiliated Hospital of Soochow University, Jiangsu Institute of Hematology, National Clinical Research Center for Blood Diseases, Suzhou 215006, China, Email: drwudepei@163.com

肝窦隙阻塞综合征(sinusoidal obstruction syndrome, SOS)也称肝静脉闭塞症(veno-occlusive disease, VOD),多发生于摄入某些毒性生物碱、高剂量放/化疗和器官移植的患者,是一种可危及生命的严重疾病。造血干细胞移植(HSCT)患者是SOS最主要的发病人群,SOS也是移植早期的重要合并症和死亡原因之一。本共识在参考该领域国外指南/共识的基础上,纳入国内的主要研究成果和临床经验,结合现时国情,为各移植单位SOS规范化诊疗提供指导性意见。

一、定义和流行病学

HSCT后SOS是指HSCT后早期发生的、预处理相关肝毒性导致的一类主要表现为黄疸、液体潴留、肝肿大等特征的临床综合征,重症患者病死率可高达80%[1-3]。

因患者特征、预处理方案、移植中心经验、诊断标准等差异,SOS发生率在不同研究中的差异较大。一项荟萃分析显示中位发生率为13.7%(0~62.3%)[4]。综合来看,自体HSCT(auto-HSCT)后发生率为3.1%~8.7%,异基因HSCT(allo-HSCT)为8.9%~14.0%[4-8]。儿童HSCT患者发生率略高于成人[9-12]。国内广西医科大学附属第一院报道allo-HSCT后SOS发生率为7.4%[13]。近年来发生率及严重程度总体有所下降,但某些药物(如CD33、CD22等单抗)的应用、增加强度预处理、二次移植等在一定程度上会增加患者发病风险。

二、发病机制

SOS的发病机制尚未明确,目前认为预处理方案相关肝毒性为首要病因。白消安(BU)、环磷酰胺(CTX)、全身放疗(TBI)等对窦隙内皮细胞(SEC)和肝细胞的毒性损伤是SOS发生的直接原因,肝小叶中心区域(肝腺泡3区)因缺乏谷胱甘肽(GSH)而更易发生损伤[14-16]。除预处理外,组织损伤产生的细胞因子、药物[钙调神经磷酸酶抑制剂(CNI)、造血生长因子、抗体药物等]、异源反应性T细胞、某些GSHS-转移酶相关基因突变、内源微生物代谢物的迁移及造血植入等也可导致或加重SEC损伤[17-24]。SEC损伤导致内皮细胞屏障破坏,窦壁完整性丧失,红细胞渗至狄氏(Disse)腔,引起内皮细胞分离,造成肝窦隙阻塞;此外,凝血-纤溶系统失衡可致微血栓形成,加重小叶中心静脉阻塞,最终形成窦后性门静脉高压。发展至重症者小叶中心坏死、纤维

化，肝功能衰竭。鉴于内皮损伤在发病机制中的中心地位，也有学者将SOS纳入HSCT相关内皮损伤综合征范畴[25-26]。

三、危险因素

SOS发病危险因素一般分为患者相关和移植相关两类。前者主要包括：年龄、体能状况、移植前肝病史/肝功能异常、疾病进展状态、地中海贫血、铁过载、腹部放疗史、应用吉妥珠单抗（Gemtuzumabozogamicin）或奥加伊妥珠单抗（Inotuzumabozogamicin）[27-29]。后者主要包括：allo-HSCT（相比auto-HSCT）、HLA不合/单倍型移植、二次移植、移植物非去T细胞、含BU或TBI预处理、氟达拉滨、CNI联合西罗莫司预防GVHD等。

识别危险因素或构建前瞻性风险评估模型有助于SOS的早期预测和预防[30]。

四、诊断、分级及鉴别诊断

典型SOS多发生于HSCT后21 d内，迟发型可发生于21 d后。可隐匿发病，也可急骤进展。主要临床表现包括右上腹压痛、黄疸、痛性肝肿大、腹水、体重增加、水肿等。实验室检查可见高胆红素血症、转氨酶升高、难以解释的血小板减少等。影像学（推荐多普勒超声）检查可发现肝肿大、腹水、胆囊壁水肿、肝/门静脉血流减慢或反向血流、门静脉增宽等[31-32]。轻症患者呈自限性，重症者可出现肾、肺、心脏等多器官功能衰竭（MOF），预后凶险。

肝组织活检病理是诊断金标准，但在移植早期实施出血风险大，不常规推荐。有经验的单位可选择经颈静脉肝活检或测量肝静脉压力梯度（HVPG）辅助诊断。近年以瞬时弹性成像技术（TE）进行肝硬度检测（LSM），预测和诊断的敏感性及特异性较高[33-35]。

目前尚无具有预测或诊断意义的生物学标志物。纤溶酶原激活物抑制物-1（PAI-1）等血凝标志物有一定的预测价值，内皮细胞损伤及炎症标志物尚在探索中[36-40]，不推荐常规检测。

SOS临床诊断多依据修订的西雅图（Seattle）标准[41]或巴尔的摩（Baltimore）标准[42]。2016年欧洲骨髓移植学会（EBMT）提出的SOS标准[3]具有较好的实用性，本共识推荐使用该标准，也可与前述2个标准并行使用。各诊断标准见表1。

儿童SOS的EBMT诊断标准[10]：无发生时间限定，至少满足2条下述表现：①难以解释的消耗性血小板减少和无效输注；②即使应用利尿剂，仍有难以解释的连续3 d体重增加或体重增加＞5%基线值；③高于基线值的肝脏肿大（建议影像学确认）；④高于基线值的腹水（建议影像学确认）；⑤连续3 d胆红素高于基线值，或72 h内胆红素≥2 mg/dl。值得注意的是，16%～20%的儿童SOS为迟发型，近30%无黄疸表现[43-44]。

本共识推荐采用美国血液学会SOS分级标准[45]（表2）及EBMT分级标准[3]（表3）进行严重程度分级。

SOS需要与以下疾病鉴别：肝脏急性GVHD、病毒性肝炎、药物性肝损伤、毛细血管渗漏综合征（CLS）、移植相关血栓性微血管病（TA-TMA）等，鉴别要点见表4。

表1　修订的西雅图、巴尔的摩和欧洲骨髓移植学会（EBMT）肝窦隙阻塞综合征（SOS）诊断标准

标准	描述
修订的西雅图标准	HSCT后20 d内出现至少2条下述表现：胆红素＞2 mg/dl，肝肿大伴右上腹痛，液体潴留致体重增加≥2%基线体重
巴尔的摩标准	HSCT后21 d内胆红素＞2 mg/dl，同时至少符合2条下述表现：痛性肝肿大，体重增加≥5%，腹水
EBMT标准	经典型SOS：HSCT后21 d内胆红素＞2 mg/dl，同时至少符合2条下述表现：痛性肝肿大，体重增加≥5%，腹水 迟发型SOS：HSCT后21 d后出现经典型SOS或病理学证实的SOS，或≥2条经典型标准且同时具备超声或血液动力学证据

注：HSCT：造血干细胞移植

表2　美国血液学会肝窦隙阻塞综合征（SOS）分级标准

分级	病情进展	胆红素（mg/dl）	转氨酶	体重增幅	血肌酐
轻度	慢，（＞6～7 d）	2～3	＜3倍正常值上限	2.0%	正常
中度	快，（4～5 d）	＞3～5	3～5倍正常值上限	2.1%～5.0%	＜2倍基线值
重度	迅速，（2～3 d）	＞5	＞5倍正常值上限	＞5.0%	≥2倍基线值

注：上述标准符合≥2条即可确认相应严重程度

五、预防

1. 一般原则：避免SOS危险因素，包括祛铁治疗、避免肝炎活动期进行HSCT、预处理方案调整（减低强度、药代动力学指导BU用药、分次TBI等）、避免合用肝毒性药物、警惕某些药物应用（CD33/CD22单抗等）增加SOS风险；液体平衡管理（避免超负荷，同时维持有效血容、避免肾灌注不足）；HSCT后早期应监测体重、腹围等变化。

2. 预防药物：①熊去氧胆酸（UDCA）：随机对照临床试验（RCT）及荟萃分析显示UDCA可降低HSCT后SOS发生率[46-49]。部分研究未能观察到上述结果，但发现Ⅲ/Ⅳ度肝脏急性GVHD发生率明显下降，1年总生存（OS）率更优[50]。目前，UDCA在国内外已得到普遍应用[25,51-52]。推荐用法：UDCA 12～15 mg·kg^{-1}·d^{-1}，移植前开始服用，移植后100 d停药。②普通肝素或低分子量肝素：临床应用和试验研究较多，RCT及荟萃分析（包括儿童及成人）结论不一[7,53-57]，国内应用较多。前列腺素E1（PGE1）：相关RCT研究缺少一致性结论，国内应用较多。③中成药：复方丹参、复方川穹嗪等，国内部分移植中心有应用经验。④去纤苷（DF）：提取自猪肠黏膜的一种单链多聚脱氧核苷酸复合物，机制尚未完全阐明。初步发现具有保护内皮、恢复血栓-纤溶平衡、抗凝及调节血小板活性等作用，不显著增加出血风险。DF是目前国外唯一获批的SOS治疗药物，尚未批准用于预防，但多个预防的RCT研究结果令人鼓舞[9,58-59]。荟萃分析显示，DF预防组SOS发生率显著低于对照组（4.7%对13.7%）[60]。除降低SOS发生率外，DF还可降低SOS相关死亡率及急性GVHD发生率[9,61-62]。推荐用法：DF 6.25 mg/kg，每6 h 1次，每次维持2 h静脉给药，自预处理开始用药，移植后30 d停药。

本共识建议，SOS高危患者，如有条件可选用DF预防，常规预防可选用UDCA、普通或低分子肝素、前列腺素E1及中成药等，也可联合用药，建议各中心根据各自经验选用[63]。鼓励积极开展相关的临床试验研究。

六、治疗

进行严重程度分级有利于分层治疗。约70%的轻症患者经暂停CNI等可疑药物并给予利尿、液体平衡管理等支持治疗即可恢复。暂停CNI时应审慎评估GVHD风险，必要时予糖皮质激素、霉酚

表3 欧洲骨髓移植学会肝窦隙阻塞综合征分级标准

分级	首次症状出现时间（d）	胆红素（mg/dl）	胆红素变化	转氨酶	体重增加	血肌酐
轻度	＞7	2～＜3		≤2倍正常值上限	＜5%	＜1.2倍移植前基线值
中度	5～7	3～＜5		＞2～5倍正常值上限	5%～＜10%	1.2～＜1.5倍移植前基线值
重度	≤4	5～＜8	48 h内倍增	＞5～8倍正常值上限	5%～＜10%	1.5～＜2倍移植前基线值
极重度	任何时间	≥8		＞8倍正常值上限	≥10%	≥2倍移植前基线值或出现其他多器官功能衰竭表现

注：当符合不同分类下的2条标准时，应归类于比较严重的分类中

表4 肝窦隙阻塞综合征（SOS）的鉴别诊断

疾病	临床特征	辅助检查
肝脏急性GVHD	淤胆性肝损伤为主，伴或不伴肝酶增高，多伴有皮肤和（或）肠道急性GVHD，孤立的肝脏急性GVHD较少见。少见痛性肝肿大及钠水潴留	无SOS超声特征
病毒性肝炎	HBV再激活：HBV感染史，急性肝炎表现伴病毒载量显著增高，排除其他病因。其他病毒感染：HCV、HEV、HSV、CMV、EBV、ADV、HHV-6等。少见痛性肝肿大、钠水潴留	同上
药物性肝损伤	评估可疑药物与肝损伤的相关程度，药物应用与肝损伤的时间关系，停药后反应等。重点关注CNI、抗真菌药物和部分抗生素。无痛性肝肿大、钠水潴留	同上
毛细血管渗漏综合征	可为植入综合征表现，也可发生于感染及CNI、细胞因子应用后。浮肿、非心源性肺水肿、低蛋白血症、对利尿剂反应差。少见黄疸、肝肿大	可有腹水征
移植相关血栓性微血管病	难以解释的肾功能和（或）中枢神经系统异常，微血管病性溶血，破碎红细胞，高血压，血浆sC5b-9增高等。少见肝受累	部分患者有腹水征

注：GVHD：移植物抗宿主病；HBV：乙型肝炎病毒；HCV：丙型肝炎病毒；HEV：戊型肝炎病毒；HSV：单纯疱疹病毒；CMV：巨细胞病毒；EBV：EB病毒；ADV：腺病毒；HHV-6：人类疱疹病毒6型；CNI：钙调神经磷酸酶抑制剂；sC5b-9：可溶性补体膜攻击复合物

酸酯、CD25单抗等药物替代。重度及极重度患者应立即启动特异性治疗。轻、中度患者接受支持治疗，严密观察并根据病情变化及时调整治疗方案，以防病情恶化。

1. 支持治疗：每日监测患者体重、腹围、尿量、出入量等，评估病情及治疗反应。去除可疑诱因，严格管理水钠摄入，利尿，输注白蛋白、血浆或成分血，维持循环血量和肾灌注。胸/腹腔大量积液时，可适度抽液以减轻压迫。低氧状态时给予氧疗或机械通气。必要时镇痛治疗，合并肾功能衰竭时进行血液透析或滤过治疗。重症患者建议转重症监护病房（ICU）或进行多学科会诊（MDT）。

2. 特异性治疗：常用药物包括DF、重组人组织型纤溶酶原激活物（rh-tPA）、糖皮质激素等。

（1）DF：DF是欧美国家唯一批准的重度SOS治疗药物，疗效和安全性已被多个较高质量的临床研究证实。完全缓解（CR）率为25.5%～55.0%，100 d生存率为38.2%～58.9%（不伴MOF者达71.0%），儿童疗效优于成人，主要不良事件为出血（肺、消化道）[64-67]。一项纳入140例SOS患者的上市后Ⅳ期研究结果显示，DF治疗后100 d生存率为58%，其中重度病例生存率为79%，极重度病例为34%[68]。推荐用法：6.25 mg·kg^{-1}·h^{-1}（2 h静脉滴注），依据治疗反应用药2～3周。有出血风险患者，可根据经验酌情减量。获得CR或发生严重出血时，可停药观察。

（2）rh-tPA：属丝氨酸蛋白酶，与纤维蛋白结合后，诱导纤溶酶原转化为纤溶酶，降解纤维蛋白，发挥溶栓活性。较早期的国外指南将其列为不能获得DF时的可选择药物之一，后基于较高的严重出血风险（近30%）而不再推荐[25]。近年国内陈峰等以低剂量rh-tPA（10 mg/d）为主方案治疗16例HSCT后重度/极重度SOS，CR率及100 d生存率均达到75%，无严重出血相关死亡[69-70]。

（3）糖皮质激素：早期应用有一定疗效。甲泼尼龙（MP）0.5 mg/kg，每日2次，反应率为63%，100 d生存率为58%[71]。Myers等[72]应用MP治疗儿童SOS（500 mg/m^2，每日2次），反应率为66.7%。应用时应警惕增加感染风险。

（4）其他：对治疗无反应、进展的SOS患者，如有条件，可尝试经颈静脉肝内门体静脉分流术（TIPS）、肝移植等挽救治疗。

共识建议采取分层治疗策略，需特异性治疗的患者在支持治疗基础上可加用DF。目前DF尚未在国内上市，各中心可根据各自经验选择低剂量rh-tPA、糖皮质激素等治疗，鼓励开展相关的临床试验研究。

（执笔：陈峰、韩悦、张晓辉）

参与共识制定和讨论的专家（以专家所在单位的首字母排序，同一单位专家按照姓氏首字母排序）：安徽省立医院（孙自敏）；安徽医科大学第四附属医院（杨明珍）；北京大学人民医院、北京大学血液病研究所（黄晓军、刘开彦、王昱、许兰平、张晓辉）；北京协和医院（周道斌）；重庆医科大学附属第一医院（刘林）；福建医科大学附属协和医院（胡建达、杨婷）；广西医科大学第一附属医院（赖永榕）；海军军医大学附属长海医院（杨建民）；河南省肿瘤医院（符粤文、宋永平）；华中科技大学同济医学院附属同济医院（张义成）；华中科技大学同济医学院附属协和医院（夏凌辉）；解放军总医院第五医学中心（胡亮钉、刘代红）；空军军医大学西京医院（高广勋）；陆军军医大学第二附属医院（张曦）；南方医科大学南方医院（刘启发）；山东大学齐鲁医院（侯明）；上海交通大学医学院附属瑞金医院（胡炯）；上海交通大学医学院附属上海儿童医学中心（陈静）；上海市第一人民医院（宋献民）；四川大学华西医院（刘霆）；苏州大学附属第一医院（陈峰、韩悦、唐晓文、王荧、王兆钺、吴德沛）；西安交通大学第一附属医院（张梅）；新疆医科大学第一附属医院（江明）；徐州医科大学附属医院（徐开林）；浙江大学医学院附属第一医院（黄河、罗依）；郑州大学第一附属医院（万鼎铭）；中国医科大学附属盛京医院（刘卓刚）；中国医学科学院血液病医院（韩明哲、姜尔烈）；中南大学湘雅医院（徐雅靖）

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