

《欧洲血管外科学会(ESVS)2021 年静脉血栓管理临床实践指南》解读



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吴洲鹏, 赵纪春, 马玉奎

四川大学华西医院血管外科(成都 610041)

欧洲血管外科学会(European Society for Vascular Surgery, ESVS)近日在线发表了首个《欧洲血管外科学会(ESVS)2021 年静脉血栓管理临床实践指南》(后文简称《ESVS 指南》)^[1]。ESVS 于 2017 年启动了制定《ESVS 指南》的流程,由 ESVS 的 16 名成员编写和批准。《ESVS 指南》涉及下肢深静脉血栓形成(deep vein thrombosis, DVT)、上肢 DVT、浅表静脉血栓形成和特殊部位静脉血栓形成;该指南还涵盖了治疗以外的主题,包括卫生经济学、特殊患者静脉血栓栓塞症(venous thromboembolism, VTE)的处理原则等。由于静脉血栓形成涉及的领域较广,因此《ESVS 指南》的适用范围不仅限于需要处理的静脉血栓形成的患者,也适用于参与该疾病诊治的临床医生,该指南中提出的诸多推荐意见得到了广大患者的积极反馈及响应。在《ESVS 指南》中,除了纳入了较多新的临床研究外,也存在一些专家共识是属于循证级别不高的新的推荐意见,需要更多的临床研究去证实,从而得出更强的推荐。笔者现就《ESVS 指南》的重要部分进行解读。

1 下肢 DVT

目前有文献^[2-3]报道,有症状性的下肢 DVT 的发病率为(50~100)/100 000,而且随着肺栓塞发病率的增加,使得 VTE 的整体发病率高于 25%;同时远期血栓后综合征(post-thrombotic syndrome, PTS)发病率也在逐年上升,其可能在 VTE 发生 3 个月后即开始出现^[4]。《ESVS 指南》中针对下肢 DVT 的诊断及治疗的推荐意见是基于最新的临床研究结果,其相对于美国胸科协会抗栓指南第 10 版(American College of Chest Physicians 10, ACCP10)^[5]的区别主要包括以下几个方面。

1.1 下肢 DVT 的诊断

目前已知的 DVT 症状、体征和其他临床危险因素虽然有助于提高 DVT 的临床诊断准确性,但这些因素不能单独用于确认或排除诊断。当将这些因素纳入临床决策工具时,可与 DVT 的个体化检测相结合,以辅助决策策略。目前已有的检查包括 D-二聚体指标、超声检查、计算机断层扫描静脉造影(computed tomography venography, CTV)、磁共振静脉造影(magnetic resonance venography, MRV)和静脉造影。在《ESVS 指南》中,对不同患者采取合理的诊断方式是作为推荐的,在诊断过程中,根据最新的文献^[6-21]及卫生经济学原则,对不同方法的选择进行了不同程度的推荐:① 当怀疑 DVT 时,建议医师在检查前先进行临床评估,并且所有参与诊断 DVT 的医疗专业人员都应该使用以上经过验证的诊断方式(IC)。② 对于怀疑有 DVT 而需要影像学检查的患者,建议首选超声检查(IC),对检查结果疑似 DVT 患者,若超声扫描结果为阴性,则 5~7 d 后复查超声进行评估(IIaC);对于怀疑近端 DVT 的患者,超声评估不确定时应考虑采用 CTV、MRV 或静脉造影检查(IIaC);对疑似小腿 DVT 的患者进行超声检查时建议采用全下肢超声(IC)。③ 对于无明显诱因的 DVT 患者并不推荐做常规的肿瘤相关性广泛筛查(IA)及遗传性血栓性疾病筛查(III C),但对于一级亲属有 VTE 病史者,建议进行遗传性血栓性疾病的检测(III C)。

1.2 下肢 DVT 的抗凝治疗

抗凝治疗是不同指南一致推荐的 VTE 的标准药物治疗方案,其中包括低分子肝素、磺达肝葵钠、直接口服抗凝药(达比加群、阿派沙班、利伐沙班等),这些药物在使用上有相对的禁忌证与适应证,需根据患者的不同基础情况加以使用。基于目前现有的最新文献,相对于 ACCP10 而言,针对抗凝药物的使用、抗凝时间的选择、药物出血风险的评估、延长抗凝的选择时机及时间上均有了一些新

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通信作者: 赵纪春, Email: zhaojc3@126.com

的推荐意见,尤其是对于直接口服抗凝药的使用、3个月以上的抗凝时间的界定方面尤为突出^[22-41],主要体现在以下几个方面:①除了既往 ACCP10 指出的急性期 3 个月的抗凝治疗外,《ESVS 指南》也特别指出,对于一过性危险因素而诱发的近端 DVT 患者,若病程超过 6 个月及以上时仍建议抗凝治疗 3 个月(IIaA);对非恶性肿瘤的持续性危险因素或暂时性危险因素诱发的近端 DVT 患者,在评估血栓和出血风险后,应考虑抗凝治疗超过 3 个月并定期重新评估(IIaC);对于无诱因的 DVT 患者,建议在继续抗凝 3 个月以后重新评估出血风险(IC);对于无诱因的近端 DVT 且有中低出血风险的患者,建议延长抗凝 3 个月以上并定期重新评估出血风险(IA)。②对于无诱因的近端 DVT、需要抗凝治疗超过 3 个月的患者,应考虑直接口服抗凝治疗而不是使用维生素 K 拮抗剂(IA);对无诱因的近端 DVT 且要求延长抗凝治疗超出 6 个月的患者(非高复发风险),应考虑减少使用直接口服抗凝剂阿派沙班(2.5 mg, 2 次/d)或利伐沙班(10 mg/d),IIaB,特别是对于无诱因的 DVT 患者,相对于 ACCP10,不建议使用阿司匹林进行延长的抗血栓治疗(IIIa)。③对于复发性下肢 DVT 的药物推荐,相对于 ACCP10,《ESVS 指南》基本仍是推荐改变抗凝药物类型或剂量,主要是将抗凝时间延长 3 个月以上(IB),同时需要考虑行超声检查残留静脉血栓及检测 D-二聚体水平(IIbB)。《ESVS 指南》认为,出血危险因素的相互作用和累加作用尚不清楚,文献证据不足。《ESVS 指南》对肝素诱导性血小板减少症治疗的推荐意见与 ACCP10 推荐意见基本一致,包括更换为直接口服抗凝剂或相应的静脉药物,比如伐卢定或阿加曲班。

1.3 下肢 DVT 的压力治疗

在 ACCP10 的推荐意见中,压力治疗并没有被作为降低 PTS 的推荐,同时对于压力治疗中采用的材料和时间都没有做详细的推荐,且推荐级别也仅仅是 II B;而在《ESVS 指南》中,新的文献^[42-53]纳入后,对压力治疗进行了更深层次的推荐,表现在以下几个方面:①对于近端 DVT 的患者,建议在 24 h 内用多层绷带或弹力袜进行 30~40 mm Hg (1 mm Hg=0.133 kPa) 早期压迫,以减轻疼痛、水肿和减少残余的静脉血栓(IA)。②对于近端 DVT 的患者,应考虑使用膝关节以下弹力袜,以降低 PTS 的风险(IIaA)。③对于近端 DVT 且如 Villalta 评分提示症状体征有限的患者,建议限制使用膝以下长袜 6 个月或 12 个月(IA)。但是压力

治疗在预防 PTS 方面的临床研究的有效性存在异质性,很大程度上尚待探索。

1.4 下肢 DVT 下腔静脉滤器安置

对于下腔静脉滤器的安置,相对于 ACCP10,《ESVS 指南》同样未做常规安置推荐,但对于存在抗凝禁忌的患者推荐使用临时性滤器(IC)^[54-55]。然而下腔静脉滤器的长期影响仍未确定。滤器植入后血栓形成的管理是一个证据很少的领域,无法推荐意见。

1.5 下肢 DVT 早期血栓清除

在早期血栓清除方面,无论是血栓清除的时机还是血栓清除后的药物使用,由于纳入了更多的临床研究,同时纳入了医患之间在该问题的相互认知方面的相关研究^[56-62],《ESVS 指南》做出了更多的推荐意见,表现在以下两个方面:①在有症状的髂股 DVT 患者中应考虑早期血栓清除策略(IIaA),但对于局限于股静脉、腘静脉或小腿静脉的 DVT 患者不推荐早期血栓清除(III B)。②对于早期接受取栓治疗的 DVT 患者,无论有无支架植入术,抗凝时间至少应与单独抗凝时间相同(IC)。

1.6 肌间静脉血栓的治疗

《ESVS 指南》相对于 ACCP10 来说,对肌间静脉血栓治疗方面的意见是颇具新颖性的。由于既往的研究较少,所以在 ACCP10 中对肌间静脉血栓的治疗推荐多是保守治疗,以随访观察为主;而在《ESVS 指南》中,由于近年来新的研究^[63-66]较多,因此,提出了更多的指导意见:①对于肌间静脉血栓形成的患者,应考虑根据症状、发展的风险因素和出血风险决定是否进行抗凝治疗(IIaC)。②对于有症状的肌间静脉血栓形成的非肿瘤、需要抗凝治疗的患者建议进行 3 个月的抗凝治疗(IA),而对于活动性肿瘤患者需要超过 3 个月的抗凝治疗(IIaC),同时指出直接口服抗凝药优于低分子肝素及华法林(IC)。③对于有症状的肌间静脉血栓形成患者,如果未接受抗凝治疗,建议进行临床重新评估并在 1 周后复查全下肢静脉超声检查,而不是既往推荐的 2 周(IB)。但需要注意的是,对于肌间静脉血栓形成患者,由于几乎完全缺乏每种临床情况所特有的随机对照研究,其抗凝药物的决定是基于低水平的证据,因此,对于这类患者延长抗凝治疗的建议仅基于风险观察数据而不是临床试验证据。

1.7 下肢浅静脉血栓形成的治疗

相对于既往的浅表静脉血栓形成的指南指导意见^[5]中,《ESVS 指南》在浅静脉血栓形成的范

围、血栓在特殊解剖部位发展的风险及药物的选择方面提出了更具体的建议,更贴近临床的需要,不仅仅是单纯的保守治疗为主,而且全局地看待了浅表静脉血栓形成是全身静脉血栓的一个部分,分辨出了它和 DVT 的关系^[67-74],主要表现在以下几个方面:①对于怀疑有下肢浅表静脉血栓形成的患者,建议进行全下肢静脉超声以确定血栓范围,并排除无症状的 DVT (IB)。②对于超声检查示下肢浅表静脉血栓形成长度 $<5\text{ cm}$ 且缺乏高风险特征(如恶性肿瘤、血栓形成或血栓接近深静脉系统)的患者不建议抗凝治疗(III C),而对于有症状性的下肢浅表静脉血栓距离隐股静脉交界处 $<3\text{ cm}$ 的患者则推荐抗凝治疗(IC)。③对于下肢浅表静脉血栓形成与隐股静脉交界处距离 $\geq 3\text{ cm}$ 且长度 $>5\text{ cm}$ 的患者,建议给予磺达肝癸钠 2.5 mg , 1次/d (IB),同时中等剂量的低分子肝素也是可行的(IIa B),建议进行45 d的抗凝治疗(IB)。④对于表现出血栓高风险和(或)解剖特征更倾向血栓蔓延的浅表静脉血栓形成的患者,可以考虑进行3个月的抗凝治疗(III C)。⑤《ESVS指南》特别指出了在浅表静脉血栓形成3个月后,可以根据患者的病情发展采用射频治疗方式进行处理(IIa C),而介入治疗未被推荐(III C),对于这类患者,没有证据表明与安慰剂相比,中等剂量的低分子肝素降低了DVT和(或)肺栓塞的发病率。对于深静脉交界处附近的浅表静脉血栓形成患者,关于治疗性抗凝药的时间缺乏足够的研究,在某些患者中将抗凝治疗延长至超过45 d的建议是基于观察数据而非随机对照试验。

2 上肢 DVT

在所有 DVT 患者中,上肢 DVT 的发病率为 $(4\sim 10)/100\ 000$ ^[69-74]。目前已经识别出两种不同类型的上肢 DVT 即原发性和继发性。原发性上肢 DVT (Pagete Schroetter 病)多由解剖异常所导致,而继发性上肢 DVT 通常与导管的使用有关,此更为普遍。在全球的静脉血栓栓塞症(GARFIELD-VTE)登记研究中,与下肢 DVT 患者相比,上肢 DVT 患者血栓发生在中心静脉置管的可能性明显更高^[75-76]。在最近的一项荟萃分析^[76]中,无原因的上肢 DVT 患者中 PTS 的比例高于下肢 DVT 患者,而且继发性上肢 DVT 患者的血栓复发率更高。在既往的文献^[69-73]及 ACCP10 中,对于上肢 DVT 的推荐意见同样包括推荐超声检查(IC)、抗凝治疗至少3个月(IC)、对于早期的血栓清除不推荐(III C)、有症状的上肢 DVT 的年轻患者在2周内的溶栓治

疗(II b C)等,但由于新的文献^[77-81]的纳入,使得其推荐级别有所改变。《ESVS指南》在有特殊解剖结构异常和导管相关性血栓的治疗方面有了一些新的推荐意见,主要有:①对于有上肢 DVT 并通过早期血栓清除术治疗的患者,如果有明确的证据表明存在胸廓出口综合征,则可以考虑首先行肋骨切除术(III C)。②对于有导管相关性血栓形成的患者,在以下情况下应考虑拔出导管:不需要继续使用、存在抗凝禁忌、抗凝药无法解决症状、血栓形成影响肢体功能或导致生命危险,这点与《导管相关性静脉血栓中国专家共识》临床实践推荐^[81]中提到的意见一致(IIa C)。③对于与导管相关性的血栓形成患者,应考虑使用低分子量肝素或华法林抗凝治疗至少3个月(IIa C)。特别需要指出的是,由于导管相关性血栓的治疗在临床实践中会有所不同,目前尚无关于抗凝持续时间的随机对照试验,仅有少量的描述了用普通肝素或维生素 K 拮抗剂进行抗凝治疗的回顾性或者前瞻性研究,关于利伐沙班使用的回顾性报道也很少。由于溶栓治疗的数据有限,仅在血栓形成的风险大于出血风险的情况下才应使用溶栓。有回顾性数据^[76-78]和两项前瞻性队列研究^[79-80]对于导管相关性血栓患者均采用抗凝治疗,建议在拔出导管后3个月使用低分子肝素或维生素 K 拮抗剂,期待更多关于导管相关性血栓的研究能够改变指南。同时对于怀疑患有上肢 DVT 的患者,各种诊断方式的相对敏感性和特异性结果均基于小型研究,其推荐证据级别都不高。另外,由于缺乏高质量的前瞻性随机研究,上肢 DVT 术后首次肋骨切除的作用也存在争议。

3 特殊人群 DVT

3.1 儿童

总的来说,儿童 VTE 发病率要比成人低很多,但近年来儿童 VTE 发病率在增加,这可能与儿童患者接受的侵入性操作日益增多有关^[82-84]。VTE 儿童患者在很多方面与成年人不同,主要差异不仅与 VTE 事件的流行病学和自然史有关,而且与抗血栓药物的药效学有关。儿童患者的大多数 DVT 事件与导管相关。儿童患者 VTE 的所有治疗选择的详细描述不在《ESVS指南》讨论范围,但与成年患者相比,儿童患者监测指标(活化部分凝血酶原时间、抗 Xa 水平等)的需求大大增加了。直接口服抗凝剂在 DVT 儿童治疗中的作用一直受到重大争论。在 EINSTEIN-Jr III 期试验^[82]中,对 500 例 VTE 儿童进行了体质量调整后的 20 mg 等效剂量利伐沙班治

疗,并与标准抗凝剂治疗(肝素治疗或改用维生素K拮抗剂)进行了比较,发现这两种治疗方法同样有效和安全。此外,与标准抗凝剂治疗相比,利伐沙班降低了血栓形成风险,期待在儿童患者中进一步研究直接口服抗凝剂治疗,所以在《ESVS指南》中仅有“儿童DVT的治疗应由在小儿血栓形成和止血方面具有专业知识的临床医生指导(IC)”。

3.2 妊娠妇女

与同年龄的非妊娠妇女相比,妊娠妇女产前VTE的发病率高10倍,产后VTE的发病率高25倍,这种增加的VTE风险发生在早期妊娠期至产后12周^[85-87]。尽管增加了血栓预防措施的使用,但VTE仍是孕产妇死亡的主要直接原因。对此,《ESVS指南》的推荐意见与既往的ACCP10基本一致,包括产前使用低分子肝素至少3个月到产后6周,不推荐D-二聚体及Wells评分;不同的是,《ESVS指南》增加了对于DVT孕妇在预计分娩日期前不到2周可以考虑使用临时的下腔静脉滤器的推荐(IIbB)^[85-87],但需注意这并非基于临床试验证据。

3.3 恶性肿瘤患者DVT

恶性肿瘤患者本身就是DVT的独立危险因素,在众多肿瘤相关的指南或血栓指南中都有其推荐意见且证据级别都较高。同样,《ESVS指南》在已有文献^[88-91]支持下,将低分子肝素和直接口服抗凝剂都提到了相当的高度,低分子肝素同样是IA级推荐;而对于非胃肠道、泌尿道的恶性肿瘤患者3~6个月的抗凝治疗(IC)及3~6个月后的延长治疗(IIaA)均推荐了直接口服抗凝剂治疗。

3.4 具有血栓形成倾向的患者

血栓形成倾向通常用于描述由于遗传和(或)获得性血栓形成异常而发展为血栓形成的倾向。遗传性血栓形成症可分为天然凝血抑制剂(抗凝血酶、C蛋白和S蛋白缺乏症)功能丧失及凝血因子V Leiden和凝血酶原G20210A突变^[92]。抗凝治疗需要对VTE发病机理的全面理解,近年来这方面的研究也是层出不穷^[93-94],因此,在《ESVS指南》中相较ACCP10提出了以下更有意义的推荐意见:①对于DVT和高危血友病患者(如抗磷脂综合征、凝血因子V Leiden突变、C蛋白或S蛋白缺乏或抗凝血酶的患者),建议进行全剂量扩展抗凝治疗并定期重新评估(IC)。②对于具有动脉或小血管血栓形成史的DVT和抗磷脂综合征患者,不应使用直接口服抗凝剂(IIIb)而是推荐华法林并维持国际标准化比值为2~3(IIaB)。③《ESVS指南》肯定了血液病专家的参与(IC)。

3.5 肾功能不全和体质量异常的患者

对肾功能不全和体质量异常患者,由于药代动力学和药效动力学的研究结果非常肯定,《ESVS指南》除了提出了肾功能的监测和药物剂量根据体质量调整的建议外,无更多改变,与既往指南一致。

总之,在《ESVS指南》中,虽然纳入了较多新的文献,也提出了较多新的观点与理念,但是仍然存在一些无法解决的具体问题,主要归因于缺乏相应的临床研究或仅仅是回顾性研究,缺乏前瞻性的随机研究,比如DVT的病因学研究、PTS的预防、特殊部位和特殊人群的血栓诊断与治疗,这些都是从事血栓研究的医务人员面临的挑战,期待更多的随机研究能够进行,以求指南的更新中能够基于这些研究得到更强的推荐意见。

重要声明

利益冲突声明:本文全体作者阅读并理解了《中国普外基础与临床杂志》的政策声明,我们没有相互竞争的利益。

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