·专题综述·

创伤性脑损伤诱发的凝血功能障碍研究进展

徐新　尚峰　曲鑫　王宁

【摘要】 创伤性脑损伤常诱发凝血功能障碍，表现为导致颅内和全身缺血性损伤的高凝状态，并迅速进展为导致出血性损伤的消耗性低凝状态，二者相互作用，严重影响预后。早期诊断、及时纠正创伤性脑损伤诱发的凝血功能障碍（TBI-IC）业已成为共识，但其发生与发展机制尚未阐明，亦缺乏有效的预防与治疗手段。本文通过对TBI-IC临床特点、病理生理学机制、治疗策略等进行综述，以为临床诊断与治疗提供理论依据。

【关键词】 脑损伤，创伤性；　血液凝固障碍；　综述

The research progress of traumatic brain injury-induced coagulopathy

XU Xin, SHANG Feng, QU Xin, WANG Ning

Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing 100053, China

Corresponding author: WANG Ning (Email: ningjing_wd@163.com)

【Abstract】 Traumatic brain injury (TBI) often develops secondary coagulopathy (TBI-IC), which is characterized by a hypercoagulable state that leading to intracranial and systemic ischemic events and rapidly developing into a consumptive hypocoagulable state that leading to hemorrhagic injuries. These two coagulative states in patients with TBI are highly integrated and closely associated with poor outcomes. It has become the consensus that early diagnosis and correction of TBI-IC improve survival and neurological outcomes. However, the underlying mechanisms of TBI-IC remain poorly understood, and there is a lack of effective treatment. This article will review the clinical course, potential pathophysiological mechanism and treatment strategy of TBI-IC, hoping to provide reference for better guidance of clinical diagnosis and treatment of TBI-IC.

【Key words】 Brain injuries, traumatic;　Blood coagulation disorders;　Review

This study was supported by the Capital Health Research and Development of Special (No. 2020-2Z-2019).

Conflicts of interest: none declared

创伤性脑损伤（TBI）具有高发生率、高病残率和高病死率的特点，我国人口基数大，创伤性脑损伤病例高于其他国家[1]。由于创伤性脑损伤的原发性脑损伤发生于瞬间，通常无法对其实施有效干预，加强针对其继发性脑损伤发病机制和干预措施的研究，是降低创伤性脑损伤病残率或病死率的关键[2]。创伤性脑损伤后继发性脑损伤机制主要包括神经炎症反应、凝血功能障碍、氧化应激反应，以及线粒体功能障碍等[2]，其中创伤性脑损伤诱发的凝血功能障碍（TBI-IC）即创伤性脑损伤凝血病是诱发继发性脑损伤的重要机制之一，以血液高凝状态并迅速进展为消耗性低凝状态为特征，二者相互作用，使患者预后不良[3-4]。据研究显示，创伤性脑损伤后伴发凝血功能障碍患者的死亡风险是不伴凝血功能障碍患者的10倍，其预后不良风险甚至可高达30倍[5]。因此，早期发现、及时纠正凝血功能障碍对降低创伤性脑损伤患者病死率、改善预后具有重要意义，但是目前对其病理生理学机制尚不十分清楚，导致诊断与治疗过程充满困惑[6]。

而对颅外创伤如四肢骨折、实质脏器损伤等继发的凝血功能障碍即创伤性凝血病（TIC）的发生机制业已阐明，包括广泛性组织损伤、失血性休克和组织低灌注引起的代谢性酸中毒、大量补液引起的血液稀释和低体温等[7-8]，此为一种“丢失性”、稀释

doi：10.3969/j.issn.1672-6731.2020.08.003

基金项目：首都卫生发展科研专项项目（项目编号：首发2020-2Z-2019）

作者单位：100053 北京，首都医科大学宣武医院神经外科

通讯作者：王宁，Email：ningjing_wd@163.com

性凝血功能障碍。然而，临床上单纯创伤性脑损伤患者鲜见大量失血，针对颅内高压需限制液体摄入量，且患者更多表现为高热而非低体温，提示TBI-IC的发生机制有别于创伤性凝血病。凝血功能障碍患者血浆D-二聚体水平可于创伤后数分钟即升高，而凝血酶原时间（PT）和活化部分凝血活酶时间（APTT）延长则出现的较晚，表明由高凝状态逐渐转至低凝状态，呈现消耗性凝血功能障碍[9]。近年细胞微囊泡（MVs）领域的新发现，或可以解释局限性创伤性脑损伤所致系统性凝血功能障碍的原因[3]；同时，组织因子（TF）释放、内皮细胞损伤、血小板功能障碍、纤溶活性异常和蛋白C（PC）系统激活等相关病理生理学机制也已取得共识。笔者以TBI-IC病理生理学机制为重点，综述该领域最新研究进展，拟为临床诊断与治疗提供理论依据。

一、流行病学特点、临床特点及诊断

1. 流行病学特点　由于目前尚无统一诊断标准，TBI-IC发生率在不同国家、不同研究团队的报道中差异较大，为10%～97%[6]。TBI-IC与创伤严重程度密切相关，常用评价指标包括Glasgow昏迷量表（GCS）评分（≤8分）、创伤严重程度评分（ISS，≥16分）、休克指数（SI≥1）等[10]；逾2/3的重型颅脑创伤患者伤后可诱发凝血功能障碍，且伤情越严重、凝血功能障碍发生越早，重症患者在入院前多已存在凝血功能障碍[11]。与钝性伤和冲击伤相比，穿通伤后凝血功能障碍发生率更高[12]；脑挫裂伤常伴有广泛性微血管和血脑屏障破坏，特别是老年患者更易发生凝血功能障碍[13]。此外，合并贫血、高血糖、低收缩压，以及影像学提示脑水肿、中线移位、蛛网膜下腔出血等均为重要危险因素[6]。值得注意的是，既往创伤性脑损伤常见于45岁以下青壮年，其中交通事故伤为主要致伤原因；随着老龄化因素的上升，近年来约有50%以上的患者为50岁以上的老年人群，且以摔伤为主[14]。摔伤主要导致脑挫裂伤，加之大多数老年人均有服用抗凝药或抗血小板药病史，故老年创伤性脑损伤患者凝血功能障碍发生率更高，且大多预后不良[15-16]。Probst等[17]基于9070例钝性创伤性脑损伤患者的研究显示，华法林或阿司匹林联合氯吡格雷服药史是创伤后进展性出血性损伤（PHI）等继发性脑损伤的重要危险因素。近年服用靶向口服抗凝药（TSOAs）的人群比例逐渐增加[18]，由于各项研究所纳入的创伤性脑损伤类型或严重程度等有所不同，造成评价TSOAs对创伤性脑损伤后进展性出血性损伤发生率和病死率影响的结论不尽一致[18-20]。

2. 临床特点　TBI-IC患者的凝血系统和纤溶系统改变可持续至创伤后3天甚至更长时间[21]。高凝状态可以导致血管内微血栓形成，由此而引起脑血流量（CBF）减少，以及铁蛋白、含铁血黄素等脑组织神经毒性物质沉积，是创伤后早期继发性脑梗死等缺血性损伤的重要原因[22]。动物实验证实，创伤性脑损伤后数小时即可见微血栓形成，形成部位与神经元损伤区域具有高度相关性[23-24]。与高凝状态继发血栓形成相比，消耗性低凝状态主要引起进展性出血性损伤，表现为在脑挫裂伤、创伤性脑出血等原发灶基础上发生的进展性颅内出血（创伤后数小时内）、迟发性颅内出血（创伤后6～48小时）或全身出血倾向[10,14]；约有50%的患者于创伤后48小时出现进展性出血性损伤，预后不良，且死亡风险超过无凝血功能障碍患者的5倍[25]。

3. 诊断　TBI-IC的临床诊断标准为常规凝血功能试验结果异常，包括凝血酶原时间、活化部分凝血活酶时间、国际标准化比值（INR）、血小板计数、纤维蛋白原（FIB）和D-二聚体等，但这些实验室指标特异性较低且无法解释创伤性脑损伤后发生凝血功能障碍的潜在原因[10]。血栓弹性描记图（TEG）可实现床旁实时监测凝血和纤溶级联反应，其诊断能力优于常规凝血功能试验，但基于血栓弹性描记图的临床诊断标准尚未建立[26]，因此进一步探明TBI-IC患者凝血系统和纤溶系统异常改变的时间进程、建立血栓弹性描记图的特异性参考值范围，具有重要意义。此外，随着针对TBI-IC病理生理学机制研究的深入，一些具有潜在临床诊断价值的生物学标志物（如细胞微囊泡）逐渐被发现并有望实现临床转化[27]。

二、潜在病理生理学机制

1. 细胞微囊泡　细胞微囊泡是细胞激活、损伤或凋亡后自胞膜表面脱落的、具有双层脂质膜结构的微小囊泡，直径100～1000 nm[3]。其形成时胞膜内层磷脂酰丝氨酸（PS）等阴离子磷脂外翻，为凝血级联反应提供磷脂表面，故具有极强的促凝活性。Nekludov等[28]的研究显示，创伤性脑损伤患者外周血和脑脊液中具有高促凝活性的细胞微囊泡（PS^+ MVs）数目显著增加，以血小板和内皮细胞源性为主。天津医科大学张建宁教授团队首次在创伤性脑损伤小鼠模型外周血和损伤脑组织中检测到神

经元和神经胶质细胞源性微囊泡，即脑源性微囊泡（BDMVs）[29-30]，此后Nekludov等[31]证实重型颅脑创伤患者外周血中亦存在这种脑源性微囊泡。因此，推测脑源性微囊泡可能是TBI-IC的启动和传播因素[29-30,32-33]：（1）创伤后血脑屏障破坏，受损脑组织释放脑源性微囊泡进入血液循环，启动凝血级联反应，诱发系统性高凝状态并迅速进展为消耗性低凝状态。（2）于小鼠尾静脉注射经体外制备的脑源性微囊泡，可模拟创伤性脑损伤小鼠凝血系统和纤溶系统改变。（3）游离线粒体（exMTs）约占脑源性微囊泡的55.2%，通过其膜表面心磷脂发挥促凝、促血小板激活作用。（4）脑源性微囊泡可以引起血管内皮细胞损伤或激活，导致血管内皮促凝活性增强或血管内皮屏障破坏，从而加重TBI-IC。（5）乳凝集素（lactadherin）可以有效清除细胞微囊泡，减轻创伤性脑损伤小鼠凝血功能紊乱和血管内皮屏障破坏程度。因此，以脑源性微囊泡为生物学标志物和治疗靶点的基础与临床研究，可以为TBI-IC的临床诊断与治疗提供新的思路。

2. 组织因子与弥散性血管内凝血　脑组织富含凝血活酶，以组织因子为主[34]。创伤性脑损伤后受损的脑组织可释放组织因子进入血液循环，通过与凝血因子Ⅶa结合，启动外源性凝血途径，同时促进内源性凝血途径，导致系统性高凝状态；随着凝血因子和血小板的耗竭，转为消耗性低凝状态，伴随继发性纤溶系统亢进，最终导致弥散性血管内凝血（DIC）[35]。弥散性血管内凝血可发生于创伤性脑损伤后6小时，由于纤维蛋白沉积和微血栓形成，导致机体缺血性损伤和难以纠正的出血倾向[36]，而且创伤性脑损伤早期发生的弥散性血管内凝血常伴随全身性炎症反应综合征、多器官功能障碍综合征等不良事件[37]。Nekludov等[28]发现，创伤性脑损伤患者外周血和脑脊液中存在表面高表达组织因子的细胞微囊泡（TF$^+$MVs），提示组织因子可通过绑定细胞微囊泡而发挥促凝作用。Tian等[29]认为，创伤性脑损伤小鼠外周血中的脑源性微囊泡通过其膜表面组织因子介导凝血酶生成及其与血小板结合而介导血小板激活，促进凝血级联反应。

3. 血管内皮细胞损伤　血管内皮细胞损伤或被激活，使其促凝-抗凝系统失衡，血管内皮促凝活性增强被认为是导致TBI-IC的早期事件。糖萼是衬于血管内皮细胞表面的一层蛋白质-多糖复合物，包含抗凝血酶Ⅲ、组织因子途径抑制物等抗凝物质，使生理状态下的血管内皮细胞具有抗凝特性[38]。由于创伤性脑损伤后交感神经兴奋和儿茶酚胺过度分泌，导致糖萼代谢受损和凝血级联反应的发生，而创伤性脑损伤后血浆糖萼降解产物多配体蛋白聚糖-1（syndecan-1）水平变化与凝血功能障碍的发生及预后不良密切相关[38-39]。血管内皮细胞损伤或激活后释放的另一关键性促血栓形成物质，为血管性血友病因子（vWF），其可通过介导血小板向血管内皮损伤部位粘附以促进血栓形成[3]；而在创伤性脑损伤急性期大量释放的高黏附活性的血管性血友病因子，具有促进血栓形成和凝血功能障碍的作用，这一作用可被特异性整合素样金属蛋白酶与凝血酶13型（ADAMTS-13）所阻断[33]。Kumar等[40]经研究显示，创伤性脑损伤患者外周血血管性血友病因子表达水平和黏附活性增强、ADAMTS-13水平相对不足，导致中至重症患者凝血功能紊乱、预后不良。进一步探究血管性血友病因子在TBI-IC发生与发展过程中的作用机制，进而开展血管性血友病因子抑制药干预TBI-IC的基础与临床转化研究具有重要意义。值得关注的是，以血管内皮细胞为核心的炎症反应与血栓形成相互促进，“血栓炎症（thromboinflammation）”的概念逐渐取得共识并受到重视[41]，相关研究主要集中在脓毒血症、心肌梗死和缺血性卒中等疾病，以及血小板、中性粒细胞胞外诱捕网（NETs）和vWF/ADAMTS13等，有可能在血栓炎症的发生与发展中发挥一定作用[41-42]。基于血栓炎症的研究可能为TBI-IC的临床诊断与治疗提供新的思路。

4. 血小板功能障碍　研究显示，血小板过度消耗与进展性出血性损伤相关：当创伤性脑损伤患者血小板计数$<175\times10^9$/L时，进展性出血性损伤风险显著增加，$<100\times10^9$/L时死亡风险增加9倍[43]；但血小板计数正常的创伤性脑损伤患者同样可发生进展性出血性损伤[44]，提示血小板计数（即血小板的“量”）可能并非起决定作用。经血栓弹性描记图分析证实，TBI-IC患者在创伤早期即存在血小板功能障碍（即血小板的“质”），表现为由二磷酸腺苷（ADP）和花生四烯酸（AA）介导的血小板聚集能力减弱[45]。其中，ADP途径抑制（ADPi）被认为是诱发TBI-IC的重要原因，ADPi≥60%的患者发生进展性出血性损伤和死亡的风险显著增加[45-46]。因此，有学者将创伤性脑损伤后血小板功能障碍定义为ADPi≥60%，并推荐其为血小板输注阈值[46-47]。但

Kay等[44]认为，ADPi≥70%可能更具临床指导价值。创伤性脑损伤后血小板功能障碍的发生机制目前尚未明确，Martin等[48]的研究表明，创伤性脑损伤后释放的细胞微囊泡表面高表达二磷酸腺苷受体P2Y12，通过竞争性结合二磷酸腺苷，从而抑制由后者介导的血小板聚集；此外，由Donahue等[49]构建的创伤性脑损伤血小板功能障碍大鼠模型，为相关机制和干预研究提供了动物研究模型。

5. 纤溶系统活性异常　目前认为，创伤性脑损伤后的高凝状态继发纤溶系统亢进可增加进展性出血性损伤等不良事件的风险[50]。D-二聚体是纤溶系统亢进的特异性标志物，血浆D-二聚体水平于创伤后显著升高，且与进展性出血性损伤和预后不良呈负相关[50-51]，尤其是入院时血浆D-二聚体≥3.04 μg/ml是预测进展性出血性损伤的重要参考指标[51]。但Xu等[52]认为，D-二聚体/纤维蛋白原比值是更具有优势的进展性出血性损伤的预测指标。不同于继发性纤溶系统亢进这一主流观点，Hijazi等[53]指出，进展性出血性损伤的发生与发展可能是受损脑组织释放组织型或尿激酶型纤溶酶原激活物（t-PA或u-PA）引起的原发性纤溶系统亢进所致。值得注意的是，亦有基于血栓弹性描记图等新型检测技术的研究显示，创伤性脑损伤患者极少合并纤溶系统亢进[54]。近年来，纤溶系统亢进的相反状态——纤溶系统阻滞（fibrinolysis shutdown）越来越受到关注，其发生机制可能与t-PA和（或）纤溶酶原激活物抑制剂-1（PAI-1）表达水平和活性失调有关[55]，其中，纤溶系统阻滞是创伤性凝血病患者最为常见的纤溶状态[56]。目前关于纤溶系统阻滞的研究较少，仅Leeper等[57]报告纤溶系统阻滞现象在儿童创伤性脑损伤患者中极为常见且与预后不良相关。创伤性脑损伤后纤溶活性改变及其与TBI-IC间的关系尚待进一步深入研究。

6. 组织低灌注与蛋白C系统激活　创伤性脑损伤后失血性休克可引起组织低灌注，使血栓调节蛋白（TM）水平升高，后者通过与凝血酶结合激活蛋白C为活化蛋白C（APC），后者可灭活凝血因子Ⅴa和Ⅷa，同时抑制PAI-1活性，从抗凝和促纤溶两方面导致低凝状态[58]。上述作用机制已经证实与创伤性凝血病密切相关[7-8]，但其在TBI-IC发生中的作用仍存争议。组织低灌注和蛋白C系统激活可加重TBI-IC，但失血性休克在创伤性脑损伤中并不常见，未合并失血性休克性组织低灌注的患者其活化蛋白C水平与TBI-IC并无关联性[37,59-60]。Sillesen等[61]经对创伤性脑损伤合并失血性休克猪模型的观察发现，创伤后即刻凝血系统和纤溶系统即出现异常，而蛋白C系统激活则发生于创伤后2小时。因此，与创伤性凝血病不同，组织低灌注和蛋白C系统激活是TBI-IC的危险因素，但非必要因素[37,59-60]。

三、治疗进展

早期纠正凝血功能障碍与降低病死率和改善预后相关，因此入院后应立即进行凝血功能试验和（或）血栓弹性描记图以监测凝血系统和纤溶系统状态[62]。目前尚无TBI-IC相关治疗指南，需借鉴创伤性凝血病的治疗方案，如2019年欧洲创伤出血高级处理特别工作组（Task Force for Advanced Bleeding Care in Trauma）发布的《严重创伤出血与凝血障碍管理欧洲指南（第5版）》（简称“欧洲指南”）[63]，但是由于二者发生机制存在差异，该方案是否适用于TBI-IC尚无明确的循证医学证据。中国神经外科重症管理协作组最新发布的《中国神经外科重症管理专家共识（2020版）》[64]对急性创伤性出凝血功能障碍给出了指导意见。

1. 针对凝血功能紊乱的治疗原则　对于创伤前有抗凝药服药史的患者，早期应用特异性拮抗药或凝血酶原复合物可以逆转抗凝药引起的凝血功能紊乱[65-66]；而合并失血性休克患者，则应重视对“致死性三联征（低体温、酸中毒和凝血功能障碍）”的积极干预，“欧洲指南”推荐限制性液体复苏方案，维持平均动脉压（MAP）> 80 mm Hg（1 mm Hg = 0.133 kPa）[63]。2019年发表于*Lancet*的氨甲环酸治疗创伤性脑损伤Ⅲ期临床试验（CRASH-3）显示，创伤后3小时内予氨甲环酸可安全、有效降低轻至中型创伤性脑损伤患者的死亡风险，但对重症患者无明显疗效[67]，推测可能与创伤后出现的不同纤溶状态有关，即氨甲环酸仅对纤溶亢进者有效[50,55]。值得注意的是，尚有小样本临床试验显示，氨甲环酸对改善进展性出血性损伤和预后无效[68]。

2. 输血治疗　输血治疗是TBI-IC的常规治疗手段，但目前大多为经验性治疗。来自欧洲和以色列等20个国家的数据显示，创伤性脑损伤患者入院后静脉输注血小板或新鲜冰冻血浆（FFP）的比例为52%和73%[69]，但二者对TBI-IC的有效性仍有较大争议，目前尚无明确结论[70-72]。对于创伤前服用抗血小板药的创伤性脑损伤患者，若合并血小板功能障碍且需接受手术治疗，建议静脉输注血小板并维

持血小板计数 > 100×10^9/L[47,63]；对于疑似进展性出血性损伤且凝血酶原时间和(或)活化部分凝血活酶时间 > 正常参考值1.50倍的患者，建议静脉输注新鲜冰冻血浆以补充凝血因子[63]。尽管已知贫血是TBI-IC的危险因素，但多数试验提示静脉输注红细胞对改善凝血功能无效，甚至可加重病情[73-74]。Yuan等[75]认为，静脉输注小剂量(20 μg/kg)重组凝血因子Ⅶ(rFⅦa)可有效纠正TBI-IC、预防进展性出血性损伤且不增加血栓形成风险。“欧洲指南”推荐，重组凝血因子Ⅶ可作为常规治疗无法控制的大出血或TBI-IC持续存在的替代方案[63]。Stolla等[76]在“TBI-IC输血治疗研究进展”中指出，目前所报道的输血治疗TBI-IC有效性和安全性的临床试验大多呈阴性结果，但这些研究中以小样本、回顾性或混杂因素较多的临床试验居多，缺乏高级别循证医学证据。此外，进一步开展不同血液成分对TBI-IC影响的机制研究将为输血治疗适应证、输血成分和输血量的选择提供理论依据。

四、小结

尽管TBI-IC的研究业已取得长足进步，但其确切的发生与发展机制尚不明确，亦缺乏有效的早期诊断和干预措施，尚待进一步的基础与临床研究。一些新兴领域如脑源性微囊泡、“血栓炎症”和纤溶系统阻滞等相关研究为TBI-IC的诊断、预防与治疗开拓了新的思路。此外，创伤性脑损伤患者同样存在老龄化趋势，针对老年创伤性脑损伤患者的个性化治疗也应是今后关注之重点。

利益冲突 无

参 考 文 献

[1] Jiang JY, Gao GY, Feng JF, Mao Q, Chen LG, Yang XF, Liu JF, Wang YH, Qiu BH, Huang XJ. Traumatic brain injury in China[J]. Lancet Neurol, 2019, 18:286-295.

[2] Maas AI, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, Bragge P, Brazinova A, Büki A, Chesnut RM, Citerio G, Coburn M, Cooper DJ, Crowder AT, Czeiter E, Czosnyka M, Diaz-Arrastia R, Dreier JP, Duhaime AC, Ercole A, van Essen TA, Feigin VL, Gao G, Giacino J, Gonzalez-Lara LE, Gruen RL, Gupta D, Hartings JA, Hill S, Jiang JY, Ketharanathan N, Kompanje EJO, Lanyon L, Laureys S, Lecky F, Levin H, Lingsma HF, Maegele M, Majdan M, Manley G, Marsteller J, Mascia L, McFadyen C, Mondello S, Newcombe V, Palotie A, Parizel PM, Peul W, Piercy J, Polinder S, Puybasset L, Rasmussen TE, Rossaint R, Smielewski P, Söderberg J, Stanworth SJ, Stein MB, von Steinbüchel N, Stewart W, Steyerberg EW, Stocchetti N, Synnot A, Ao BT, Tenovuo O, Theadom A, Tibboel D, Videtta W, Wang KK, Williams WH, Wilson L, Yaffe K; InTBIR Participants and Investigators. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research[J]. Lancet Neurol, 2017, 16:987-1048.

[3] Zhang J, Zhang F, Dong JF. Coagulopathy induced by traumatic brain injury: systemic manifestation of a localized injury[J]. Blood, 2018, 131:2001-2006.

[4] van Gent JA, van Essen TA, Bos MH, Cannegieter SC, van Dijck JT, Peul WC. Coagulopathy after hemorrhagic traumatic brain injury, an observational study of the incidence and prognosis[J]. Acta Neurochir (Wien), 2020, 162:329-336.

[5] Talving P, Benfield R, Hadjizacharia P, Inaba K, Chan LS, Demetriades D. Coagulopathy in severe traumatic brain injury: a prospective study[J]. J Trauma, 2009, 66:55-62.

[6] Maegele M, Schöchl H, Menovsky T, Maréchal H, Marklund N, Buki A, Stanworth S. Coagulopathy and haemorrhagic progression in traumatic brain injury: advances in mechanisms, diagnosis, and management[J]. Lancet Neurol, 2017, 16:630-647.

[7] Kornblith LZ, Moore HB, Cohen MJ. Trauma - induced coagulopathy: the past, present, and future[J]. J Thromb Haemost, 2019, 17:852-862.

[8] Duque P, Mora L, Levy JH, Schöchl H. Pathophysiological response to trauma - induced coagulopathy: a comprehensive review[J]. Anesth Analg, 2020, 130:654-664.

[9] Nakae R, Takayama Y, Kuwamoto K, Naoe Y, Sato H, Yokota H. Time course of coagulation and fibrinolytic parameters in patients with traumatic brain injury[J]. J Neurotrauma, 2016, 33:688-695.

[10] Maegele M, Aversa J, Marsee MK, McCauley R, Chitta SH, Vyakaranam S, Walsh M. Changes in coagulation following brain injury[J]. Semin Thromb Hemost, 2020, 46:155-166.

[11] Albert V, Arulselvi S, Agrawal D, Pati HP, Pandey RM. Early posttraumatic changes in coagulation and fibrinolysis systems in isolated severe traumatic brain injury patients and its influence on immediate outcome[J]. Hematol Oncol Stem Cell Ther, 2018, 12:32-43.

[12] Martin G, Shah D, Elson N, Boudreau R, Hanseman D, Pritts TA, Makley AT, Foreman B, Goodman MD. Relationship of coagulopathy and platelet dysfunction to transfusion needs after traumatic brain injury[J]. Neurocrit Care, 2018, 28:330-337.

[13] Carnevale JA, Segar DJ, Powers AY, Shah M, Doberstein C, Drapcho B, Morrison JF, Williams JR, Collins S, Monteiro K, Asaad WF. Blossoming contusions: identifying factors contributing to the expansion of traumatic intracerebral hemorrhage[J]. J Neurosurg, 2018, 129:1305-1316.

[14] Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury[J]. Nat Rev Neurol, 2013, 9:231-236.

[15] Scotti P, Séguin C, Lo BW, de Guise E, Troquet JM, Marcoux J. Antithrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes[J]. J Neurosurg, 2019, 5:1-10.

[16] Hecht JP, LaDuke ZJ, Cain-Nielsen AH, Hemmila MR, Wahl WL. Effect of preinjury oral anticoagulants on outcomes following traumatic brain injury from falls in older adults[J]. Pharmacotherapy, 2020, 40:604-613.

[17] Probst MA, Gupta M, Hendey GW, Rodriguez RM, Winkel G, Loo GT, Mower WR. Prevalence of intracranial injury in adult patients with blunt head trauma with and without anticoagulant or antiplatelet use[J]. Ann Emerg Med, 2020, 75:354-364.

[18] Zeeshan M, Jehan F, O′Keeffe T, Khan M, Zakaria ER, Hamidi M, Gries L, Kulvatunyou N, Joseph B. The novel oral anticoagulants (NOACs) have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI[J]. J Trauma Acute Care Surg, 2018, 85:915-920.

[19] Prexl O, Bruckbauer M, Voelckel W, Grottke O, Ponschab M, Maegele M, Schöchl H. The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old[J]. Scand J Trauma Resusc Emerg Med, 2018, 26:20.

[20] Nederpelt CJ, van der Aalst SJ, Rosenthal MG, Krijnen P, Huisman MV, Peul WC, Schipper IB. Consequences of pre-injury utilization of direct oral anticoagulants in patients with traumatic brain injury: a systematic review and Meta-analysis [J]. J Trauma Acute Care Surg, 2020, 88:186-194.

[21] Greuters S, van den Berg A, Franschman G, Viersen VA, Beishuizen A, Peerdeman SM, Boer C; ALARM-BLEEDING Investigators. Acute and delayed mild coagulopathy are related to outcome in patients with isolated traumatic brain injury[J]. Crit Care, 2011, 15:R2.

[22] Veenith TV, Carter EL, Geeraerts T, Grossac J, Newcombe VF, Outtrim J, Gee GS, Lupson V, Smith R, Aigbirhio FI, Fryer TD, Hong YT, Menon DK, Coles JP. Pathophysiologic mechanisms of cerebral ischemia and diffusion hypoxia in traumatic brain injury[J]. JAMA Neurol, 2016, 73:542-550.

[23] Schwarzmaier SM, de Chaumont C, Balbi M, Terpolilli NA, Kleinschnitz C, Gruber A, Plesnila N. The formation of microthrombi in parenchymal microvessels after traumatic brain injury is independent of coagulation factor Ⅺ [J]. J Neurotrauma, 2016, 33:1634-1644.

[24] Hopp S, Albert-Weissenberger C, Mencl S, Bieber M, Schuhmann MK, Stetter C, Nieswandt B, Schmidt PM, Monoranu CM, Alafuzoff I, Marklund N, Nolte MW, Sirén AL, Kleinschnitz C. Targeting coagulation factor Ⅻ as a novel therapeutic option in brain trauma[J]. Ann Neurol, 2016, 79: 970-982.

[25] Juratli TA, Zang B, Litz RJ, Sitoci KH, Aschenbrenner U, Gottschlich B, Daubner D, Schackert G, Sobottka SB. Early hemorrhagic progression of traumatic brain contusions: frequency, correlation with coagulation disorders, and patient outcome: a prospective study[J]. J Neurotrauma, 2014, 31:1521-1527.

[26] Rao A, Lin A, Hilliard C, Fu R, Lennox T, Barbosa R, Schreiber M, Rowell S. The utility of thromboelastography for predicting the risk of progression of intracranial hemorrhage in traumatic brain injury patients[J]. Neurosurgery, 2017, 64:182-187.

[27] Gan ZS, Stein SC, Swanson R, Guan S, Garcia L, Mehta D, Smith DH. Blood biomarkers for traumatic brain injury: a quantitative assessment of diagnostic and prognostic accuracy [J]. Front Neurol, 2019, 10:446.

[28] Nekludov M, Mobarrez F, Gryth D, Bellander BM, Wallen H. Formation of microparticles in the injured brain of patients with severe isolated traumatic brain injury[J]. J Neurotrauma, 2014, 31:1927-1933.

[29] Tian Y, Salsbery B, Wang M, Yuan H, Yang J, Zhao Z, Wu X, Zhang Y, Konkle BA, Thiagarajan P, Li M, Zhang J, Dong JF. Brain-derived microparticles induce systemic coagulation in a murine model of traumatic brain injury[J]. Blood, 2015, 125: 2151-2159.

[30] Zhao Z, Wang M, Tian Y, Hilton T, Salsbery B, Zhou EZ, Wu X, Thiagarajan P, Boilard E, Li M, Zhang J, Dong JF. Cardiolipin-mediated procoagulant activity of mitochondria contributes to traumatic brain injury-associated coagulopathy in mice[J]. Blood, 2016, 127:2763-2772.

[31] Nekludov M, Bellander BM, Gryth D, Wallen H, Mobarrez F. Brain-derived microparticles in patients with severe isolated TBI [J]. Brain Inj, 2017, 31:1856-1862.

[32] Zhou Y, Cai W, Zhao Z, Hilton T, Wang M, Yeon J, Liu W, Zhang F, Shi FD, Wu X, Thiagarajan P, Li M, Zhang J, Dong JF. Lactadherin promotes microvesicle clearance to prevent coagulopathy and improves survival of severe TBI mice[J]. Blood, 2018, 131:563-572.

[33] Wu Y, Liu W, Zhou Y, Hilton T, Zhao Z, Liu W, Wang M, Yeon J, Houck K, Thiagarajan P, Zhang F, Shi FD, Wu X, Li M, Dong JF, Zhang J. von Willebrand factor enhances microvesicle-induced vascular leakage and coagulopathy in mice with traumatic brain injury[J]. Blood, 2018, 132:1075-1084.

[34] Drake TA, Morrissey JH, Edgington TS. Selective cellular expression of tissue factor in human tissues: implications for disorders of hemostasis and thrombosis[J]. Am J Pathol, 1989, 134:1087-1097.

[35] McCully SP, Schreiber MA. Traumatic brain injury and its effect on coagulopathy[J]. Semin Thromb Hemost, 2013, 39:896-901.

[36] Sun Y, Wang J, Wu X, Xi C, Gai Y, Liu H, Yuan Q, Wang E, Gao L, Hu J, Zhou L. Validating the incidence of coagulopathy and disseminated intravascular coagulation in patients with traumatic brain injury: analysis of 242 cases [J]. Br J Neurosurg, 2011, 25:363-368.

[37] Wada T, Gando S, Maekaw K, Katabami K, Sageshima H, Hayakawa M, Sawamura A. Disseminated intravascular coagulation with increased fibrinolysis during the early phase of isolated traumatic brain injury[J]. Crit Care, 2017, 21:219.

[38] Albert V, Subramanian A, Agrawal D, Pati HP, Gupta SD, Mukhopadhyay AK. Acute traumatic endotheliopathy in isolated severe brain injury and its impact on clinical outcome[J]. Med Sci (Basel), 2018, 6:5.

[39] Rodriguez GE, Cardenas JC, Cox CS, Kitagawa RS, Stensballe J, Holcomb JB, Johansson PI, Wade CE. Traumatic brain injury is associated with increased syndecan-1 shedding in severely injured patients[J]. Scand J Trauma Resusc Emerg Med, 2018, 26:102.

[40] Kumar MA, Cao W, Pham HP, Raju D, Nawalinski K, Maloney-Wilensky E, Schuster J, Zheng XL. Relative deficiency of plasma a disintegrin and metalloprotease with thrombospondin type 1 repeats 13 activity and elevation of human neutrophil peptides in patients with traumatic brain injury [J]. J Neurotrauma, 2019, 36:222-229.

[41] Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms [J]. Blood, 2019, 133:906-918.

[42] Stoll G, Nieswandt B. Thrombo-inflammation in acute ischaemic stroke: implications for treatment[J]. Nat Rev Neurol, 2019, 15: 473-481.

[43] Schnüriger B, Inaba K, Abdelsayed GA, Lustenberger T, Eberle BM, Barmparas G, Talving P, Demetriades D. The impact of platelets on the progression of traumatic intracranial hemorrhage [J]. J Trauma, 2010, 68:881-885.

[44] Kay AB, Morris DS, Collingridge DS, Majercik S. Platelet dysfunction on thromboelastogram is associated with severity of blunt traumatic brain injury[J]. Am J Surg, 2019, 218:1134-1137.

[45] Huang S, Tang Y, Lin W, Wen K, Han W, Lin Z, Han M. Study on coagulation profiles and platelet function in trauma-induced coagulopathy caused by three types of injury [J]. Injury, 2020, 51:1312-1320.

[46] Daley MJ, Enright Z, Nguyen J, Ali S, Clark A, Aydelotte JD, Teixeira PG, Coopwood TB, Brown CV. Adenosine diphosphate platelet dysfunction on thromboelastogram is independently associated with increased morality in traumatic brain injury[J]. Eur J Trauma Emerg Surg, 2017, 43:105-111.

[47] Furay E, Daley M, Teixeira PG, Coopwood TB, Aydelotte JD, Malesa N, Tellinghuisen C, Ali S, Brown LH, Brown CV. Goal-directed platelet transfusions correct platelet dysfunction and may improve survival in patients with severe traumatic brain injury[J]. J Trauma Acute Care Surg, 2018, 85:881-887.

[48] Martin GE, Pugh AM, Moran R, Veile R, Friend LA, Pritts TA, Makley AT, Caldwell CC, Goodman MD. Microvesicles generated following traumatic brain injury induce platelet dysfunction via adenosine diphosphate receptor[J]. J Trauma Acute Care Surg, 2019, 86:592-600.

[49] Donahue DL, Beck J, Fritz B, Davis P, Sandoval-Cooper MJ, Thomas SG, Yount RA, Walsh M, Ploplis VA, Castellino FJ. Early platelet dysfunction in a rodent model of blunt traumatic brain injury reflects the acute traumatic coagulopathy found in humans[J]. J Neurotrauma, 2014, 31:404-410.

[50] Fair K, Farrell D, McCully B, Rick E, Dewey EN, Hilliard C, Dean R, Lin AL, Hinson HE, Barbosa RR, Schreiber M, Rowell SE. Fibrinolytic activation in patients with progressive intracranial hemorrhage after traumatic brain injury [J]. J Neurotrauma, 2019.[Online ahead of print]

[51] Karri J, Cardenas JC, Matijevic N, Wang YW, Choi S, Zhu L, Cotton BA, Kitagawa R, Holcomb JB, Wade CE. Early fibrinolysis associated with hemorrhagic progression following traumatic brain injury[J]. Shock, 2017, 48:644-650.

[52] Xu DX, Du WT, Li X, Wu ZX, Yu GF. D-dimer/fibrinogen ratio for the prediction of progressive hemorrhagic injury after traumatic brain injury[J]. Clin Chim Acta, 2020, 507:143-148.

[53] Hijazi N, Abu Fanne R, Abramovitch R, Yarovoi S, Higazi M, Abdeen S, Basheer M, Maraga E, Cines DB, Higazi AA. Endogenous plasminogen activators mediate progressive intracerebral hemorrhage after traumatic brain injury in mice [J]. Blood, 2015, 125:2558-2567.

[54] Samuels JM, Moore EE, Silliman CC, Banerjee A, Cohen MJ, Ghasabyan A, Chandler J, Coleman JR, Sauaia A. Severe traumatic brain injury is associated with a unique coagulopathy phenotype[J]. J Trauma Acute Care Surg, 2019, 86:686-693.

[55] Moore HB, Moore EE. Temporal changes in fibrinolysis following injury[J]. Semin Thromb Hemost, 2020, 46:189-198.

[56] Moore HB, Moore EE, Liras IN, Gonzalez E, Harvin JA, Holcomb JB, Sauaia A, Cotton BA. Acute fibrinolysis shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2, 540 severely injured patients[J]. J Am Coll Surg, 2016, 222:347-355.

[57] Leeper CM, Neal MD, McKenna CJ, Gaines BA. Trending fibrinolytic dysregulation: fibrinolysis shutdown in the days after injury is associated with poor outcome in severely injured children[J]. Ann Surg, 2017, 266:508-515.

[58] Griffin JH, Zlokovic BV, Mosnier LO. Activated protein C, protease activated receptor 1, and neuroprotection[J]. Blood, 2018, 132:159-169.

[59] Lustenberger T, Talving P, Kobayashi L, Barmparas G, Inaba K, Lam L, Branco BC, Demetriades D. Early coagulopathy after isolated severe traumatic brain injury: relationship with hypoperfusion challenged[J]. J Trauma, 2010, 69:1410-1414.

[60] Dekker SE, Duvekot A, de Vries HM, Geeraedts LM Jr, Peerdeman SM, de Waard MC, Boer C, Schober P. Relationship between tissue perfusion and coagulopathy in traumatic brain injury[J]. J Surg Res, 2016, 205:147-154.

[61] Sillesen M, Rasmussen LS, Jin G, Jepsen CH, Imam A, Hwabejire JO, Halaweish I, DeMoya M, Velmahos G, Johansson PI, Alam HB. Assessment of coagulopathy, endothelial injury, and inflammation after traumatic brain injury and hemorrhage in a porcine model[J]. J Trauma Acute Care Surg, 2014, 76:12-20.

[62] Epstein DS, Mitra B, Cameron PA, Fitzgerald M, Rosenfeld JV. Normalization of coagulopathy is associated with improved outcome after isolated traumatic brain injury [J]. J Clin Neurosci, 2016, 29:64-69.

[63] Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, Komadina R, Maegele M, Nardi G, Riddez L, Samama CM, Vincent JL, Rossaint R. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition[J]. Crit Care, 2019, 23:98.

[64] Chiu CC, Liao YE, Yang LY, Wang JY, Tweedie D, Karnati HK, Greig NH, Wang JY. Neuroinflammation in animal models of traumatic brain injury[J]. J Neurosci Methods, 2016, 272:38-49.

[65] Wiegele M, Schöchl H, Haushofer A, Ortler M, Leitgeb J, Kwasny O, Beer R, Ay C, Schaden E. Diagnostic and therapeutic approach in adult patients with traumatic brain injury receiving oral anticoagulant therapy: an Austrian interdisciplinary consensus statement[J]. Crit Care, 2019, 23:62.

[66] Shin SS, Marsh EB, Ali H, Nyquist PA, Hanley DF, Ziai WC. Comparison of traumatic intracranial hemorrhage expansion and outcomes among patients on direct oral anticoagulants versus vitamin kantagonists[J]. Neurocrit Care, 2020, 32:407-418.

[67] CRASH-3 Trial Collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial[J]. Lancet, 2019, 394:1713-1723.

[68] Fakharian E, Abedzadeh-Kalahroudi M, Atoof F. Effect of tranexamic acid on prevention of hemorrhagic mass growth in patients with traumatic brain injury[J]. World Neurosurg, 2018, 109:e748-753.

[69] Huijben JA, van der Jagt M, Cnossen MC, Kruip M, Haitsma IK, Stocchetti N, Maas AI, Menon DK, Ercole A, Maegele M, Stanworth SJ, Citerio G, Polinder S, Steyerberg EW, Lingsma HF. Variation in blood transfusion and coagulation management in traumatic brain injury at the intensive care unit: a survey in 66 neurotrauma centers participating in the collaborative European neurotrauma effectiveness research in traumatic brain injury study[J]. J Neurotrauma, 2017.[Online ahead of print]

[70] Zhang LM, Li R, Zhao XC, Zhang Q, Luo XL. Increased transfusion of fresh frozen plasma is associated with mortality or worse functional outcomes after severe traumatic brain injury: a retrospective study[J]. World Neurosurg, 2017, 104:381-389.

[71] Nakae R, Yokobori S, Takayama Y, Kanaya T, Fujiki Y, Igarashi Y, Suzuki G, Naoe Y, Fuse A, Yokota H. A retrospective study of the effect of fibrinogen levels during fresh frozen plasma transfusion in patients with traumatic brain injury [J]. Acta Neurochir (Wien), 2019, 161:1943-1953.

[72] Brogi E, Corbella D, Coccolini F, Gamberini E, Russo E, Agnoletti V, Forfori F. The role of platelet transfusions after intracranial hemorrhage in patients on antiplatelet agents: a systematic review and Meta-analysis[J]. World Neurosurg, 2020, 11:S1878-8750(20)30687-2.

[73] Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC; Epo Severe TBI Trial Investigators; Baldwin A, Rivera Lara L, Saucedo-Crespo H, Ahmed O, Sadasivan S, Ponce L, Cruz-Navarro J, Shahin H, Aisiku IP, Doshi P, Valadka A, Neipert L, Waguspack JM, Rubin ML, Benoit JS, Swank P. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial[J]. JAMA, 2014, 312:36-47.

[74] Vedantam A, Yamal JM, Rubin ML, Robertson CS, Gopinath SP. Progressive hemorrhagic injury after severe traumatic brain injury: effect of hemoglobin transfusion thresholds [J]. J

Neurosurg, 2016, 125:1229-1234.
[75] Yuan Q, Wu X, Du ZY, Sun YR, Yu J, Li ZQ, Wu XH, Mao Y, Zhou LF, Hu J. Low-dose recombinant factor Ⅶa for reversing coagulopathy in patients with isolated traumatic brain injury[J]. J Crit Care, 2015, 30:116-120.
[76] Stolla M, Zhang F, Meyer MR, Zhang J, Dong JF. Current state of transfusion in traumatic brain injury and associated coagulopathy[J]. Transfusion, 2019, 59:1522-1528.

（收稿日期：2020-08-12）
（本文编辑：彭一帆）

·文献速览·

论著/

鞘内/脑室内注射抗生素和抗真菌药治疗中枢神经系统感染

Intrathecal antibacterial and antifungal therapies

Nau R[a, b], *Blei C*[c], *Eiffert H*[a, d]

[a]*Institute of Neuropathology, University Medical Center, Göttingen, Germany*
[b]*Department of Geriatrics, Protestant Hospital Göttingen-Weende, Göttingen, Germany*
[c]*Hospital Pharmacy, University Medical Center, Göttingen, Germany*
[d]*Amedes MVZ for Laboratory Medicine, Medical Microbiology and Infectiology, Göttingen, Germany*

Clin Microbiol Rev, 2020, 33:e00190-19. DOI: 10.1128/CMR.00190-19.

血脑屏障和血脑脊液屏障可以保护中枢神经系统免受循环中内源性和外源性物质的影响，从而确保中枢神经系统的正常功能；但是这些屏障也限制了全身性应用抗感染药物后其在中枢神经系统的有效治疗浓度。多重耐药病原体引起的中枢神经系统感染，若全身给药无法达到有效治疗浓度，可采取鞘内/脑室内注射抗生素，而易于通过血脑屏障和血脑脊液屏障或者药物毒性较低允许每日增加剂量的抗生素不建议鞘内/脑室内注射。鞘内/脑室内治疗的常用抗生素包括氨基糖苷类、多粘菌素、达托霉素、替加环素和万古霉素等；抗真菌药两性霉素B和卡泊芬净亦可用于鞘内/脑室内注射（表1）。脑室内给药可确保药物在中枢神经系统均匀分布，而腰椎穿刺鞘内给药通常无法在脑室获得有效的治疗浓度。例如，分别向革兰阴性细菌性脑膜炎患儿的腰椎内或脑室内注射庆大霉素和妥布霉素5～10 mg后，绘制脑室、脑池和腰大池脑脊液药物浓度-时间曲线，发现鞘内注射后腰大池药物浓度迅速达峰值，鞘内注射后14小时脑池脑脊液药物浓度达峰值，但脑室脑脊液中未检测到药物浓度；而脑室内注射可达到较高的腰大池脑脊液药物浓度，给药后2小时即达峰值，表明脑室内注射抗感染药物可迅速分布至整个脑脊液空间。个体化药物剂量由脑脊液容积和脑脊液清除率决定。分子量＞1000 g/mol的中度亲脂性和分子量＞400 g/mol的亲水性抗感染药物，每日一次即可。鞘内给药后应夹闭引流管15～120分钟，以利于抗感染药物在脑脊液的均匀分布。如果治疗失败，应监测抗感染药物的谷浓度。

表1 成人鞘内/脑室内注射抗感染药物种类及剂量

Table 1. Types and doses of intrathecal/intraventricular injection of antibiotics in adults

抗感染药物	推荐剂量及间隔时间	不良反应	抗感染药物	推荐剂量及间隔时间	不良反应
庆大霉素	**4～10 mg**（1～20 mg）/**24 h**	短暂性听力丧失，癫痫发作，无菌性脑膜炎，脑脊液嗜酸性粒细胞增多，痛性神经根炎	万古霉素	**10～20 mg**（5～50 mg）/**24 h**	脑脊液白细胞计数增加，头痛，恶心，红人综合征，可能的短暂性听力损损害或共济失调
妥布霉素	**5～10 mg**（5～50 mg）/**24 h**	类似庆大霉素	替考拉宁	**5～20 mg/24 h**	头痛，皮疹，短暂性脑脊液白细胞计数增加
奈替米星	**7.5～15 mg**（3～150 mg）/**24 h**	类似庆大霉素	替甲环素	**1～10 mg/24 h；2～4 mg/12 h**	无严重不良反应
阿米卡星	**30 mg**（5～50 mg）/**24 h**（5～100 mg/24～48 h）	类似庆大霉素	美罗培南	**10 mg/12 h**	高剂量时癫痫发作
链霉素	**1 mg/kg/12～48 h**	短暂性听力丧失，癫痫，脊神经根炎，横贯性脊髓炎，蛛网膜炎，截瘫	两性霉素B	**0.1～0.5 mg/24 h（24～48 h）**	耳鸣，发烧，寒战，恶心，呕吐，畏光，复视，脑病，帕金森综合征，蛛网膜炎
多粘菌素E甲磺酸钠（12 500 U＝1 mg）	**10 mg**（1.6～40 mg）/**24 h**	脑膜炎；高剂量时癫痫发作，食欲不振，烦躁不安，嗜酸性粒细胞增多，水肿，疼痛，脑室出血	两性霉素B脂质体	**1 mg/24 h**	在患有念珠菌性脑室炎的4岁男童中，脑室注射脂质体Amb无严重不良反应
多粘菌素B	**5 mg/24 h**	与多粘菌素E相似	卡泊芬净	**5～10 mg**（1～10 mg）/**24 h**	恶心，头痛
达托霉素	**5～10 mg/24 h**（2.5～10 mg/12～72 h）	发热			

注：（1）由于鞘内给药药物进入脑室效果通常欠佳，故增加鞘内注射剂量似乎是合理的，但是鞘内注射的药物毒性作用特别是氨基糖苷类和多粘菌素毒性较脑室内注射更高，这可能是由于椎管内长期存在高浓度的抗生素所致，因此不建议增加鞘内注射药物剂量。（2）临床常用药物剂量及间隔时间以黑体字表示，括号中值为临床不常用的剂量或间隔

（首都医科大学宣武医院神经外科 曲鑫、徐立新，药剂科 王之舟编译）