

脓毒症的抗凝治疗

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【关键词】 脓毒症； 抗凝； 治疗

目前已经公认,脓毒症是由于感染引起的宿主过度全身炎症反应综合征^[1-2]。炎症和凝血系统复杂的相互作用是脓毒症的发病机制之一^[3-4]。脓毒症的炎症反应打破了凝血系统的平衡,使其向促凝状态倾斜。研究认为,宿主对入侵的致病微生物的初始反应可能是由 Toll 样受体(TLR)介导的。TLR 是一种模式识别受体(PRRs),可以识别细菌、病毒和真菌细胞壁上的特异性细胞壁分子^[5]。微生物病原体被 TLR 识别,从而触发复杂的宿主免疫反应。最初,促炎介质如白细胞介素-1(IL-1)、肿瘤坏死因子- α (TNF- α)等释放,诱导白细胞活化,导致组织因子(TF)的异常表达,激活凝血途径。因为凝血系统的激活,内源性抗凝因子如抗凝血酶(AT)、肝素和活化蛋白 C(APC)消耗,纤溶活性受到抑制。凝血级联的活化、内源性抗凝因子的消耗和纤溶功能受损,微循环血栓形成,造成组织缺氧,导致器官功能不全。同时,凝血系统中的物质可以反过来明显调节炎症反应^[6-7]。因此,脓毒症的起始触发是炎症级联过程中过度活化及由其所导致的凝血功能障碍。目前已经有很多针对特异性的炎症反应和凝血级联中介质的药物所进行的研究报道,如糖皮质激素、TNF 拮抗剂、IL-1 拮抗剂、抗内毒素抗体和 AT 等。遗憾的是,并没有发现这些药物能够改善脓毒症患者的生存率,而且在一些情况下,这些治疗本身甚至会增加病死率^[8]。目前惟一被大型前瞻性临床随机研究证实有效的抗凝药物是 APC。

在体内的凝血系统中,主要有 3 种抗凝途径调节凝血系统的活化,即 AT、蛋白 C(PC)系统和组织因子途径抑制

物(TFPI)。在脓毒症诱导的凝血活化中,这 3 种抗凝途径的功能都受到了抑制。现主要从以上 3 个方面介绍脓毒症抗凝治疗的进展。

1 APC

APC 是人体抗凝系统的一个重要组成部分,在血液循环中以无活性状态的酶原(即 PC)形式存在,当凝血酶与其内皮表面受体(血栓调节蛋白, TM)以 1:1 的比例形成复合物,裂解 PC,形成具有促进纤维蛋白溶解、抑制血栓形成及抑制炎症反应等多种生物活性的 APC。2001 年,一项包括 11 个国家 164 个中心的随机双盲多中心重组人活化蛋白 C(rhAPC)治疗脓毒症的研究(PROWESS 研究)结果发表了。1 690 例发病 24 h 内的严重脓症患者入选,予以安慰剂或 APC 治疗。结果表明,APC 使死亡相对风险下降 19.4%,同时使死亡风险降低 6.1%($P=0.005$),但严重出血发生率较高(3.5%比 2.0%, $P=0.06$)^[9]。在对 PROWESS 研究进行析因分析后表明,急性生理学与慢性健康状况评分系统 I(APACHE I)评分 ≥ 25 分的患者应用 APC 治疗后的整体生存时间更长,3 个月、6 个月、1 年和 2.5 年时的标志性生存率更高;APACHE I 评分 <25 分的患者 APC 的应用使 1 年的标志性生存率显著降低($P=0.04$),但是在其他时间点没有差异^[10]。

随后的 ADDRESS 研究^[11]尝试入选 1.1 万例低死亡风险的严重脓症患者(APACHE I 评分 <25 分或单器官功能衰竭)。因为在入选了 2 640 例患者后分析表明几乎没有有效的可能性,所以这一研究早期就终止了。除此之外,APC 组严重出血事件的发生率要高于安慰剂组(3.9%比 2.2%, $P=0.01$)。这些数据和 PROWESS 的数据强而有力地表明 APC 不应该用于低死亡风险的严重脓症患者;对于单器官功能衰竭和近期手术(30 d 内)患者的进一步研究表明,与安慰剂相比,APC 治疗会显著增加病死率。

RESOLVE 研究^[12]主要是对儿科患者应用 APC 的有效性和安全性评估。研究结果未能证实严重脓症患者可以从 APC 治疗中获益。虽然副作用和严重出血的发生率在两组间相似,但是 APC 治疗组中枢神经系统出血的例数更多,尤其是 60 d 内的患儿。

APC 是目前惟一被高质量随机对照研究证实可以降低严重脓症患者病死率的药物。

2 抗凝血酶-III(AT-III)

AT-III 是人体内最重要的抗凝物质,约占血浆生理性抗凝活性的 75%^[13]。血浆中 AT 的降低与严重脓症患者弥散性血管内凝血(DIC)的发生率和病死率密切相关^[14-15]。在脓毒症动物模型中,AT 可以降低死亡率,并有限制甚至能预防进一步发展为器官功能不全的作用^[16-19]。这一研究结果已经被严重脓毒症患者的 I 期临床实验和荟萃分析(Meta 分析)证实^[20-23]。

然而,在一项关于大剂量 AT-III 治疗严重脓毒症的大型国际 I 期前瞻性随机对照研究(KyberSept 研究)中并没有得出改善脓症患者 28 d 病死率的结论^[24]。在 KyberSept 研究中,历史性对照研究结果显示,对于简化急性生理学评分 I(SAPS I)预期病死率在 30%~60% 的严重脓症患者来说,大剂量的 AT-III 治疗可以使其获益,尽管 AT-III 可以增加患者的出血并发症,但也可以增加他们的 90 d 生存率,且明显高于对照组($P=0.04$);然而当 AT-III 与小剂量肝素合用时,肝素会削弱 AT-III 的抗炎活性,增加出血的概率^[25];另外,这项研究的亚组析因分析表明,不接受肝素治疗和满足 DIC 诊断的患者可以从 AT-III 治疗中获益,但是这一结果仍需进一步的前瞻性随机对照研究证实^[26]。LaRosa 和 Opal^[27]通过大规模严重脓症患者 I 期临床观察证实,AT-III 不能改善 28 d 及最终病死率,但部分患者可以从受益。

DOI:10.3760/cma.j.issn.1003-0603.

2011.02.018

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Hoffmann 等^[28]通过前瞻性调查,将 40 例严重脓毒症患者随机分成两组,20 例接受传统治疗,20 例进行 AT 替代治疗,并使血浆中 AT 活性 $\geq 120\%$,连续 14 d。结果显示,AT 替代治疗组能明显增强凝血酶原活性、纤维蛋白原的浓度和 APC 活性,可明显减轻严重脓毒症患者的凝血反应,有益于严重脓毒症患者。另有研究表明,AT 替代治疗对严重脓毒症或脓毒性休克并发 DIC 的患者有益^[20,29-31]。严重脓毒症患者给予 AT 后 D-二聚体水平迅速明显下降^[32]。

3 TFPI

理论上,治疗 DIC 最合理的抗凝剂是直接拮抗 TF 活性的制剂,包括 TFPI、灭活的 FⅡa 以及可以有效而特异性抑制 TF-FⅡa 和 FXa 三重复合物的重组 NAPc2。

研究表明,在脓毒症动物模型中,同时应用抗生素和重组 TFPI 可以降低死亡率^[33-35]。在关于 TFPI 的 I 期和 II 期临床研究中,与安慰剂组相比,脓毒症患者应用重组 TFPI 可以轻度降低 28 d 病死率,而且无明显的副作用^[36-38]。但是大型的 III 期临床研究并没有得出应用重组 TFPI 可以改善生存率的结果。与安慰剂组相比,TFPI 治疗组 28 d 病死率增加(34.2%比 33.9%),并且出血的发生率增加^[39]。这一研究没有得出有意义的结果可能存在以下几个原因:①缺乏对出血事件的定义标准;②应用肝素可能会改善安慰剂组患者的存活;③研究初始阶段 TFPI 治疗可以改善患者的存活,但是后期接受 TFPI 治疗组的病死率戏剧性增加,这导致为了完成研究而增加入选患者的数量^[40]。

研究发现,医院获得性肺炎(CAP)患者肺内 TF 的表达增加,这可能是由于炎症和凝血活化的直接结果。TF 水平是机体控制凝血的关键机制。CAP 时,内源性 TFPI 水平不足以完全拮抗增加的 TF 水平,因此,给予治疗剂量的 TFPI 可能有助于维持这一平衡。2004 年由 Chiron 进行的一项 III 期安慰剂对照临床研究(CAPTIVATE 研究)发现,TFPI 治疗可以使严重 CAP 患者获益。CAPTIVATE 研究预期纳入约 16 个国家 200 个中心的 2 100 例患者^[41],目前这一研究的最终结果还未发表。Laterre 等^[42]的回顾性研究发现,CAP 患者中应用 TFPI 和安慰剂患者的病死率分别为

27.9%和 32.7%,在有明确病原微生物感染的患者中,应用肝素和未用肝素患者的病死率分别为 29.3%(17/58)和 51.9%(28/54), $P < 0.02$,TFPI 治疗不能显著降低 CAP 患者的病死率,但是进一步的分析表明,在不接受肝素治疗并且有明确病原微生物感染的患者中可以改善生存率。

4 肝素

实验室研究表明肝素至少可以部分抑制脓毒症中的凝血活化^[43-44];非对照病例研究表明,肝素可以有效治疗脓毒症 DIC 患者。但是目前并没有在大型临床对照研究中得出治疗有效的结果^[45]。但是包括 rhAPC、AT-Ⅲ 和 TFPI 在内的大样本多中心研究数据的分析显示,小剂量肝素在临床对脓毒症患者可能有保护作用^[46-47]。在 PROWESS(rhAPC)、KyberSept(AT-Ⅲ)以及 OPTIMIST(TFPI)3 项大型研究中^[46,48-49],共有 2 987 例接受安慰剂治疗的患者,接受肝素治疗和未接受肝素治疗患者死亡的比值比(OR)为 0.65(95%可信区间 0.55~0.76, $P < 0.000 01$);在每项研究中,应用肝素治疗均可改善安慰剂患者组的生存率;虽然试验中肝素的应用并不是随机的,后随机化比较有明显的局限性,但是在 3 个有不同纳入标准的不同的研究人群中(基本涵盖了疾病的自然异质性)均得出了一致的结果,这强烈支持肝素除了已知的抗凝和抗血栓作用外,还可以降低脓毒症患者的病死率这一假说。国内有动物实验表明,肝素可下调脓毒症大鼠 IL-6 和 TNF- α 的表达^[50]。

近期一项对严重脓毒症患者应用 APC 的研究表明,小剂量肝素可以轻度(但没有统计学意义)改善 28 d 病死率。同时这一研究还强调,DIC 和凝血指标异常患者不能停用肝素。治疗剂量的肝素适用于有临床表现的血栓栓塞或广泛纤维蛋白沉积的患者,如爆发性紫癜或肢体末端缺血^[51]。2008 年,Zarychanski 等^[52]为评价对感染性休克患者静脉应用治疗剂量普通肝素的疗效,进行了回顾性、倾向配对、多中心的队列研究,这一研究结论认为早期静脉应用治疗剂量肝素可能会降低感染性休克患者的病死率,尤其对疾病严重程度高的患者。但是仍需随机临床研究证实这一结论。从生物学效应来说,肝素作为传统抗凝剂对脓毒症患者可能发挥了和 APC 相似的

作用,但其应用时机、合适剂量及治疗疗程都没有确定答案^[53]。

2009 年 Jaimes 等^[54]发表了关于普通肝素治疗脓毒症的随机、双盲、安慰剂对照、单中心的临床研究。这一研究共有 319 例脓毒症患者入选。这些患者被随机分为接受安慰剂治疗或是普通肝素(500 U/h,持续 7 d)治疗。结果发现两组出院患者的平均住院时间没有差异($P = 0.976$),多器官功能障碍(MOD)评分的改善程度相同($P = 0.24$);安慰剂组 28 d 病死率为 16%,而普通肝素治疗组为 14%($P = 0.652$)。关于 28 d 病死率的亚组分析(根据感染部位、入组时 APACHE II 评分、MOD 评分和 D-二聚体分组)也没有得出任何有意义的结果。仅在肝素治疗组发生 1 例严重的副作用,但没有任何并发症。但是这一研究本身有局限性:如入选对象是脓毒症患者,其疾病严重程度较轻,其预后评价的最主要指标并不是 28 d 病死率等。

总之,脓毒症的发病机制相当复杂,与凝血、纤溶及炎症反应均有密切关系。脓毒症时,大量的炎症介质释放启动凝血系统,血液处于高凝状态,抗凝能力减弱,纤溶系统抑制,而凝血紊乱又加重脓毒症,并促进其发展为多器官功能障碍综合征(MODS)。抗凝介质不仅能重新恢复凝血平衡,还能有效抑制炎症反应的弥散。因此,理论上,凝血抑制剂替代治疗脓毒症是有效、可靠的。脓毒症不仅是一种炎症性疾病,同时也是一种凝血障碍性疾病,抗凝治疗不但有充分的理论依据,同时也有临床的实践支持,脓毒症的抗凝治疗具有广阔的研究空间和临床应用前景^[55]。但是,脓毒症发病过程中凝血酶联激活的详细机制尚不明了,使用抗凝剂还需谨慎,尤其要避免增加出血危险性。到目前为止,在脓毒症的抗凝治疗方面,只有 rhAPC 被肯定是有有效的,其他抗凝剂如肝素等的治疗效果仍有待进一步深入的研究。

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(收稿日期: 2010-12-25)

(本文编辑: 李银平)

• 科研新闻速递 •

肿瘤坏死因子相关凋亡诱导配体可提高脓毒症生存率

对于外科危重症患者来说,脓毒症是导致死亡的重要原因之一。以往研究表明肿瘤坏死因子相关凋亡诱导配体(TRAIL)是肿瘤细胞中细胞凋亡的诱导剂,在调节炎症反应中也起重要作用,但在脓毒症中的作用机制尚不清楚,近日德国学者对此进行了研究。实验人员利用雌性C57BL/6小鼠制作升结肠支撑管腹膜炎脓毒症模型(CASP),并于发生脓毒症后1、24、48h静脉注射鼠重组体TRAIL。实验表明,TRAIL可在CASP中起保护作用,静脉应用鼠重组体TRAIL明显延长了脓毒症小鼠的生存时间,使大量效应细胞迁移至腹腔杀灭微生物,脾脏和肠系膜淋巴结中中性粒细胞蓄积量也明显减少。通过本次实验,研究者认为TRAIL将来有望应用于脓毒症的治疗。刘先奇,方涛,编译自《Crit Care Med》,2010,38:2169-2174;胡森,审校

自动提取技术可以提高脓毒症感染病原体检测速度和灵敏度

脓毒症是导致全球住院患者高发病率和高病死率的主要原因之一。近期研究者通过使用分子生物学技术,使早期快速检测脓毒症患者的病原体成为可能。一种多重聚合酶链反应(PCR)分析技术能够检测血液感染中最常见的25个病原体DNA,在节省时间和操作的同时避免了传统技术在自动选取过程的复杂实验室工作。为评估自动化操作的可行性,研究者从重症监护病房(ICU)的106个临床样本中选取76个样本,采用平行对照法评估手动和自动检测在同一时间获得的血培养结果。结果表明自动提取病原体DNA不仅缩短了3.57h的工作流程,还提高了分子检测对所检测血培养阳性的灵敏度。

崔倩,编译自《PLoS One》,2010,5:e13387;尹明,审校

对儿童烧伤患者采用晶液体联合胶液体进行复苏疗效更佳

由于儿童对过度损伤的耐受性差,在临床上如何对烧伤儿童进行更好的液体复苏尚无定论。最近美国的医务工作者对采用晶液体联合胶液体对烧伤儿童进行液体复苏的效果与单纯采用晶液体治疗进行了对比研究。研究人员选取2004年1月1日至2009年5月1日烧伤面积大于15%的53例在年龄、性别、体重及伤后入院时间无明显差异的儿童作为研究对象,其中29例患儿只使用晶液体进行复苏(LR组),24例患儿在使用晶液体复苏的同时适时补充胶液体(ALB组)。疗效采用每小时复苏比(I/O)来表示,即每小时复苏用液体量与每小时尿量的比值。研究结果显示:ALB组患者的I/O及病床周转率明显高于LR组患者。学者们认为,I/O是评价烧伤休克液体复苏的有效指标,且儿童烧伤时采用晶液体联合胶液体进行复苏的效果比单用晶液更好。

韩晓春,方涛,编译自《J Burn Care Res》,2010-12-02(电子版);胡森,审校

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年, 卷(期): 2011, 23 (2)

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