恶性梗阻性黄疸介入治疗后胆道感染的研究进展

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摘 要: 恶性梗阻性黄疸多由胆胰恶性肿瘤引起,主要表现为肝功能受损、胆汁淤积,治疗方法包括经内镜逆行性胰胆管造影术(ERCP)支架植入、经皮肝穿刺胆道引流(PTCD)、经内镜鼻胆管引流术(ENBD)等。胆道感染是恶性梗阻性黄疸介入治疗后的严重并发症之一,可致感染性休克,危及患者生命。本文总结胆道感染的危险因素、原因、近年来病原菌谱、耐药及抗生素选择等情况,对恶性梗阻性黄疸介入治疗后胆道感染的研究进展进行综述,以期减少胆道感染的发生。

关键词: 恶性梗阻性黄疸; 介入治疗; 危险因素; 胆道感染; 研究进展
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Research progress of biliary tract infection after interventional treatment of malignant obstructive jaundice

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Abstract: Malignant obstructive jaundice is mostly caused by biliopancreatic malignant tumors, mainly manifested as hepatic dysfunction and cholestasis. Treatment methods includes endoscopic retrograde cholangiopancreatography (ERCP) stent implantation, percutaneous transhepatic cholangial drainage (PTCD), endoscopic nose biliary drainage(ENBD) and other interventional operations. Biliary tract infection is one of serious complications after interventional treatment of malignant obstructive jaundice, and can cause septic shock and threaten the life of the patients. By summarizing the risk factors, causes, pathogenic bacteria spectrum, drug resistance and antibiotic selection in recent years, this paper reviewed the research progress of biliary tract infection after interventional treatment of malignant obstructive jaundice in order to reduce the occurrence of biliary tract infection.

Key words: malignant obstructive jaundice; interventional treatment; risk factors; biliary tract infection; research progress

梗阻性黄疸作为临床常见疾病,可根据梗阻性质分为良性梗阻性黄疸(BOJ)与恶性梗阻性黄疸(MOJ)。MOJ 是指各种恶性肿瘤导致左右肝管、肝总管、胆总管受到压迫或侵犯,引发胆管狭窄,最终引起肝功能损害、胆汁淤积的临床疾病,引起 MOJ 的恶性肿瘤主要包括胆管癌、胰腺癌、肝癌、十二指肠壶腹癌、胆囊癌以及各种转移性肿瘤[1-3]。MOJ 首选的治疗方式是外科手术,但一般发现时肿瘤已进展为晚期,患者已失去手术机会,因此 MOJ 的治疗以姑息性介入治疗为主。介入治疗方式包括经内镜逆行性胰胆管造影术(ERCP)支架植入、经皮肝穿刺胆道引流(PTCD)和胆道支架植入术(PTBS)。此外,对于 ERCP 或 PTBD 失败的患者,也可以采用超声内镜引导下胆道引流术(EUS-BD)的治疗方式,但是其有效性及安全性尚需更大规模的实验验证[4-5]。

胆道感染是介入治疗后的严重并发症之一,包括急性胆囊炎、急性胆管炎、肝脓肿等,若不及时处理易造成患者全身炎性反应综合征、感染性休克甚至死亡[6]。研究[7-8]表明, MOJ 患者介入

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治疗后的胆道感染发生率远远高于一般文献中所报道发生率。同时，EVERETT B T 等[9]研究提示，与 BOJ 患者相比，经 ERCP 支架植入后胆管炎的发生率在 MOJ 患者中较高，表明 MOJ 患者介入治疗后发生胆道感染的可能性更大。

1　MOJ 介入治疗后胆道感染危险因素及原因

1.1　危险因素

既往文献得出，影响 MOJ 介入术后胆道感染的可能因素如下。① 患者一般情况：年龄、性别、是否合并慢性疾病（糖尿病、冠心病等）、既往胆道手术史、术前黄疸时间；② 肿瘤梗阻：梗阻部位、梗阻长度、肿瘤分期、肿瘤类型；③ 术前检测指标：术前胆红素水平、术前肝功能水平、术前感染指标、术前患者状态评分、血红蛋白、低白蛋白血症、外周血单核细胞表型、胆汁培养结果；④ 手术相关：支架类型、支架通畅时间、引流方式、引流量、手术操作时间[10-16]。患者术前状态越好，肿瘤分期越早，手术引流越充分，术后胆道感染发生率也就越低。研究[11]表明，PTCD、ENBD 及 ERCP 支架植入术导致的术后胆道感染率无差异，但还有一些其他因素影响术后胆道感染发生率。与塑料支架相比，金属支架在经 ERCP 支架植入术后胆管炎的发生率较低[17-18]，尤其是对于远端胆道梗阻而言。XIA M X 等[7]研究结果显示，恶性肝门部狭窄患者经 ERCP 植入塑料支架和肿瘤 Bismuth 分型Ⅳ级术后出现的胆管炎发生率较高。一项单中心回顾性研究[19]结果提示，胆道支架穿过胆囊管开口、术中造影剂溢入胆道和自膨式金属支架植入是恶性胆道梗阻患者胆道支架植入术后胆囊炎的危险因素，与另一项研究[20]报道结果相符。LIU C 等[21]研究发现，当恶性狭窄部位超过十二指肠乳头 3 cm 时，支架跨越 Oddis括约肌比未跨越的患者术后胆道感染发生率低。以上因素均可能影响患者术后胆道感染的发生。此外，研究[22-24]表明，射频消融技术、放射性粒子^{125}I 及放射性支架与常规支架植入术后并发症的发生率比较，差异无统计学意义（$P > 0.05$）。但由于相关病例数量较少，还需进一步研究证实。

1.2　原因

正常人体内胆道胆汁是无菌的[25]，胆汁的通畅有助于防止多种疾病的发生。MOJ 患者由于胆道梗阻，胆汁引流往往不通畅，行介入治疗时，容易将肠道内的细菌带入胆道内，引起胆道感染。此外，肿瘤患者免疫功能及对感染的抵抗力下降，肠道内的细菌可通过 Oddis 括约肌和门静脉系统移位至肝外以及肝内胆管，在胆汁中继续滋生，同时，十二指肠乳头行切开或扩张后，肠道菌群还可经受损上皮侵入血液引起菌血症甚至全身感染[26]。肿瘤常常侵犯肝内胆道，使其互不交通，特别是肝门部胆管癌Ⅲ、Ⅳ型患者，而放置支架并不能完全实现所有分支均有效引流，胆汁持续淤积，更易导致细菌繁殖[27]。这些都是 MOJ 患者介入治疗后发生胆道感染的原因。

2　介入治疗后发生胆道感染的病原菌谱及耐药谱变化

介入治疗后出现胆道感染的 MOJ 患者，临床工作应总结其病原菌谱及耐药情况，尽早使用敏感抗菌药物，防止胆道感染加重，避免出现感染性休克。ZHAO J 等[28]研究显示，近 6 年来引起胆道感染最常见的仍然是肠杆菌（肠球菌、大肠埃希菌、肺炎克雷伯菌）和肠球菌（屎肠球菌、粪肠球菌），但其对常用抗生素高度耐药，对哌拉西林他唑巴坦、碳青霉烯、阿米卡星、万古霉素等抗生素有高敏感性，这与相关研究[29]结果相符，在该研究中，接受术前胆道引流的壶腹癌患者，胆汁菌群对氨苄西林-舒巴坦耐药率为 63%，未接受壶腹癌患者的耐药率为 18%。这种耐药率的差异还表现在哌拉西林-他唑巴坦、环丙沙星和亚胺培南等抗生素中。接受胆道支架植入术后，MOJ 患者的胆汁培养结果更倾向于肠球菌及多重耐药菌生长[30-31]。

由此可见，随着抗生素的广泛使用及胆汁培养技术的进步，虽然大肠埃希菌、肠球菌仍是胆道感染最常见的致病菌，但对于经介入治疗的 MOJ 患者而言，胆汁病原菌变得更具侵袭性及耐药性，对于临床常用抗生素表现出更低的敏感性，影响患者预后，为临床医生在治疗胆道感染的抗生素选择上带来极大挑战。

3　胆道感染抗生素选择

3.1　经验性抗感染治疗

《急性胆管炎、胆囊炎抗菌药物东京指南 2018 版》[32]要求临床医生一旦怀疑患者存在胆道感染，应立即开始抗感染治疗。对于感染性休克的患者，指南要求在确诊后 1 h 内给予抗菌药。

但如果经验性抗生素治疗的药物选择不当,急性胆道感染继发病死率将从 8% 增加至 15%[33]。因此,对于重度社区获得性急性胆管炎和胆囊炎患者,指南推荐使用具有抗假单胞菌活性的药物作为初始经验性治疗;对于肠球菌属感染患者,首选万古霉素治疗;对于万古霉素耐药的屎肠球菌和粪肠球菌感染患者,可使用利奈唑胺或达托霉素治疗[32, 34-35]。但这些选择仍然需要临床医生根据所在地区流行的病原菌学、耐药情况及患者自身机体情况做出调整。

3.2 关注抗生素选择

除经验性抗感染外,临床医生还应该关注抗生素的组织渗透性、在胆汁内的排泄量及抗菌活性。恶性梗阻性患者由于胆道梗阻,全身应用抗生素的胆汁排泄量较低[36]。一项关于胆道感染中胆汁内药物浓度研究[37]表明,具有良好胆道和胆囊壁穿透性的抗生素治疗胆道感染更有效。WOBSER H 等[38]研究结果提示,除替格环素外,利奈唑胺、环丙沙星、美罗培南等其他抗生素在胆汁中对粪肠球菌的抗菌活性均显著低于肉汤。总之,尽管多数抗生素表现出良好的胆道渗透性,但阿莫西林、头孢羟氨苄、头孢西丁、厄他培南、庆大霉素、阿米卡星和甲氧普林的胆道渗透率较差[39]。临床医生在患者胆道感染的情况下选择抗生素时需考虑其胆道渗透性及抗菌活性等因素对疗效的影响,必要时调整给药剂量及频次,以达到更好的疗效。

3.3 预防性措施

近年来,对于胆道感染的处理还包括预防性相关措施:一是预防性使用抗生素。如美国胃肠内镜学会[26]主张对有肝移植病史或者胆道梗阻的患者进行预防性抗感染,一般患者不建议行 ERCP 前进行常规预防性抗感染治疗。欧洲胃肠内镜学会[40]则建议对可能出现胆道引流不全、免疫功能严重受损,以及需胆道镜检查的患者,在 ERCP 之前都进行抗生素预防,并在术后继续使用[41]。二是局部使用抗生素。研究[38, 42]表明,为了预防 ERCP 术后发生胆管炎及胆囊炎,可在造影剂中加入抗菌剂,或可以联用不同抗生素和抗真菌药物;若术前已经合并胆管炎,建议在阻塞的胆管中局部应用抗生素。三是使用其他胆管造影剂。已有文献[43-44]证明,空气和二氧化碳胆道造影能够降低高位恶性梗阻患者术后胆管炎的有效性。然而,空气胆道造影会出现空气栓塞风险,病死率可达 40%,但二氧化碳因为较高的肠道组织吸收性和极罕见的栓塞事件,已被欧洲胃肠内镜学会推荐应用[45]。

4 小 结

综上所述,对于 MOJ 介入治疗后发生胆道感染的治疗,目前国内外并无相关指南,临床上多参考 BOJ 合并胆道感染的治疗方案。但是,由于 MOJ 患者存在的胆道梗阻、胆汁引流不畅、肿瘤状态导致机体免疫功能下降,且介入治疗可能造成胆道损伤,出现病原菌学改变和耐药率上升等问题。因此,临床医生应结合本地区流行的病原菌学及耐药情况酌情选择抗生素。原则上患者一旦出现术后胆道感染,如发热、黄疸加重及白细胞计数增加等,应立即留取胆汁或者血进行培养,并及时给予抗感染治疗,同时保持胆道通畅。此外,如何降低术后胆道感染发生率、预防和系统治疗 MOJ 介入治疗后发生的胆道感染,仍是未来临床需要关注的问题。

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