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文献综述 REVIEW

幽门螺杆菌与消化性溃疡并出血的研究现状

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幽门螺杆菌是消化性溃疡的确定性致病因素, 其在溃疡并出血的作用尚不十分明确. 目前, 幽门螺杆菌在消化性溃疡并出血的感染率受检测方法、药物等影响不尽相同. 幽门螺杆菌感染在一定程度上增加了消化性溃疡并出血的危险性, 从长远上根除幽门螺杆菌可以降低溃疡出血风险, 促进溃疡愈合.

关键词: 幽门螺杆菌; 消化性溃疡; 消化性溃疡并出血

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■背景资料
消化性溃疡(PU)并出血是上消化道出血的最常见病因, 约占所有病因的50%, 约有80%的溃疡病出血可自行停止, 但其病情发展迅速, 病死率高. *H.pylori*是PU的确定性致病因素, 也是PUB的危险因素.

0 引言

消化性溃疡(peptic ulcer, PU)是常见病和多发病, 呈世界性分布, 约有10%的人患过此病. 出血是PU最常见的并发症, 也是上消化道大出血的常见原因, 约占所有病因的50%[1], 其死亡率高达10%[2]. 自1983年Marshall等从人胃黏膜组织中培养出了幽门螺杆菌(*Helicobacter pylori*, *H.pylori*)后, 各国学者纷纷进行研究, 一致认为*H.pylori*是PU的确定性致病因素. 然而目前关于*H.pylori*感染与PU并出血(peptic ulcer bleeding, PUB)的关系却不十分明确, 本文旨在对*H.pylori*感染及其根除后对PUB的影响作一综述.

1 *H.pylori*导致PUB的机制

目前认为, *H.pylori*引起PU的发病机制主要有两种学说: 一是Goodwin的“漏屋顶假说(hypothesis of leaking roof)”: 这是目前较为经典的学说, 即在胃和十二指肠黏膜受损的情况下, *H.pylori*感染导致H^+反弥散, 进一步导致黏膜损伤造成溃疡. 这一假说强调了*H.pylori*感染导致防御因素的减弱, *H.pylori*主要通过释放脂多糖、尿素酶和空泡细胞毒素损害黏膜屏障及其防御机制[3]; 另一种是Levi的胃泌素联系学说: *H.pylori*定植过程中尿素酶分解尿素产生氨, 导致胃窦部的pH值升高, 反馈性地促进胃泌素释放, 使循环中的胃泌素水平升高, 引起高胃酸, 从而导致胃黏膜损害[4]. 溃疡并发出血多由于溃疡基底或其周围

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Advances in understanding relationship between *Helicobacter pylori* infection and peptic ulcer bleeding

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Helicobacter pylori (*H.pylori*) is a definite causative factor for peptic ulcer; however, its role in peptic ulcer bleeding is not very clear. Detection of *H.pylori* infection in patients with peptic ulcer bleeding is often affected by methods and drugs used. *H.pylori* infection increases, to some extent, the risk of peptic ulcer bleeding. Eradication of *H.pylori* may reduce the risk of peptic ulcer bleeding and promote ulcer healing.

Key Words: *Helicobacter pylori*; Peptic ulcer; Peptic ulcer bleeding

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■研发前沿
PUB患者中*H.pylori*感染率受众多因素影响, 缺少一个统一的诊断标准, 因此尽快明确出血状态下*H.pylori*检测的敏感性降低的机制, 找到有效而准确的检测方法已成为目前研究的重点. 但随着耐药菌株的迅速增加, 各种药物联合方案的根除率逐渐降低, 如何高效、经济地根除*H.pylori*成为研究的热点.

血管破裂所致. 因此, 认为*H.pylori*感染在PUB患者中起着重要的病原学作用.

2 *H.pylori*在PUB中的感染率

在PUB患者中, *H.pylori*感染率仍存在争议. Chen等[5]研究发现*H.pylori*的感染率高达90.5%, 而其他文献报道*H.pylori*的感染率则没有那么高, 处于20%-70%[6], 除地区因素外, 主要是由于判断感染的标准和检测方法的不同造成感染率的差异. 若以快速尿素酶试验(rapid urease test, RUT)或尿素呼气试验(urea breath test, UBT)任何一项阳性, 即判定其为*H.pylori*感染, 则感染率明显增高[5], 反之两者均阳性才判定为*H.pylori*感染, 其阳性率则有所下降. 目前, 大部分研究采用了RUT检测*H.pylori*的感染, 其阳性率为20%-60%[6], 组织学检测*H.pylori*的阳性率为61%-89%, 高于RUT[7]. 绝大部分研究[8,9]认为*H.pylori*在PUB患者的感染率明显低于未出血患者.

值得注意的是, 近期应用抗生素、质子泵抑制剂(proton pump inhibitors, PPIs)、铋剂等药物, 因有引起胃内酸碱度的改变和暂时抑制*H.pylori*的作用, 会使*H.pylori*检查(除外血清学检查)呈假阴性, 其假阴性率可达13%[8]. 另外, 在溃疡出血和未出血患者不同的检测方法其敏感性不同, 血液的存在也可能影响胃的*H.pylori*检测. 关于引起PU患者在出血状态下*H.pylori*检测的敏感性减低的原因目前尚无统一的解释. Houghton等[10]认为是人类血浆中含有某种能直接杀死*H.pylori*的因子, Leung等[11]认为血清白蛋白对*H.pylori*指示剂的缓冲作用所致, 而Archimandritis等[12]、Tang等[13]则认为胃内血液的存在不会影响检测结果, Lee等[14]和Parry等[15]也认为胃黏膜标本暴露在血液中不能解释为什么出血患者RUT敏感性降低. 其原因尚待进一步研究, 推测与*H.pylori*菌量减少或尿素酶活性降低有关.

目前, 尚不清楚短期常规剂量或高剂量的奥美拉唑是否对*H.pylori*在溃疡出血患者胃内的定植有影响. Udd等[16]研究了不同剂量奥美拉唑的治疗效果, 发现奥美拉唑治疗3 d后*H.pylori*的检测转阴是剂量依赖性的. 研究发现[17], 大多数*H.pylori*阳性的溃疡出血患者, 除部分行高剂量PPIs治疗外, 其*H.pylori*检测结果亦阳性. 因此, 可以认为, *H.pylori*感染的诊断依赖于活检的时机, 并且与PPIs治疗开始的时间有关, 为避免由于PPIs治疗造成的假阴性结果, 应尽早行UBT检测. 但UBT受诸如药物、上消化道出血、胃内其他产生尿素酶细菌等因素影响, 可能出现假阴性或假阳性, 尤其在有胃部分切除手术史的患者中准确性有限. 若第1次检测阴性, 需在出血停止后4-8 wk或行*H.pylori*根除治疗后再次行*H.pylori*检测以排除*H.pylori*感染[18].

3 *H.pylori*感染对PUB的影响

*H.pylori*感染是PUB的一个重要因素[19]. 目前大部分研究认为*H.pylori*感染增加了PU患者出血的危险性. Kuyvenhoven等[20]的研究显示: *H.pylori*感染导致PUB的相对危险度增加了1.5倍, 并且*H.pylori*感染可能在一定程度上加剧了非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)使用患者溃疡出血的风险, 但其影响作用似乎比较轻微. Huang等[21]的荟萃分析显示*H.pylori*感染使PUB的风险增加了1.79倍. 在一定程度上, *H.pylori*的再感染可能是溃疡再出血的原因之一[22]. Arkkila等[23]的研究发现*H.pylori*阴性的PUB患者, 溃疡愈合率为95%, 而*H.pylori*阳性患者其溃疡愈合率为8%, 远远低于*H.pylori*阴性患者; 而*H.pylori*阴性的PUB患者溃疡恶化率为2%, *H.pylori*阳性患者其溃疡恶化率为38%. 因此可以认为*H.pylori*感染降低溃疡愈合率, 易导致溃疡恶变.

其次, *H.pylori*感染对PUB的影响与*H.pylori*的基因型相关. 细胞毒素相关基因A(cytotoxin associated gene product A, CagA)阳性的*H.pylori*感染患者, 溃疡并出血的风险增加[24], 其风险是NSAIDs使用患者的3倍[25]. Perng等[26]对168例患者进行前瞻性研究, 通过DNA提取和聚合酶链反应检测CagA, 并对vacA和iceA进行分型, 发现PUB患者vacA s1a和m1T明显少于未出血组, 认为*H.pylori* vacA s1a和m1T的存在在一定程度上可以预防或减少溃疡出血.

也有资料显示, *H.pylori*可能不是溃疡并出血的独立因素. Sotoudehmanesh等[27]的Logistic回归分析显示, 在总体感染率较低的情况下, 考虑溃疡部位的影响时, 胃溃疡并出血*H.pylori*感染率较十二指肠溃疡并出血高, 提示*H.pylori*感染可能不是PUB的独立因素; 而不考虑溃疡部位, *H.pylori*感染在控制PUB的混杂因素中是个保护性因素. 另有研究[28]发现, 在十二指肠溃疡出血患者, 与*H.pylori*阳性相比, *H.pylori*阴性患者症状更加严重, 其再出血率、手术率和死亡率都较高, 甚至可以认为*H.pylori*感染是保护性

因素, 这可能与*H.pylori*阴性患者症状不明显, 往往以上消化道出血为首发症状来就诊. 总体上, 我们可以认为*H.pylori*感染是PUB患者的一个主要致病因素, 其存在增加了PU患者出血的可能.

4 对*H.pylori*阳性的PUB患者是否需要行*H.pylori*根除治疗

尽管*H.pylori*在PUB患者的感染率较低, 绝大多数的研究[29,30]表明, 从长远角度讲, 根除*H.pylori*可以显著降低溃疡患者再出血的风险, 促进溃疡愈合. 一项荟萃分析[22]显示: 成功根除*H.pylori*后, 溃疡患者的再出血率可以降低到1%. 根除*H.pylori*在统计学上有显著意义, 除能减少溃疡复发外, 还能防止溃疡进一步恶化、出血[31]. 而目前关于*H.pylori*对出血急性期的溃疡患者短期再出血率的影响的资料较少见. Schilling等的研究发现, 一旦内镜止血成功后, *H.pylori*感染的存在并不影响PUB患者的短期(<21 d)再出血率[32,33].

目前, 对于有长期应用NSAIDs的溃疡出血患者, 是否有根除*H.pylori*的必要存在一定的争论. 目前普遍认为*H.pylori*感染和NSAIDs, 不仅是PUB的独立的危险因素, 而且有协同作用[34], 因此倾向于行*H.pylori*根除治疗, 认为根除*H.pylori*可减少PUB的危险, 在一定程度上可以预防溃疡及再出血的发生[35,36]. 但Aabakken等[37]认为NSAIDs相关性溃疡出血的患者不需要根除*H.pylori*.

大量资料[38-41]表明, 所有的溃疡出血患者, 都必须行*H.pylori*检测, 一旦检测结果为阳性, 不论是否使用NSAIDs, 都必须给予*H.pylori*根除治疗. 如果*H.pylori*根除成功, 不需要长期抑酸维持治疗[42].

5 结论

PUB患者中*H.pylori*感染率受众多因素影响, 缺少一个统一的诊断标准, 因此尽快明确出血状态下*H.pylori*检测的敏感性降低的机制, 找到有效而准确的检测方法已成为目前研究的重点. 目前治疗*H.pylori*感染采用抗生素加PPIs或秘剂的联合疗法, 其疗效约为90%. 但随着耐药菌株的迅速增加, 各种药物联合方案的根除率逐渐降低, 如何高效、经济地根除*H.pylori*成为研究的热点. 随着疫苗研究的发展, 在不远的将来, 疫苗接种可能成为预防*H.pylori*感染、降低*H.pylori*相关性疾病发病率的最佳选择.

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■应用要点

本文系统地阐明*H.pylori*感染及其根除后对PUB的影响, 虽存在一定争议, 但能推动临床领域对其进一步的研究; 在一定程度上能提高临床对于*H.pylori*的PUB的认识, 有利于对溃疡并出血的防治.

■同行评价
本文具有一定的临床参考价值, 但创新性一般.

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