世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2011年2月28日; 19(6): 614-618
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

酒精性急性胰腺炎发病机制及临床特征

余贤恩

■背景资料
急性胰腺炎(AP)是由胆道疾病、酒精、高脂血症等多种原因引起的全身炎症性疾病. Frey等研究表明AP发病率已明显增加, Yadav等报道美国酒精性急性胰腺炎(AAP)发病率从7.5例/10万人增加到8.1例/10万人, 约增加12%.

余贤恩, 广西百色市人民医院消化科 广西壮族自治区百色市 533000
通讯作者: 余贤恩, 533000, 广西壮族自治区百色市, 广西百色市人民医院消化科. yuxianenys@163.com
收稿日期: 2010-11-11 修回日期: 2011-01-20
接受日期: 2011-01-23 在线出版日期: 2011-02-28

Alcoholic acute pancreatitis: pathogenesis and clinical characteristics

Xian-En Yu

Xian-En Yu, Department of Gastroenterology, People's Hospital of Baise, Baise 533000, Guangxi Zhuang Autonomous Region, China
Correspondence to: Xian-En Yu, Department of Gastroenterology, People's Hospital of Baise, Baise 533000, Guangxi Zhuang Autonomous Region, China. yuxianenys@163.com
Received: 2010-11-11 Revised: 2011-01-20
Accepted: 2011-01-23 Published online: 2011-02-28

Abstract
Animal and clinical studies have shown that alcohol and its metabolic products, endotoxin, viral infection, drinking pattern, smoking, obesity, genetic variability, and gene polymorphisms were very important in the pathogenesis of alcoholic acute pancreatitis (AAP). The morbidity of AAP has been increased in the past decade, and male gender is strongly associated with increased risk of AAP. The mortality of AAP is high, while the quality of life of survivors of severe AAP is low. In this paper, we review the pathogenesis and clinical characteristics of AAP.

Key Words: Alcoholic acute pancreatitis; Pathogenesis; Clinical characteristics

Yu XE. Alcoholic acute pancreatitis: pathogenesis and clinical characteristics. Shijie Huaren Xiaohua Zazhi 2011; 19(6): 614-618

摘要
动物实验及临床研究表明, 酒精及其代谢产物、细菌内毒素、病毒感染、饮酒方式、吸烟、肥胖及宿主的基因突变及基因多态性在酒精性急性胰腺炎发生中具有重要作用. 酒精性急性胰腺炎的发病率已明显增加, 其以男性为主, 病死率高, 重症存活者生活质量低下. 本文综述了酒精性急性胰腺炎的发病机制及临床特征.

关键词: 酒精性急性胰腺炎; 发病机制; 临床特征

余贤恩. 酒精性急性胰腺炎发病机制及临床特征. 世界华人消化杂志 2011; 19(6): 614-618
http://www.wjgnet.com/1009-3079/19/614.asp

■同行评议者
黄颖秋, 教授, 本溪钢铁(集团)有限责任公司总医院消化内科

0 引言
急性胰腺炎(acute pancreatitis, AP)是由胆道疾病、酒精、高脂血症等多种原因引起的全身炎症性疾病. Frey等[1]研究表明AP发病率已明显增加, Yadav等[2]报道美国酒精性急性胰腺炎(alcoholic acute pancreatitis, AAP)发病率从7.5例/10万人增加到8.1例/10万人, 约增加12%. 酒精消费与胰腺炎的关系在国际上受重视已超过100多年, 分析认为酒精消费与发生胰腺炎的危险之间存在量一效关系[3]. 并非所有嗜酒的人都发生胰腺炎, 既往认为5%嗜酒者有胰腺炎的临床表现[4], Maruyama等[5]报道日本男性嗜酒者9.1%-17.4%患酒精性胰腺炎. 为何只有少部分嗜酒者发生胰腺炎? 因此, 进一步探索及了解AAP发病机制及临床表现特征, 对于胰腺炎的预防、诊治很有意义.

1 AAP发病机制
AAP的发生是酒精、宿主、环境因素的相互作用及共同影响的结果, 这些作用及影响无论在动物还是在人体都具有一定的特征.

1.1 动物实验
1.1.1 酒精及其代谢产物的作用: 给大鼠喂食酒精, 8 wk后胰腺RNA表达出现改变, 激活的转录因子3、热休克蛋白70、热休克蛋白27及mesotrypsinogen增加, 而叶酸转运蛋白、金属硫蛋白减少, 引起胰腺实质损失、持续炎症及纤维化. 乙醇也使大鼠血清及胰腺组织中的铁离子增加, 此与胰腺的氧化损伤有关[6], 而且非氧化代谢产

物-脂肪酸乙酯中介了AP早期胰腺细胞损伤[7,8]. 用乙醇喂养♂Wistar大鼠后, 大鼠胰腺caspase表达减少, cathepsin B表达增加, 阻止细胞凋亡, 促进细胞死亡. 胰腺细胞的死亡(坏死)就会导致胰腺炎[9].

乙醇对离体的大鼠胰腺腺泡细胞(pancreatic acinar cell, PAC)的损伤是通过蛋白激酶C-ε(protein kinase C-ε, PKC-ε)来激活NF-κB而发生的, 其增强CCK-8引起的NF-κB激活的作用至少部分是通过PKC-ε来实现的[10], 并使胰腺PKC-α中介的Munc18c细胞膜电位改变, 进而导致胰腺炎[11]. Siech等[12]对离体大鼠PAC及胰腺星状细胞(pancreatic stellate cells, PSC)进行了详细研究. PAC培养24 h后, 再加入乙醇及/或脂肪(VLDL), 通过检测淀粉酶、脂肪酶、乳酸酶、细胞凋亡因子、氧化应激物等了解PAC功能及培养PSC来了解恢复情况. 加入观察物培养6 h后发现, VLDL及酒精通过氧化应激来加重PAC的损伤, 且出现具有量一效变化关系的细胞凋亡及/或死亡. VLDL及酒精还促进PSC增生及细胞外基质蛋白的合成.

长期用乙醇喂养大鼠, 可使其白细胞黏附性增加, 导致胰腺微循环障碍[13], 增加动物重症坏死性胰腺炎(severe necrotizing pancreatitis, SNP)肝脏、胰腺损伤, 而氧化钆可以改善肝、胰微循环, 减少肝、胰的损伤程度[14,15].

1.1.2 细菌感染-细菌内毒素的作用: 对大鼠在体及离体胰腺研究发现, 细菌内毒素-脂多糖(lipopolysaccharide, LPS)增加酒精引起的胰腺组织损伤及纤维化. 撤除酒精后, 胰腺损伤(包括纤维化)会恢复, 并增加PSC凋亡. 如果继续使用酒精, 则使胰腺损伤永存, 并阻止PSC凋亡. 酒精及LPS明显抑制PSC凋亡, LPS的这种作用可以被Toll样受体4 siRNA所阻滞[16,17]. 研究还发现用酒精喂养的大鼠注射LPS后, 出现多器官损伤, 胰腺坏死及炎症较非酒精喂养的动物严重, 且这种损伤与LPS之间存在量一效关系. LPS引起胰腺损伤是胰腺细胞坏死, 而非凋亡[18,19]. 说明内毒素协同酒精对胰腺损伤.

1.1.3 病毒感染: Jerrells等[20]对小鼠研究发现, 让酒精喂养C57BL/6小鼠感染科萨其病毒B3, 动物胰腺、脾脏的病毒增加, 体液免疫下降, 结果出现较严重胰腺炎. 表明病毒感染是酒精引起胰腺炎的一个重要共同致病因素.

1.2 临床研究 基因-环境因素共同促发了人群患酒精性胰腺炎[21], 即酒精、宿主性别、年龄、民族、种族、体质量指数、吸烟情况、饮酒方式及饮食等情况以及各因素间的相互影响在酒精性胰腺炎发生中具有重要作用. Whitcomb提出了Sentinel Acute Pancreatitis Event(SAPE)假设模型, 酒精作用于中枢神经系统及胰腺, 影响细胞死亡或凋亡、组织内巨噬细胞及星状细胞的反应及功能, 酒精还影响免疫系统反应; 中枢神经系统对胰腺进行调节; 吸烟等环境因素也影响对炎症反应及星状细胞功能.

1.2.1 酒精种类及饮酒方式的影响: 各种酒精饮料含有乙醇及多种非乙醇成分, 可以引起胰腺细胞发生不同反应[22], Barreto等[23]报道, 印度乡村生产的酒精含有多种副产物, 如丁醇、丙醇、乙醛、醋酸及微量的甲醇, 而含有这些副产物的酒精较白兰地、威士忌等导致了人群中酒精性胰腺炎高发病率.

饮酒方式对胰腺炎发生也有影响. 饮酒超过100 g/d(8次/d), 饮酒时间>5-10年, 则发生酒精性胰腺炎, 但也有报道饮酒≥60 g/d, 20-30年发生酒精性胰腺炎. 饮酒量与胰腺炎的相关性不如饮酒量与酒精性肝炎或肝硬化的相关性那么高. 近来研究认为每天饮酒4次是发生酒精性胰腺炎的阈值[3].

1.2.2 吸烟的影响: 超过90%酒精性胰腺炎患者是长期吸烟者. 吸烟是酒精性胰腺炎的共同病因, 吸毒也会增加AP的发病率[2,24]. DiMagno等[25]报道吸烟是发生AP、复发性AP及慢性胰腺炎的共同病因, 且存在量一效关系. 但也有报道吸烟与慢性胰腺炎明显相关, 而与AP相关的证据不足[26].

1.2.3 肥胖的影响: 肥胖多伴有高脂血症及高粘血症, 易造成胰腺微循环障碍. 同时脂肪组织及脂联素的作用, 使免疫功能失调. 肥胖不仅是AP发生局部及全身并症的危险因素, 也是酒精性慢性胰腺炎的重要危险因素[27,28].

1.2.4 炎症细胞因子及调节物的影响: 炎症细胞因子及调节物参与了许多炎症反应及细胞组织坏死过程. 炎症性细胞因子IL-6、IL-8及TNF-α、抵抗素、生长素释放肽在AAP发生及发展中具有重要促进作用[29,30]. SAP患者血高迁移率族蛋白1(high-mobility group box chromosomal protein 1, HMGB1)浓度增加, 且与AP严重程度有关, 其导致严重炎症及器官衰竭[31].

1.2.5 基因的影响: 基因突变及基因多态性在AP发生中具独特作用. 基因差异会引起是否患病以及病变程度不同的结局.

■相关报道
Barreto等报道, 印度乡村生产的酒精含有多种副产物, 如丁醇、丙醇、乙醛、醋酸及微量的甲醇, 而含有这些副产物的酒精较白兰地、威士忌等导致了人群中酒精性胰腺炎高发病率.

■同行评价
本文内容详实, 对临床工作有一定的参考价值.

酗酒者及酒精中毒者的乙醇脱氢酶、乙醛脱氢酶、微粒体细胞色素P-450系统都具有基因多态性. 且乙醇脱氢酶2及乙醛脱氢酶2的多态性是亚洲人患酒精性肝硬化、酒精性胰腺炎及酒精中毒危险因素[2]. Miyassaka等[4]研究认为羧化脂肪酶(carboxyl ester lipase, CEL)基因的多态性, 尤其是L等位基因增加, 与酒精性胰腺炎发生密切相关. Chao等[32]报道, CD14基因中的C等位基因与中国人患AAP密切相关. 而囊性纤维化跨膜传导调节因子(cystic fibrosis transmembrane regulator, CFTR)、免疫反应性阳离子胰蛋白酶原(cationic trypsinogen, PRSS1)、蛋白酶抑制因子Kazal型1(serine protease inhibitor Kazal type 1, SPINL1)基因突变增加AP发生, 且CFTR基因突变在ARP患者中常见, 但在慢性胰腺炎中不明显. 而N34S SPINK1基因突变在急性复发性胰腺炎及慢性胰腺炎中不明显. 61%的急性复发性胰腺炎患者至少携带1种基因突变及/或基因多态性[2,33]. 但对日本378名健康者及604例胰腺疾病患者研究发现, AP患者无基因变异携带者, 且AP患者的p.G191R基因较健康者少见[34]. Joergensen等[35]对首次AP发作的青年患者进行研究表明, 32%特发性胰腺炎患者的病因是基因病变, 在全部AP患者中4%病因是基因问题. 所以有关基因对胰腺炎的影响还需要研究不同性别、民族、种族、年龄等相关情况.

2 AAP的临床特征

2.1 临床表现及诊断 AAP多见于男性, 男/女为2.5-5/1, 好发于年龄为35-44岁的男性及25-34岁的女性. 大多有腹痛或者AP复发的相关表现[2]. Nardback等[36]研究发现, 首次发生AAP者, 腹痛、恶心、呕吐等大部分症状是出现在停止饮酒数小时到48 h内. 超声内镜检查发现酒精性胰腺炎患者的胰腺在早期已有明显图像改变[37]. Kim等[38]研究发现, 与急性胆源性胰腺炎相比, AAP病例胰腺CT检查显示胰腺周围的渗出病变更明显、更严重. SPINK1基因特异性使得AAP病例胰腺组织出现坏死、慢性损害等改变[39,40].

依据病史及临床表现, 对AAP诊断不难. 血清二唾液酸转铁蛋白是AAP区别于其他AP在病因诊断上准确、简便、快速的生化标志物[41,42].

2.2 发病率增加 有关AAP发病率报道不一致. Miyasaka等[4]于2005年报道5%嗜酒者患AAP. 对重度酒精依赖者研究发现至少3%患AAP[24], 而Yadav等[2]报道美国AAP发病率从7.5例/10万人增加到8.4例/10万人. Maruyama等[5]研究表明9.1%-17.4%饮酒日本男子患AAP, 而且发现患者开始饮酒的年龄较轻, 每天饮酒量大. 在荷兰研究表明, 1992-2004年住院AP及慢性胰腺炎患者已增加, 增长为11.8-19.2例/100 000人/年, 并预测认为, 与2004年相比, 2010年至少增加9.9%[43].

2.3 复发率受多因素影响 半数AAP复发, 复发者的C-反应蛋白及白细胞均较高[44]. 持续饮酒是复发的重要危险因素, 假性囊肿形成似乎与胰腺炎复发密切相关[45], 而基因改变也在急性复发性胰腺炎中具有重要作用[46]. 为减少AAP复发, Nordback等[47]进行了一个2年的对照研究, 一组为住院期间的单次健康教育咨询, 另一组为每隔半年定期健康教育咨询. 结果显示定期健康教育咨询组5例AP患者复发9次, 而对照组13例AP患者复发20次. 第1个半年时两组复发率相近(4次/5次), 后续观察发现定期教育组复发率较对照组明显减少(5次/15次, $P = 0.02$). 研究表明, 通过定期健康教育咨询以减少酒精消费, 可以防止AAP复发.

2.4 病死率较高 酒精性胰腺炎病死率较非酒精性胰腺炎的高[1,48]. Deng等[49]研究表明, 狂饮者中男性患胰腺炎较多、血三酰甘油较高、Balthazar CT评分高、APCHE Ⅱ评分较高、总的并发症及总的病死率较高. Lowenfels等[50]报道表明AP总的病死率<5%. 病死率增加与肥胖率及饮酒量增加等有关.

2.5 重症存活者的生活质量较低 存活者生活质量与组织器官受疾病损伤程度、康复效果等有关. 与胆源性AP相比, AAP易转化为慢性胰腺炎[44], 慢性胰腺炎患者生活质量较其他疾病患者生活质量差, 而酒精性慢性胰腺炎患者生活质量又较非酒精性慢性胰腺炎患者生活质量差[2]. 酒精性胰腺炎的胰腺坏死感染者经手术治疗后活质量仍较低[51-53].

总之, 无论是动物实验或是临床研究都显示AP发生与酒精、吸烟、肥胖、细菌内毒素、病毒感染、基因多态性及基因突变等共同致病因素有关. AAP发病率逐年提高, 其病死率也较高. 因此积极地进行健康宣传教育, 减少酒精消费是降低AP发生及防止其复发的有效途径.

3 参考文献

1 Frey CF, Zhou H, Harvey DJ, White RH. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. *Pancreas* 2006; 33: 336-344

2 Yadav D, Papachristou GI, Whitcomb DC. Alcohol-associated pancreatitis. *Gastroenterol Clin North Am* 2007; 36: 219-238, vii
3 Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. *JOP* 2009; 10: 387-392
4 Miyasaka K, Ohta M, Takano S, Hayashi H, Higuchi S, Maruyama K, Tando Y, Nakamura T, Takata Y, Funakoshi A. Carboxylester lipase gene polymorphism as a risk of alcohol-induced pancreatitis. *Pancreas* 2005; 30: e87-e91
5 Maruyama K, Otsuki M. Incidence of alcoholic pancreatitis in Japanese alcoholics: survey of male sobriety association members in Japan. *Pancreas* 2007; 34: 63-65
6 Kiziler AR, Aydemir B, Gulyasar T, Unal E, Gunes P. Relationships among iron, protein oxidation and lipid peroxidation levels in rats with alcohol-induced acute pancreatitis. *Biol Trace Elem Res* 2008; 124: 135-143
7 Gukovsky I, Lugea A, Shahsahebi M, Cheng JH, Hong PP, Jung YJ, Deng QG, French BA, Lungo W, French SW, Tsukamoto H, Pandol SJ. A rat model reproducing key pathological responses of alcoholic chronic pancreatitis. *Am J Physiol Gastrointest Liver Physiol* 2008; 294: G68-G79
8 Kubisch CH, Gukovsky I, Lugea A, Pandol SJ, Kuick R, Misek DE, Hanash SM, Logsdon CD. Long-term ethanol consumption alters pancreatic gene expression in rats: a possible connection to pancreatic injury. *Pancreas* 2006; 33: 68-76
9 Wang YL, Hu R, Lugea A, Gukovsky I, Smoot D, Gukovskaya AS, Pandol SJ. Ethanol feeding alters death signaling in the pancreas. *Pancreas* 2006; 32: 351-359
10 Satoh A, Gukovskaya AS, Reeve JR Jr, Shimosegawa T, Pandol SJ. Ethanol sensitizes NF-kappaB activation in pancreatic acinar cells through effects on protein kinase C-epsilon. *Am J Physiol Gastrointest Liver Physiol* 2006; 291: G432-G438
11 Cosen-Binker LI, Lam PP, Binker MG, Gaisano HY. Alcohol-induced protein kinase Calpha phosphorylation of Munc18c in carbachol-stimulated acini causes basolateral exocytosis. *Gastroenterology* 2007; 132: 1527-1545
12 Siech M, Zhou Z, Zhou S, Bair B, Alt A, Hamm S, Gross H, Mayer J, Beger HG, Tian X, Kornmann M, Bachem MG. Stimulation of stellate cells by injured acinar cells: a model of acute pancreatitis induced by alcohol and fat (VLDL). *Am J Physiol Gastrointest Liver Physiol* 2009; 297: G1163-G1171
13 Grauvogel J, Daemmrich TD, Ryschich E, Gebhard MM, Werner J. Chronic alcohol intake increases the severity of pancreatitis induced by acute alcohol administration, hyperlipidemia and pancreatic duct obstruction in rats. *Pancreatology* 2010; 10: 603-612
14 Cuthbertson CM, Christophi C. Disturbances of the microcirculation in acute pancreatitis. *Br J Surg* 2006; 93: 518-530
15 Schneider L, Hackert T, Longerich T, Hartwig W, Fritz S, Krych R, Fortunato F, Gebhard MM, Werner J. Effects of gadolinium chloride and glycine on hepatic and pancreatic tissue damage in alcoholic pancreatitis. *Pancreas* 2010; 39: 502-509
16 Vonlaufen A, Phillips PA, Xu Z, Zhang X, Yang L, Pirola RC, Wilson JS, Apte MV. Withdrawal of alcohol promotes regression while continued alcohol intake promotes persistence of LPS-induced pancreatic injury in alcohol-fed rats. *Gut* 2011; 60: 238-246
17 Vonlaufen A, Xu Z, Daniel B, Kumar RK, Pirola R, Wilson J, Apte MV. Bacterial endotoxin: a trigger factor for alcoholic pancreatitis? Evidence from a novel, physiologically relevant animal model. *Gastroenterology* 2007; 133: 1293-1303
18 Sarady-Andrews JK, Liu F, Gallo D, Nakao A, Overhaus M, Ollinger R, Choi AM, Otterbein LE. Biliverdin administration protects against endotoxin-induced acute lung injury in rats. *Am J Physiol Lung Cell Mol Physiol* 2005; 289: L1131-L1137
19 Fortunato F, Deng X, Gates LK, McClain CJ, Bimmler D, Graf R, Whitcomb DC. Pancreatic response to endotoxin after chronic alcohol exposure: switch from apoptosis to necrosis? *Am J Physiol Gastrointest Liver Physiol* 2006; 290: G232-G241
20 Jerrells TR, Vidlak D, Strachota JM. Alcoholic pancreatitis: mechanisms of viral infections as cofactors in the development of acute and chronic pancreatitis and fibrosis. *J Leukoc Biol* 2007; 81: 430-439
21 Whitcomb DC. Gene-environment factors that contribute to alcoholic pancreatitis in humans. *J Gastroenterol Hepatol* 2006; 21 Suppl 3: S52-S55
22 Feick P, Gerloff A, Singer MV. Effect of non-alcoholic compounds of alcoholic drinks on the pancreas. *Pancreatology* 2007; 7: 124-130
23 Barreto SG, Jardine D, Phillips P, Bhatia M, Saccone GT. Can by-products in country-made alcohols induce acute pancreatitis? *Pancreas* 2010; 39: 1199-1204
24 Yadav D, Eigenbrodt ML, Briggs MJ, Williams DK, Wiseman EJ. Pancreatitis: prevalence and risk factors among male veterans in a detoxification program. *Pancreas* 2007; 34: 390-398
25 DiMagno MJ, DiMagno EP. Chronic pancreatitis. *Curr Opin Gastroenterol* 2010; 26: 490-498
26 Sand J, Lankisch PG, Nordback I. Alcohol consumption in patients with acute or chronic pancreatitis. *Pancreatology* 2007; 7: 147-156
27 Martínez J, Johnson CD, Sánchez-Payá J, de Madaria E, Robles-Díaz G, Pérez-Mateo M. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. *Pancreatology* 2006; 6: 206-209
28 Ammann RW, Raimondi S, Maisonneuve P, Mullhaupt B. Is obesity an additional risk factor for alcoholic chronic pancreatitis? *Pancreatology* 2010; 10: 47-53
29 Novovic S, Andersen AM, Ersbøll AK, Nielsen OH, Jorgensen LN, Hansen MB. Proinflammatory cytokines in alcohol or gallstone induced acute pancreatitis. A prospective study. *JOP* 2009; 10: 256-262
30 Daniel P, Leśniowski B, Jasińska A, Pietruczuk M, Małecka-Panas E. Usefulness of assessing circulating levels of resistin, ghrelin, and IL-18 in alcoholic acute pancreatitis. *Dig Dis Sci* 2010; 55: 2982-2987
31 Yasuda T, Ueda T, Takeyama Y, Shinzeki M, Sawa H, Nakajima T, Ajiki T, Fujino Y, Suzuki Y, Kuroda Y. Significant increase of serum high-mobility group box chromosomal protein 1 levels in patients with severe acute pancreatitis. *Pancreas* 2006; 33: 359-363
32 Chao YC, Chu HC, Chang WK, Huang HH, Hsieh TY. CD14 promoter polymorphism in Chinese alcoholic patients with cirrhosis of liver and acute pancreatitis. *World J Gastroenterol* 2005; 11: 6043-6048
33 Cavestro GM, Zuppardo RA, Bertolini S, Sereni G, Frulloni L, Okolicsanyi S, Calzolari C, Singh SK, Sianesi M, Del Rio P, Leandro G, Franzè A, Di

Mario F. Connections between genetics and clinical data: Role of MCP-1, CFTR, and SPINK-1 in the setting of acute, acute recurrent, and chronic pancreatitis. *Am J Gastroenterol* 2010; 105: 199-206
34 Kume K, Masamune A, Takagi Y, Kikuta K, Watanabe T, Satoh K, Satoh A, Hirota M, Hamada S, Shimosegawa T. A loss-of-function p.G191R variant in the anionic trypsinogen (PRSS2) gene in Japanese patients with pancreatic disorders. *Gut* 2009; 58: 820-824
35 Joergensen M, Brusgaard K, Crüger DG, Gerdes AM, Schaffalitzky de Muckadell OB. Incidence, etiology and prognosis of first-time acute pancreatitis in young patients: a population-based cohort study. *Pancreatology* 2010; 10: 453-461
36 Nordback I, Pelli H, Lappalainen-Lehto R, Sand J. Is it long-term continuous drinking or the post-drinking withdrawal period that triggers the first acute alcoholic pancreatitis? *Scand J Gastroenterol* 2005; 40: 1235-1239
37 Thuler FP, Costa PP, Paulo GA, Nakao FS, Ardengh JC, Ferrari AP. Endoscopic ultrasonography and alcoholic patients: can one predict early pancreatic tissue abnormalities? *JOP* 2005; 6: 568-574
38 Kim YS, Kim Y, Kim SK, Rhim H. Computed tomographic differentiation between alcoholic and gallstone pancreatitis: Significance of distribution of infiltration or fluid collection. *World J Gastroenterol* 2006; 12: 4524-4528
39 Pezzilli R, Morselli-Labate AM. Alcoholic pancreatitis: pathogenesis, incidence and treatment with special reference to the associated pain. *Int J Environ Res Public Health* 2009; 6: 2763-2782
40 Pandol SJ, Raraty M. Pathobiology of alcoholic pancreatitis. *Pancreatology* 2007; 7: 105-114
41 Pérez-Mateo M. How we predict the etiology of acute pancreatitis. *JOP* 2006; 7: 257-261
42 Methuen T, Kylänpää L, Kekäläinen O, Halonen T, Tukiainen E, Sarna S, Kemppainen E, Haapiainen R, Puolakkainen P, Salaspuro M. Disialotransferrin, determined by capillary electrophoresis, is an accurate biomarker for alcoholic cause of acute pancreatitis. *Pancreas* 2007; 34: 405-409
43 Spanier BW, Dijkgraaf MG, Bruno MJ. Trends and forecasts of hospital admissions for acute and chronic pancreatitis in the Netherlands. *Eur J Gastroenterol Hepatol* 2008; 20: 653-658
44 Yasuda T, Ueda T, Takeyama Y, Shinzeki M, Sawa H, Nakajima T, Kuroda Y. Long-term outcome of severe acute pancreatitis. *J Hepatobiliary Pancreat Surg* 2008; 15: 397-402
45 Pelli H, Lappalainen-Lehto R, Piironen A, Järvinen S, Sand J, Nordback I. Pancreatic damage after the first episode of acute alcoholic pancreatitis and its association with the later recurrence rate. *Pancreatology* 2009; 9: 245-251
46 Keim V. Role of genetic disorders in acute recurrent pancreatitis. *World J Gastroenterol* 2008; 14: 1011-1015
47 Nordback I, Pelli H, Lappalainen-Lehto R, Järvinen S, Räty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. *Gastroenterology* 2009; 136: 848-855
48 Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006; 33: 323-330
49 Deng L, Xue P, Huang L, Yang X, Wan M, Xia Q. Binge drinking aggravates the outcomes of first-attack severe acute pancreatitis. *Pancreas* 2010; 39: 149-152
50 Lowenfels AB, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. *Curr Gastroenterol Rep* 2009; 11: 97-103
51 Papachristou GI, Papachristou DJ, Morinville VD, Slivka A, Whitcomb DC. Chronic alcohol consumption is a major risk factor for pancreatic necrosis in acute pancreatitis. *Am J Gastroenterol* 2006; 101: 2605-2610
52 Reszetow J, Hać S, Dobrowolski S, Stefaniak T, Wajda Z, Gruca Z, Sledziński Z, Studniarek M. Biliary versus alcohol-related infected pancreatic necrosis: similarities and differences in the follow-up. *Pancreas* 2007; 35: 267-272
53 Cinquepalmi L, Boni L, Dionigi G, Rovera F, Diurni M, Benevento A, Dionigi R. Long-term results and quality of life of patients undergoing sequential surgical treatment for severe acute pancreatitis complicated by infected pancreatic necrosis. *Surg Infect* (Larchmt) 2006; 7 Suppl 2: S113-S116

编辑 李薇 电编 何基才