

巴尔通体感染性心内膜炎的研究进展

刘云彦^{1,2,3} 栗冬梅^{1,3*} 刘起勇^{1,3} 陈忠科^{2*}

(1. 中国疾病预防控制中心传染病预防控制所 传染病预防控制国家重点实验室 北京 102206)

(2. 山东大学 生命科学学院 山东 济南 250100)

(3. 感染性疾病诊治协同创新中心 江苏 杭州 310003)

摘要: 感染性心内膜炎一直是威胁人类健康的重要疾病之一。近年来人类正面临着此病发病率持续上升的局面, 其诊断、治疗和预防依然是目前需要解决的重要临床和公共卫生问题。本文介绍了感染性心内膜炎疾病的最新研究进展, 分析了国内外报道的 538 份巴尔通体感染性心内膜炎的病例, 重点阐述了巴尔通体和相关心内膜炎的流行病学、实验室诊断、治疗以及发病的危险因素和预防控制措施。预测这些研究将对人类理解和控制巴尔通体感染性心内膜炎具有重要的指导意义。

关键词: 感染性心内膜炎, 巴尔通体, 实时荧光定量 PCR, 诊断, 猫抓病

Research progress on *Bartonella* endocarditis: a review of the literatures

LIU Yun-Yan^{1,2,3} LI Dong-Mei^{1,3*} LIU Qi-Yong^{1,3} CHEN Zhong-Ke^{2*}

(1. State Key Laboratory for Infectious Diseases Prevention and Control, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China)

(2. School of Life Science, Shandong University, Jinan, Shandong 250100, China)

(3. Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, Jiangsu 310003, China)

Abstract: Infective endocarditis (IE) remains one of the major diseases, which poses a serious threat to human health. In recent years, human being is facing an increased incidence rate of IE and therefore accurate diagnosis and effective treatment as well as preventive measurements become urgent clinical and public health issues. This review summaries the recent progress of IE in laboratory diagnosis, treatment, the risk factors and preventive measures concerning *Bartonella* species and BE, including 538 *Bartonella* endocarditis (BE) cases and their epidemiology. It is anticipated that associated studies have substantial significance on the understanding and control of BE of human being.

Keywords: Infective endocarditis, *Bartonella*, Real-time quantity PCR, Diagnosis, Cat scratch disease

基金项目: 国家自然科学基金项目(No. 81101286); 国家科技重大项目(No. 2012ZX10004219-002)

*通讯作者: 栗冬梅: Tel: 86-10-58900741; Fax: 86-10-58900739; 信箱: lidongmei@icdc.cn

陈忠科: Tel: 86-531-88364723-8611; 信箱: zhongkechen@sdu.edu.cn

收稿日期: 2014-05-04; 接受日期: 2014-06-25; 优先数字出版日期(www.cnki.net): 2014-08-14

感染性心内膜炎(Infective endocarditis, IE)是一类严重威胁生命、临床表现极其复杂且诊断十分困难的疾病^[1]。该病的病因复杂,依据初起临床表现、潜在心脏疾病、涉及病原微生物和并发症存在与否等表现出各种各样的形式,其治疗需内科医生、心脏病专家、外科医生、微生物学家、传染病专家、神经学家、神经外科学家、放射科学家和病理学家等的会诊与治疗^[2]。自从磺胺类药和青霉素出现,IE治疗得到了很大改观,不再是普遍致命性的疾病^[3]。在过去30年里,预防和治疗水平虽然有了很大提高,但发病率和死亡率依然比较高^[1],每年发病率为3–10例/100 000人,住院死亡率为9.6%–26.0%^[4]。Netzer等^[5]报道IE死亡率在20世纪50年代约为40.0%–60.0%,20世纪70年代到80年代降到约为30.0%,1980–1995年约为16.0%–27.0%。Slipczuk等^[6]研究近五十年IE流行病显示在20世纪70年代住院死亡率为24.4%–36.8%,并且之后一直保持在这个水平。

引起IE病原体有链球菌(*Streptococcus* spp.)、葡萄球菌(*Staphylococcus* spp.)、柯克斯体(*Coxiella* spp.)、巴尔通体(*Bartonella* spp.)、衣原体(*Chlamydia* spp.)、棒状杆菌(*Corynebacterium* spp.)、布鲁氏菌(*Brucella* spp.)、肠杆菌科(*Enterobacteriaceae* spp.)、真菌(Fungi)等^[7]。其诊断方法除依据临床表现外,主要依据微生物学检查,比如血液及瓣膜组织培养分离病原体、血清学、组织病理学和核酸分子诊断^[7]。报道血培养阴性心内膜炎(Blood culture negative endocarditis, BCNE)患者在IE患者中约占2.5%–31.0%^[8–10],主要是由于一类营养条件要求苛刻、生长缓慢、难以培养的病原体,即巴尔通体与柯克斯体引起^[8],其中巴尔通体感染性心内膜炎(*Bartonella* endocarditis, BE)发病率在IE患者中约占4.5%^[3,6]。Slipczuk等^[6]报道全世界BCNE患者在20世纪60年代约占18%,20世纪70年代约占14%,20世纪80年代约占23%,20世纪90年代约占20%,21世纪前十年约占14%,近十年处于下降趋势。英国报道伦敦圣托马斯医院1975–2000年516份心内

膜炎病例,研究显示BCNE患者约占12.2%,BE发病率在BCNE患者中约占11%^[9]。在法国BE发病率在IE患者中约占30%^[10–11],在巴西BE患者在BCNE患者中约占3.9%^[12]。

巴尔通体引起的相关疾病属于被忽视的疾病(Neglected disease),但引起的心内膜炎严重影响人类健康,造成卫生经济负担,因此重新认识这种病原体以及相关疾病势在必行。在此,本文分析了52篇文献报道的538例BE的临床症状、诊断和治疗等,阐述了巴尔通体和相关心内膜炎的流行概况、实验室诊断、治疗和预防措施等。

1 BE 报告病例分析

本文收集了1993–2013年英国、法国、美国、印度、瑞典和希腊等全世界范围内报道的52篇文献^[7,12–62],共计538例BE,其中47篇文献详细描述110例患者情况,5篇文献只报道BE病例数共428例^[7,55–56,61–62]。统计时剔除重叠病例报道。在有性别记录的108名患者中,男性占78.7% (85例),女性占21.3% (23例),男女发病率比例约4:1。患者年龄在4–81岁之间,40岁以下患者占34.6% (37例),40岁以上的占65.4% (70例),老年患者居多。报道有瓣膜病史患者占34.5% (38例)。从动物接触史看,主要报道接触猫、狗、兔和猴等,并有体虱和蚤类滋生情况。从预后情况看,报道71例患者中死亡占19.7% (14例),治愈占80.3% (57例)。从诊断方法看,主要有辅助的超声心动图检查、血清学、血培养、瓣膜培养和核酸分子检查。在88例患者中,赘生物患者占75% (66例)。在受累的瓣膜损伤中(91例),主动脉瓣膜占79.1% (72例),二尖瓣膜占30.8% (28例),三尖瓣膜5.5% (5例)和肺动脉瓣膜4.4% (4例)。血清学检测阳性患者占81.8% (90例)。血培养阳性患者占8.1% (9例)。瓣膜培养阳性患者占11.8% (13例)。血样和瓣膜PCR检测阳性患者占63.6% (70例)。

综合各种方法检测感染人心内膜炎的巴尔通体主要有8种,在110个病例患者中,由五日热巴

尔通体(*B. quintana*, Bq)感染的患者占 50.0% (55 例), 汉赛巴尔通体(*B. henselae*, Bh)占 23.6% (26 例), 另外还有文森巴尔通体博格霍夫亚种(*B. vinsonii* subsp. *berkhoffii*, Bvb)(2 例)、文森巴尔通体阿鲁潘亚种(*B. vinsonii* subsp. *arupensis*, Bva)(5 例)、阿尔萨斯巴尔通体(*B. alsatica*, Ba)(2 例)、伊丽莎白巴尔通体(*B. elizabethae*, Be)(1 例)、克勒巴尔通体(*B. koehlerae*, Bk)(1 例)和 *Candidatus B. mayotimonensis*(1 例), 未确定种的患者有 17 例。

2 巴尔通体流行概况

巴尔通体是一群革兰染色阴性、氧化酶阴性、营养条件要求苛刻、兼性细胞内寄生的需氧杆菌, 主要寄生在人、猫、狗和啮齿动物等血管内皮细胞和红细胞内, 通过跳蚤、体虱和白蛉等传播, 可引起人类卡瑞恩病、猫抓病、战壕热、杆菌性血管瘤、心内膜炎等疾病。尽管在自然界存在已久、分布广泛, 且有该病暴发流行, 但人们对巴尔通体认知程度仍然有限。随着新发传染病出现, 目前已定义了 27 个种, 种类越来越多, 引发疾病谱也相当复杂, 故越来越受到国内外生物医学界的重视, 我国也把巴尔通体病定为 14 种新发传染病之一。

近年来, 感染人类疾病的巴尔通体种类越来越多, 共报道 13 种, 其中 8 种可感染人引起心内膜炎, 此外至少有 6 种巴尔通体(*B. quintana*, *B. henselae*, *B. bovis*, *B. vinsonii* subsp. *berkhoffii*, *B. clarridgeiae*, *B. washoensis*)可感染动物引起心内膜炎^[63-69]。Bq 是主要的病原体, 且是首次被确认为 BE 的物种, 最先引起人们注意的是在第一次大战期间暴发且死亡率较高的战壕热^[70], Bh 和 Bvb 次之, 并可导致严重的瓣膜损伤。报道 Bq 感染心内膜炎的危险因素主要有免疫缺陷病、酗酒、无家可归和体虱感染, 经常发生在以前没有瓣膜疾病的人群, 而 Bh 感染心内膜炎主要与猫和猫蚤接触, 经常发生在已患有瓣膜疾病人群中^[59]。此外, 巴尔通体具有不完全的宿主特异性, Bh 和 Bk 的主要宿主是猫^[71-73]; Bq 的主要宿主是人类和其他灵长类动

物^[74-76]; Bvb 宿主为郊狼、狐狸和狗, 其中郊狼和狐狸是野生宿主, 狗是与人类更为亲密的宿主动物^[64]; Be 和 Bva 的宿主是啮齿动物^[59]; Ba 报道的唯一宿主是兔^[52]; *Candidatus B. mayotimonensis* 从心内膜炎病人中分离^[53], 未确定宿主。

3 巴尔通体实验室诊断

心内膜炎诊断标准首先应符合杜克(Duke)诊断标准^[77]。对于 BE, 血清学诊断只能作为辅助, 而血液及瓣膜组织培养分离病原体以及核酸检测才可作为确诊手段。

3.1 分离培养

适合分离的标本有血液、淋巴组织、皮肤、心脏瓣膜及其他器官的活检标本。最常用的是人工培养基分离培养, 固体培养需添加动物全血, 在 37 °C 含 5% CO₂ 的血培养基(如含 5% 羊血的胰酶大豆琼脂、哥伦比亚琼脂、巧克力琼脂等)上生长, 也可在含小牛血清的肉汤及组织中培养。一般培养 12-14 d 可看到典型的菌落生长, 有时需 45 d, 原代培养通常需 5-30 d, 传代培养需 35 d。液体培养无需添加动物全血, 更接近于宿主体内的环境, 明显加快培养速度, 为更难培养的菌提供了很好的解决办法。国外 Riess 等^[78]发现在果蝇细胞培养基中添加胎牛血清、谷氨酰胺和蔗糖后可使巴尔通体生长良好, 具有操作方便稳定的优点。国内已建立以昆虫细胞培养基(Schneider's insect medium, SIM)为基础的液体培养方法, 成分更简单、易于操作、生长良好^[79]。细胞培养是最有效的分离培养, 国外常用的细胞是人血管内皮细胞 ECV304, 对血液和淋巴标本来说也是比较好的方法^[80]。这些方法对巴尔通体培养和研究具有重要的应用价值, 但在判断结果时只靠肉眼观察, 没有足够可靠的依据, 降低了实验准确性, 此外还有部分待测样本在培养前使用过抗生素, 容易导致阴性结果。

3.2 血清学检测

目前一般采用间接免疫荧光抗体测定法(IFA)、酶联免疫吸附法(ELISA)、免疫印迹分析(Western

blotting)^[81], 其中 IFA 是最常用诊断 BE 的方法。报道在总体人群中采用 IFA 方法检测血清抗体, 当血清抗体滴度为 1:1 600 时, 其阳性符合率为 0.884^[82]。最新研究显示当血清抗体滴度为 1:1 600 时, 其阳性符合率为 0.672, 敏感率为 0.771; 当抗体滴度为 1:800 时, 其阳性符合率为 0.398, 而敏感率达到 0.895, 然而这一较低性符合率是由于在确定正常人群实验参考值时, 包含了一系列患有慢性 Bq 菌血症的流浪汉人群, 提高了正常人群的抗体滴度^[62]。国内杨小冉等采用 ELISA 和 IFA 方法检测北京市昌平地区健康人群体检血清标本中 Bh 抗体阳性率, 分别为 34.5% 和 35.6%^[83]。血清学检测是 BE 最实用的诊断方法, 但灵敏度差, 不能很好区分 Bq 和 Bh, 容易与衣原体等其他微生物出现交叉反应。

3.3 核酸诊断

(1) 普通 PCR。检测巴尔通体主要基于 16S rRNA、16S-23S rRNA ITS、*gltA*、*groEL*、*ftsZ* 和 *ribC* 基因 PCR 扩增。目前, 栗冬梅等已采用普通 PCR 扩增上述基因和测序的方法在北京、山东和云南等地的猫、狗、鼠、蚤和蜱中检测出 Bq、Bh、Bvb 和 Bc 等巴尔通体^[84-87]。虽然普通 PCR 已是快速检测病原体常用的一种技术, 但还存在很大缺陷, 如引物结合缺乏特异性、实验室污染和临床上 PCR 抑制物存在造成假阴性等。我们在实际工作中发现, 对于直接检测临床样品, 不敏感和假阳性是存在较多的问题, 特别是应用巢式 PCR 时, 敏感性虽然增加, 但是污染造成的假阳性问题仍然比较突出, 因此限制了在临床上的推广应用。

(2) 实时荧光定量 PCR (Real-time quantity PCR, qPCR)。目前用于微生物病原体检测的 qPCR 多为探针法。优点是对目标序列有很高的特异性, 依据序列特异性探针区别物种, 特异性准确率更高, 解决了荧光染料非特异的缺点, 且反应结束后不需要进行寡核苷酸熔解曲线分析, 缩短了实验时间。

单重实时荧光探针定量 PCR: 国外报道通过扩增 *ssrA* 基因建立实时荧光探针 PCR 方法检测巴尔

通体属^[88]。国内本实验室已建立了单重实时荧光定量 PCR 方法检测一些常见的巴尔通体, 如 Bvb^[89]、Bh、Bq、Be 和 Bb (尚未发表), 其他实验室也有报道采用 TaqMan-MGB 探针技术建立了检测 Bh 和 Bq 单重实时荧光定量 PCR 方法^[90]。这些方法虽然克服常规 PCR 技术的不足, 并可对未经 PCR 扩增的原始模板进行定量, 特异性、敏感性和重现性相对更好, 但是一个 PCR 体系只能检测一种或一类病原体, 不能同时检测多种病原体, 导致待测样品和试剂使用量相对比较多, 与目前发展的多重实时荧光探针 PCR 相比还是有些不足。

多重实时荧光探针定量 PCR, 在单一管中有效的区分多种病原体, 具有高效性、经济简便性等优点, 节约样本的同时又达到了经济实用、加速实验进程等。缺点是要合成昂贵的探针, 且在设计引物探针时要避免引物和引物、探针和探针及引物和探针之间二聚体, 给设计合适组合的引物探针带来一定的困难。该方法在其他致病菌如曲霉菌等检测应用广泛, 而在巴尔通体检测上还没有相关报道。

(3) 高分辨率熔解曲线分析技术 (High-resolution melting analysis, HRM)。是在实时荧光定量 PCR 上发展的一种新技术, 克服了无需使用特异性探针即可分析核酸熔解曲线的变化, 克服了不饱和染料如 SYBR Green 的一些缺点, 如荧光强度较低、稳定性差, 标记 DNA 双链时不能保证全部 PCR 产物都嵌合上染料, 嵌合到产物中的染料如果在扩增过程中不能及时脱落, 抑制 PCR 反应等。该技术主要采用饱和染料如 LC Green 等有更强大 DNA 结合能力和很低抑制作用, 解链过程中不会发生重排, 使熔解过程中发出的荧光信号具有更高的分辨率。结合多重 PCR 方法建立 HRM 方法根据其特定 T_m 值和熔解曲线有效区分 T_m 差异的多种物种。与多重实时荧光探针 PCR 相比, 操作相对简单, 不需制作标准曲线, 仅用 T_m 值即可判断结果; 不需合成探针, 成本低。但还有些不足, 可以检测任何双链 DNA 序列的扩增, 没有引物特异性。国外已报道采用 SYBR 染料建立检测巴尔通体荧光定

量 PCR 方法, 用作巴通体心内膜炎的诊断^[61], 最新报道采用饱和染料 cyto9 扩增 *rpoB*、*gltA*、ITS 测序检测巴尔通体^[91-93]。

目前, 国内外尚未见应用多重实时荧光探针 PCR 和 HRM 方法同时检测鉴定多种巴尔通体。感染人心内膜炎的巴尔通体最常见的病原体为 Bq、Bh 和 Bvb, 因此有必要建立灵敏度高、快速同时检测这 3 种病原体的方法, 为 BE 检测工作提供更有效的手段。鉴于上述两种方法各自优缺点, 本研究试验建立这两种方法检测巴尔通体, 通过实验比较其特异性灵敏性。

4 治疗

迄今 BE 最佳治疗方法还没有建立。疑似 IE, 治疗主要选用头孢曲松钠、强力霉素、万古霉素、庆大霉素、红霉素和利福平等; 疑似 BE, 推荐头孢曲松[100 mg/(kg·d)]和强力霉素[2-4 mg/(kg·d)]6 周, 再加 2 周庆大霉素[3 mg/(kg·d)]; 确认 BE, 推荐 6 周强力霉素, 随后再服用 2 周庆大霉素^[57]。手术治疗对 BE 并不是必须的, 主要通过患者临床症状来确定, 对于瓣膜疣状赘生物、治疗 2 周后依然有栓塞、心室衰竭、发生难治性急性心力衰竭、瓣膜穿孔和腱索离断等需考虑手术治疗^[2,57-58,94-95]。尽管如此, 仍然有 1/3 急性病例由于治疗时机等因素而预后不良, 特别是治疗前病程长、抗生素不敏感、剂量或疗程不足和有严重肺、脑或心内膜损害的病例大多在停药后 6 周容易复发, 复发率约 5%-10%, 复发病例再治疗时, 应采取联合用药, 加大剂量和延长疗程, 甚至推荐终身治疗^[95]。

5 防控措施

目前还没有有效的免疫预防方法, 主要采取综合性防控办法。首先应经常全面地杀虫^[15,27]灭鼠, 消除鼠类和吸血节肢动物的孳生。对豢养宠物(特别是猫、狗和兔等)的家庭需特别注意宠物及环境卫生, 避免被动物抓咬伤等, 一般不建议 HIV 患者豢养宠物。其次对有风湿性瓣膜病或先天性心脏病患

者需注意口腔卫生, 及时处理各种感染病灶, 施行手术或器械检查前应给予抗生素^[2,74]。此外巴尔通体感染的患者大部分是一些社会弱势群体, 如吸毒者、慢性酗酒者、流浪人群、HIV 阳性患者、无家可归和卫生条件差的人群, 需提高人群免疫力以及改善他们的生活状况, 养成良好的生活习惯等。

6 结语

巴尔通体生长缓慢、营养条件要求苛刻而难于分离培养是造成诊断困难的原因之一, 其次所引起 IE 没有明显临床特征, 许多病例没有被识别出来, 因此实际 BE 感染率远比我们知道的多。分子生物学诊断技术的迅速发展将有助于提高 BE 的诊断, 增加 BE 病例报道的数目。随着研究不断深入, 引发 BE 的新种将不断出现, 人们发现不同种巴尔通体所致疾病的严重性也各不相同, 更增加了此种疾病的复杂性。目前, 造成该病原体肆虐的原因以及致病机理尚不十分清楚, 其感染途径也较为复杂, 给诊断、治疗和预防措施的制定带来了困难。BE 潜隐发病, 临床上以心脏瓣膜损害为主, 严重者甚至威胁生命, 及早发现和治疗可以避免不良的预后, 因此需引起广大临床及预防医学工作者高度的重视。鉴于此, 建立快速灵敏的巴尔通体检测方法是当前的迫切需要, 为巴尔通体引起一系列疾病的早期诊断和治疗提供先决条件。

参考文献

- [1] Lisby G, Gutschik E, Durack DT. Molecular methods for diagnosis of infective endocarditis[J]. Infectious Disease Clinics of North America, 2002, 16(2): 393-412
- [2] Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the task force on the prevention, diagnosis, and treatment of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for infection and cancer[J]. European Heart Journal, 2009, 30(19): 2369-2413
- [3] Bor DH, Woolhandler S, Nardin R, et al. Infective endocarditis in the U.S., 1998-2009: a nationwide study[J]. PLoS One, 2013, 8(3): e60033
- [4] Fedeli U, Schievano E, Buonfrate D, et al. Increasing incidence and mortality of infective endocarditis: a population-based study through a record-linkage system[J]. BMC Infectious Diseases, 2011, 11: 48
- [5] Netzer RO, Zollinger E, Seiler C, et al. Infective endocarditis:

- clinical spectrum, presentation and outcome. An analysis of 212 cases 1980–1995[J]. Heart (British Cardiac Society), 2000, 84(1): 25-30
- [6] Slipeczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review[J]. PLoS One, 2013, 8(12): e82665
- [7] Fournier PE, Thuny F, Richet H, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases[J]. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America, 2010, 51(2): 131-140
- [8] Maguina C, Gotuzzo E. Bartonellosis: new and old[J]. Infectious Disease Clinics of North America, 2000, 14(1): 1-22
- [9] Lamas CC, Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years[J]. Heart (British Cardiac Society), 2003, 89(3): 258-262
- [10] Chaloner GL, Harrison TG, Birtles RJ. *Bartonella* species as a cause of infective endocarditis in the UK[J]. Epidemiology and Infection, 2013, 141(4): 841-846
- [11] Houpijian P, Raoult D. Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases[J]. Medicine, 2005, 84(3): 162-173
- [12] Lim MH, Chung DR, Kim WS, et al. First case of *Bartonella quintana* endocarditis in Korea[J]. Journal of Korean Medical Science, 2012, 27(11): 1433-1435
- [13] Spach DH, Callis KP, Paaauw DS, et al. Endocarditis caused by *Rochalimaea quintana* in a patient infected with human immunodeficiency virus[J]. Journal of Clinical Microbiology, 1993, 31(3): 692-694
- [14] Drancourt M, Mainardi JL, Brouqui P, et al. *Bartonella (Rochalimaea) quintana* endocarditis in three homeless men[J]. The New England Journal of Medicine, 1995, 332(7): 419-423
- [15] Spach DH, Kanter AS, Daniels NA, et al. *Bartonella (Rochalimaea)* species as a cause of apparent “culture-negative” endocarditis[J]. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America, 1995, 20(4): 1044-1047
- [16] Bergmans AM, Coenen JL, Bakhuizen R, et al. Endocarditis in a Dutch patient caused by *Bartonella quintana*[J]. Clinical Microbiology and Infection: the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 1997, 3(6): 692-695
- [17] Bruneel F, D'estanque J, Fournier PE, et al. Isolated right-sided *Bartonella quintana* endocarditis in an immunocompetent adult[J]. Scandinavian Journal of Infectious Diseases, 1998, 30(4): 424-425
- [18] Znazen A, Rolain JM, Hammami N, et al. High prevalence of *Bartonella quintana* endocarditis in Sfax, Tunisia[J]. The American Journal of Tropical Medicine and Hygiene, 2005, 72(5): 503-507
- [19] Yoda M, Hata M, Sezai A, et al. First report of *Bartonella quintana* endocarditis in Japan[J]. Circulation Journal: Official Journal of the Japanese Circulation Society, 2008, 72(6): 1022-1024
- [20] Balakrishnan N, Menon T, Fournier PE, et al. *Bartonella quintana* and *Coxiella burnetii* as causes of endocarditis, India[J]. Emerging Infectious Diseases, 2008, 14(7): 1168-1169
- [21] Ehrenborg C, Hagberg S, Alden J, et al. First known case of *Bartonella quintana* endocarditis in Sweden[J]. Scandinavian Journal of Infectious Diseases, 2009, 41(1): 73-75
- [22] Dimopoulos S, Eleftherakis E, Charitos C, et al. *Bartonella quintana* endocarditis as a cause of severe aortic insufficiency and heart failure[J]. Hellenic Journal of Cardiology: HJC=Hellenike Kardiologike Epitheorese, 2012, 53(6): 476-479
- [23] Dzipova O, Pekova S, Sojkova N, et al. Infective endocarditis due to *Bartonella quintana*: a severe disease and underdiagnosed etiology[J]. Folia Microbiologica, 2013, 58(6): 491-494
- [24] Sondermeijer HP, Claas EC, Orendi JM, et al. *Bartonella quintana* prosthetic valve endocarditis detected by blood culture incubation beyond 10 days[J]. European Journal of Internal Medicine, 2006, 17(6): 441-443
- [25] Jalava J, Kotilainen P, Nikkari S, et al. Use of the polymerase chain reaction and DNA sequencing for detection of *Bartonella quintana* in the aortic valve of a patient with culture-negative infective endocarditis[J]. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America, 1995, 21(4): 891-896
- [26] Hadfield TL, Warren R, Kass M, et al. Endocarditis caused by *Rochalimaea henselae*[J]. Human Pathology, 1993, 24(10): 1140-1141
- [27] Holmes AH, Greenough TC, Balady GJ, et al. *Bartonella henselae* endocarditis in an immunocompetent adult[J]. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America, 1995, 21(4): 1004-1007
- [28] Baorto E, Payne RM, Slater LN, et al. Culture-negative endocarditis caused by *Bartonella henselae*[J]. The Journal of Pediatrics, 1998, 132(6): 1051-1054
- [29] De La Rosa GR, Barnett BJ, Ericsson CD, et al. Native valve endocarditis due to *Bartonella henselae* in a middle-aged human immunodeficiency virus-negative woman[J]. Journal of Clinical Microbiology, 2001, 39(9): 3417-3419
- [30] Rodrick D, Dillon B, Dexter M, et al. Culture-negative endocarditis due to Houston Complex *Bartonella henselae* acquired in Noumea, New Caledonia[J]. Journal of Clinical Microbiology, 2004, 42(4): 1846-1848
- [31] Tsuneoka H, Yanagihara M, Otani S, et al. A first Japanese case of *Bartonella henselae*-induced endocarditis diagnosed by prolonged culture of a specimen from the excised valve[J]. Diagnostic Microbiology and Infectious Disease, 2010, 68(2): 174-176
- [32] Pachirat O, Kosoy M, Bai Y, et al. The first reported case of endocarditis in Thailand[J]. Infectious Disease Reports, 2011, 3(1): e9
- [33] Endara SA, Roati AA, Alizzi AM, et al. Aortic valve endocarditis caused by *Bartonella henselae*: a rare surgical entity[J]. The Heart Surgery Forum, 2001, 4(4): 359-360
- [34] Atamanyuk I, Raja SG, Kostolny M. *Bartonella henselae* endocarditis of percutaneously implanted pulmonary valve: a case report[J]. The Journal of Heart Valve Disease, 2011, 20(1): 94-97
- [35] Van Tooren RM, Van Leusen R, Bosch FH. Culture negative endocarditis combined with glomerulonephritis caused by *Bartonella* species in two immunocompetent adults[J]. The Netherlands Journal of Medicine, 2001, 59(5): 218-224
- [36] Lejko-Zupanc T, Slemenik-Pusnik C, Kozelj M, et al. Native valve endocarditis due to *Bartonella henselae* in an immunocompetent man[J]. Wiener Klinische Wochenschrift, 2008, 120(7/8): 246-249
- [37] Sankatsing SU, Kolader ME, Bouma BJ, et al. 18F-fluoro-2-deoxyglucose positron emission tomography-negative endocarditis lenta caused by *Bartonella henselae*[J]. The Journal of Heart Valve Disease, 2011, 20(1): 100-102
- [38] Dreier J, Vollmer T, Freytag CC, et al. Culture-negative infective endocarditis caused by *Bartonella* spp.: 2 case reports and a review of the literature[J]. Diagnostic Microbiology and

- Infectious Disease, 2008, 61(4): 476-483
- [39] Raoult D, Fournier PE, Drancourt M, et al. Diagnosis of 22 new cases of *Bartonella* endocarditis[J]. Annals of Internal Medicine, 1996, 125(8): 646-652
 - [40] Lepidi H, Fournier PE, Raoult D. Quantitative analysis of valvular lesions during *Bartonella* endocarditis[J]. American Journal of Clinical Pathology, 2000, 114(6): 880-889
 - [41] Breathnach AS, Hoare JM, Eykyn SJ. Culture-negative endocarditis: contribution of *Bartonella* infections[J]. Heart (British Cardiac Society), 1997, 77(5): 474-476
 - [42] Lamas C, Favacho A, Ramos RG, et al. *Bartonella* native valve endocarditis: the first Brazilian case alive and well[J]. The Brazilian Journal of Infectious Diseases: an Official Publication of the Brazilian Society of Infectious Diseases, 2007, 11(6): 591-594
 - [43] Vikram HR, Bacani AK, Devaleria PA, et al. Bivalvular *Bartonella henselae* prosthetic valve endocarditis[J]. Journal of Clinical Microbiology, 2007, 45(12): 4081-4084
 - [44] Walls T, Moshal K, Trounce J, et al. Broad-range polymerase chain reaction for the diagnosis of *Bartonella henselae* endocarditis[J]. Journal of Paediatrics and Child Health, 2006, 42(7/8): 469-471
 - [45] Kreisel D, Pasque MK, Damiano RJ Jr, et al. *Bartonella* species-induced prosthetic valve endocarditis associated with rapid progression of valvular stenosis[J]. The Journal of Thoracic and Cardiovascular Surgery, 2005, 130(2): 567-568
 - [46] Lesprit P, Noel V, Chazouilleres P, et al. Cure of *Bartonella* endocarditis of a prosthetic aortic valve without surgery: value of serologic follow-up[J]. Clinical Microbiology and Infection: the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 2003, 9(3): 239-241
 - [47] Klein JL, Nair SK, Harrison TG, et al. Prosthetic valve endocarditis caused by *Bartonella quintana*[J]. Emerging Infectious Diseases, 2002, 8(2): 202-203
 - [48] Roux V, Eykyn SJ, Wyllie S, et al. *Bartonella vinsonii* subsp. *berkhoffii* as an agent of afebrile blood culture-negative endocarditis in a human[J]. Journal of Clinical Microbiology, 2000, 38(4): 1698-1700
 - [49] Fenollar F, Sire S, Raoult D. *Bartonella vinsonii* subsp. *arupensis* as an agent of blood culture-negative endocarditis in a human[J]. Journal of Clinical Microbiology, 2005, 43(2): 945-947
 - [50] Bai Y, Kosoy MY, Diaz MH, et al. *Bartonella vinsonii* subsp. *arupensis* in humans, Thailand[J]. Emerging Infectious Diseases, 2012, 18(6): 989-991
 - [51] Raoult D, Roblot F, Rolain JM, et al. First isolation of *Bartonella alsatica* from a valve of a patient with endocarditis[J]. Journal of Clinical Microbiology, 2006, 44(1): 278-279
 - [52] Jeanclaude D, Godmer P, Leveiller D, et al. *Bartonella alsatica* endocarditis in a French patient in close contact with rabbits[J]. Clinical Microbiology and Infection: the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 2009, 15(Suppl. 2): 110-111
 - [53] Lin EY, Tsigrelis C, Baddour LM, et al. *Candidatus Bartonella mayotimonensis* and endocarditis[J]. Emerging Infectious Diseases, 2010, 16(3): 500-503
 - [54] Daly JS, Worthington MG, Brenner DJ, et al. *Rochalimaea elizabethae* sp. nov. isolated from a patient with endocarditis[J]. Journal of Clinical Microbiology, 1993, 31(4): 872-881
 - [55] Raoult D, Fournier PE, Vandenesch F, et al. Outcome and treatment of *Bartonella* endocarditis[J]. Archives of Internal Medicine, 2003, 163(2): 226-230
 - [56] Fournier PE, Lelievre H, Eykyn SJ, et al. Epidemiologic and clinical characteristics of *Bartonella quintana* and *Bartonella henselae* endocarditis: a study of 48 patients[J]. Medicine, 2001, 80(4): 245-251
 - [57] Das BB, Wasser E, Bryant KA, et al. Culture negative endocarditis caused by *Bartonella henselae* in a child with congenital heart disease[J]. The Pediatric Infectious Disease Journal, 2009, 28(10): 922-925
 - [58] Pitchford CW, Creech CB, Peters TR, et al. *Bartonella henselae* endocarditis in a child[J]. Pediatric Cardiology, 2006, 27(6): 769-771
 - [59] Olarte L, Ampofo K, Thorell EA, et al. *Bartonella vinsonii* endocarditis in an adolescent with congenital heart disease[J]. The Pediatric Infectious Disease Journal, 2012, 31(5): 531-534
 - [60] Avidor B, Graidy M, Efrat G, et al. *Bartonella koehlerae*, a new cat-associated agent of culture-negative human endocarditis[J]. Journal of Clinical Microbiology, 2004, 42(8): 3462-3468
 - [61] Zeaiter Z, Fournier PE, Greub G, et al. Diagnosis of *Bartonella* endocarditis by a real-time nested PCR assay using serum[J]. Journal of Clinical Microbiology, 2003, 41(3): 919-925
 - [62] Fournier PE, Mainardi JL, Raoult D. Value of microimmunofluorescence for diagnosis and follow-up of *Bartonella* endocarditis[J]. Clinical and Diagnostic Laboratory Immunology, 2002, 9(4): 795-801
 - [63] Maillard R, Petit E, Chomel B, et al. Endocarditis in cattle caused by *Bartonella bovis*[J]. Emerging Infectious Diseases, 2007, 13(9): 1383-1385
 - [64] Cockwill KR, Taylor SM, Philibert HM, et al. *Bartonella vinsonii* subsp. *berkhoffii* endocarditis in a dog from Saskatchewan[J]. The Canadian Veterinary Journal La Revue Veterinaire Canadienne, 2007, 48(8): 839-844
 - [65] Perez C, Hummel JB, Keene BW, et al. Successful treatment of *Bartonella henselae* endocarditis in a cat[J]. Journal of Feline Medicine and Surgery, 2010, 12(6): 483-486
 - [66] Chomel BB, Wey AC, Kasten RW. Isolation of *Bartonella washoensis* from a dog with mitral valve endocarditis[J]. Journal of Clinical Microbiology, 2003, 41(11): 5327-5332
 - [67] Breitschwerdt EB, Atkins CE, Brown TT, et al. *Bartonella vinsonii* subsp. *berkhoffii* and related members of the alpha subdivision of the Proteobacteria in dogs with cardiac arrhythmias, endocarditis, or myocarditis[J]. Journal of Clinical Microbiology, 1999, 37(11): 3618-3626
 - [68] Chomel BB, Mac Donald KA, Kasten RW, et al. Aortic valve endocarditis in a dog due to *Bartonella clarridgeiae*[J]. Journal of Clinical Microbiology, 2001, 39(10): 3548-3554
 - [69] Kelly P, Rolain JM, Maggi R, et al. *Bartonella quintana* endocarditis in dogs[J]. Emerging Infectious Diseases, 2006, 12(12): 1869-1872
 - [70] Spach DH, Kanter AS, Dougherty MJ, et al. *Bartonella (Rochalimaea) quintana* bacteremia in inner-city patients with chronic alcoholism[J]. The New England Journal of Medicine, 1995, 332(7): 424-428
 - [71] Jameson P, Greene C, Regnery R, et al. Prevalence of *Bartonella henselae* antibodies in pet cats throughout regions of North America[J]. The Journal of Infectious Diseases, 1995, 172(4): 1145-1149
 - [72] Droz S, Chi B, Horn E, et al. *Bartonella koehlerae* sp. nov., isolated from cats[J]. Journal of Clinical Microbiology, 1999, 37(4): 1117-1122
 - [73] Rolain JM, Fournier PE, Raoult D, et al. First isolation and detection by immunofluorescence assay of *Bartonella koehlerae* in erythrocytes from a French cat[J]. Journal of Clinical Microbiology, 2003, 41(8): 4001-4002
 - [74] Huang R, Liu Q, Li G, et al. *Bartonella quintana* infections in captive monkeys, China[J]. Emerging Infectious Diseases, 2011,

- 17(9): 1707-1709
- [75] O'rourke LG, Pitulle C, Hegarty BC, et al. *Bartonella quintana* in cynomolgus monkey (*Macaca fascicularis*)[J]. *Emerging Infectious Diseases*, 2005, 11(12): 1931-1934
- [76] Sui LH, Zeng L, Zhang GZ, et al. Isolation of *Bartonella quintana* from rhesus monkeys and analysis of the *gltA* gene sequence[J]. *Acta Laboratorum Animalis Scientia Sinica*, 2012, 20(4): 62-65 (in Chinese)
隋丽华, 曾林, 张广州, 等. 恒河猴五日热巴尔通体的分离和柠檬酸合成酶基因的序列分析[J]. *中国实验动物学报*, 2012, 20(4): 62-65
- [77] Qian J. Diagnostic criteria (Duke) of infective endocarditis [J]. *Chinese Circulation Journal*, 2003, 18(3): 205-205 (in Chinese)
钱杰. 感染性心内膜炎诊断标准(Duke)[J]. *中国循环杂志*, 2003, 18(3): 205-205
- [78] Riess T, Dietrich F, Schmidt KV, et al. Analysis of a novel insect cell culture medium-based growth medium for *Bartonella* species[J]. *Applied and Environmental Microbiology*, 2008, 74(16): 5224-5227
- [79] Li DM, Miao ZG, Song XP, et al. Optimization of liquid growth conditions and determination of growth curves for *Bartonella* species[J]. *Microbiology China*, 2012, 39(11): 1695-1702 (in Chinese)
栗冬梅, 苗志刚, 宋秀平, 等. 巴尔通体液体培养条件简化及生长曲线观察[J]. *微生物学通报*, 2012, 39(11): 1695-1702
- [80] La Scola B, Raoult D. Culture of *Bartonella quintana* and *Bartonella henselae* from human samples: a 5-year experience (1993 to 1998)[J]. *Journal of Clinical Microbiology*, 1999, 37(6): 1899-1905
- [81] Houpikian P, Raoult D. Western immunoblotting for *Bartonella* endocarditis[J]. *Clinical and Diagnostic Laboratory Immunology*, 2003, 10(1): 95-102
- [82] Zhang LJ, He JR, Hai R, et al. Research progress on *Bartonella* endocarditis[J]. *Chinese Journal of Epidemiology*, 2005, 26(10): 815-816 (in Chinese)
张丽娟, 贺金荣, 海荣, 等. 巴尔通体感染性心内膜炎的研究进展[J]. *中华流行病学杂志*, 2005, 26(10): 815-816
- [83] Yang XR, Liu QY, Cui BY, et al. Using direct enzyme linked immunosorbent assay for the detection of IgG antibody on *Bartonella henselae* among healthy people in Changping, Beijing[J]. *Chinese Journal of Epidemiology*, 2007, 28(7): 688-691 (in Chinese)
杨小冉, 刘起勇, 崔步云, 等. 间接酶联免疫吸附试验检测北京市昌平地区体检人群中汉赛巴尔通体抗体[J]. *中华流行病学杂志*, 2007, 28(7): 688-691
- [84] Li DM, Meng FX, Qin ZJ, et al. Isolation of *Bartonella henselae* from cat in Shandong[J]. *Chinese Journal of Vector Biology and Control*, 2005, 16(6): 452 (in Chinese)
栗冬梅, 孟凤霞, 秦增军, 等. 山东省家猫检出汉赛巴尔通体[J]. *中国媒介生物学及控制杂志*, 2005, 16(6): 452
- [85] Li DM, Meng FX, Song XP, et al. Isolation of pathogenic *Bartonella*—*Bartonella vinsonii* subsp. *Berkhoffii* from dog blood in Shandong [J]. *Chinese Journal of Epidemiology*, 2006, 27(4): 333-338 (in Chinese)
栗冬梅, 孟凤霞, 宋秀平, 等. 从山东省家犬血液中分离出致病性巴尔通体——文森巴尔通体伯格霍夫亚种[J]. *中华流行病学杂志*, 2006, 27(4): 333-338
- [86] Li DM, Liu QY, Yu DZ, et al. Molecular evidence of *Bartonella* species from fleas in Yunnan[J]. *Chinese Journal of Vector Biology and Control*, 2005, 16(1): 5-8 (in Chinese)
栗冬梅, 刘起勇, 俞东征, 等. 用 PCR 方法检出蚤类携带巴尔通体[J]. *中国媒介生物学及控制杂志*, 2005, 16(1): 5-8
- [87] Li DM, Liu QY, Yu DZ, et al. Isolation and detection of *Bartonella* from fleas and ticks [J]. *Chinese Journal of Zoonoses*, 2005, 21(12): 1052-1058, 1074 (in Chinese)
栗冬梅, 刘起勇, 俞东征, 等. 蚤、蜱中巴尔通体的分离培养及检测鉴定[J]. *中国人兽共患病杂志*, 2005, 21(12): 1052-1058, 1074
- [88] Diaz MH, Bai Y, Malania L, et al. Development of a novel genus-specific real-time PCR assay for detection and differentiation of *Bartonella* species and genotypes[J]. *Journal of Clinical Microbiology*, 2012, 50(5): 1645-1649
- [89] Li DM, Song XP, Wang J, et al. Real-time PCR-based detection of *Bartonella vinsonii* subsp. *Berkhoffii* by TaqMan minor groove binder probe[J]. *Acta Microbiologica Sinica*, 2013, 53(9): 976-983 (in Chinese)
栗冬梅, 宋秀平, 王君, 等. TaqMan-MGB 探针检测文森巴尔通体伯格霍夫亚种实时荧光定量 PCR 方法的建立及应用[J]. *微生物学报*, 2013, 53(9): 976-983
- [90] Chen ML, Zhang JB, Sun ZJ, et al. Detection of *Bartonella quintana* by a quantitative real-time polymerase chain reaction[J]. *Chinese Journal of Zoonoses*, 2006, 22(6): 510-513, 557 (in Chinese)
陈梅玲, 张晶波, 孙长俭, 等. 实时荧光定量 PCR 检测五日热巴通体[J]. *中国人兽共患病学报*, 2006, 22(6): 510-513, 557
- [91] Morick D, Baneth G, Avidor B, et al. Detection of *Bartonella* spp. in wild rodents in Israel using HRM real-time PCR[J]. *Veterinary Microbiology*, 2009, 139(3/4): 293-297
- [92] Morick D, Osinga N, Gruys E, et al. Identification of a *Bartonella* species in the harbor seal (*Phoca vitulina*) and in seal lice (*Echinophthirius horridus*)[J]. *Vector Borne and Zoonotic Diseases* (Larchmont, NY), 2009, 9(6): 751-753
- [93] Gutierrez R, Morick D, Gross I, et al. *Bartonellae* in domestic and stray cats from Israel: comparison of bacterial cultures and high-resolution melt real-time PCR as diagnostic methods[J]. *Vector Borne and Zoonotic Diseases* (Larchmont, NY), 2013, 13(12): 857-864
- [94] Sabe MA, Shrestha NK, Menon V. Contemporary drug treatment of infective endocarditis[J]. *American Journal Cardiovascular Drugs: Drugs, Devices, and Other Interventions*, 2013, 13(4): 251-258
- [95] Zhang ZX, Li YF. Research progress of *Bartonella* diseases[J]. *Animal Husbandry & Veterinary Medicine*, 2012, 44(11): 91-95 (in Chinese)
张振兴, 李玉峰. 巴尔通体病研究进展[J]. *畜牧与兽医*, 2012, 44(11): 91-95