· 特约专稿 ·

拉沙热研究进展

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摘　要：拉沙热（Lassa fever，LF）由拉沙病毒（Lassa virus，LASV）引起，是一种通过鼠类传播给人的急性出血性动物源性传染病，病死率高。主要在西非地区流行，但在全球多个国家发现输入性病例。本文主要针对拉沙病毒的病原学特点、疾病流行现状、临床特征、实验室检测、治疗及预防进展进行综述。同时，建议在全球经济一体化的大形势下，加强对拉沙热国际防控的关注度，建立国际联防联控防治策略和措施，并将其纳入全球防控体系。

关键词：拉沙热；流行病学；防控

Research progress on Lassa fever

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Abstract: Lassa fever (LF) caused by Lassa virus (LASV) is an acute hemorrhagic zoonotic disease transmitted to humans by rodent. The disease has high mortality, and mainly endemic in West Africa. However, the imported cases have been reported in many countries worldwide. In this review, we focus on the etiology of Lassa virus, disease prevalence, clinical features, laboratory testing, treatment and prevention. In light of the global economic integration, it is recommended that the strengthening of prevention and control of Lassa fever, establishment of international strategies on prevention measures, and integration into the global system should be paid more attention.

Key words: Lassa fever; Epidemiology; Prevention and control

拉沙热（Lassa fever，LF）由拉沙病毒（Lassa virus，LASV）引起，是一种急性出血性动物源性传染病，主要通过鼠类传播给人。目前，拉沙热的流行区域已从西非扩散到非洲内陆，且在欧洲（英国、德国）、美洲（美国、加拿大）、亚洲（日本）等国均有输入性病例的报道。

首例拉沙热病例发现于 20 世纪 50 年代[1-2]。1969 年，两名尼日利亚东北部地区拉沙镇教会医院的医护人员被 1 名美国护士传染后死亡，最终从死亡病例的血液标本中成功分离出该病毒，并以分离地点命名[2]。自 1969 年以后，拉沙热在尼日利亚纳萨拉瓦州、塔拉巴州、约贝州等多个地区暴发[3-5]。与 2014 年西非大规模暴发的埃博拉疫情地区分布类似，拉沙热主要在西非塞拉利昂、几内亚、尼日利亚、利比里亚等地区暴发流行[6-7]，且发病率和病死率较高。据估计，西非每年有 30 万～50 万人感染拉沙病毒，死亡5 000～10 000例[1,6-11]。此外，由于多乳鼠（*Mastomys natalensis*）在西非地区广泛分

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布，对主要流行区的周边国家存在一定的潜在安全性威胁[7]。近年来，不断有拉沙热病例报道。2014年，贝宁确诊首例拉沙热病例；加纳自2011年首次报道拉沙热病例后，于2013年出现2例输入性病例[12-13]；英国于2009年由马里输入首例拉沙热病例[14]；在靠近几内亚湾的科特迪瓦、多哥及西非内陆国家布基纳法索均有拉沙热病例报道[15-19]。然而，由于疾病高发地区医疗条件落后，缺乏有效疫苗和抗病毒药物及实验室精密检测仪器，导致患者接受治疗时间滞后，进一步加剧了西非地区国家的经济负担。

本文主要针对拉沙病毒的病原学特点、疾病流行现状、临床特点、实验室检测、治疗及预防进展等进行综述，以期进一步增加对拉沙热的认识，提高防控意识。

1 病原学特征

拉沙病毒属沙粒病毒科，基因组由2节段单负链RNA组成[20-21]，与淋巴细胞脉络丛脑膜炎病毒(lymphocytic choriomeningitis virus，LCMV)同属旧世界群(LCM族)，而新世界群主要包括塔卡里伯病毒(Tacaribe virus)、胡宁病毒(Junin virus)、马丘波病毒(Machupo virus)、阿马帕里病毒(Amapari virus)等[22]。病毒大小60～280 nm，呈非对称性，有包膜[22-23]。核内为单负链RNA，分别为S RNA和L RNA。S RNA(22S)约3 400个碱基，编码主要结构蛋白[24]：核衣壳蛋白(nuclocapsid protein，N)；糖蛋白(glycoprotein，G)，进一步切割为G1和G2，参与构成病毒的包膜和刺突，为病毒特异性中和抗原。L RNA(31S)约7 200个碱基，编码RNA依赖的RNA聚合酶(RNA-dependent RNA polymerase，RdRP)和调节蛋白Z[25]。研究显示，Z蛋白可通过直接作用于翻译起始因子eIF4E，阻止mRNA翻译网织红细胞溶解产物；此外，在感染时，Z蛋白通过作用于早幼粒细胞性白血病(promyelocytic leukemia，PML)蛋白而避免宿主细胞凋亡[26]。

2 流行病学特征

2.1 病毒储存宿主及感染途径

鼠类为拉沙病毒的主要储存宿主，包括多乳鼠、家鼠、草鼠等[27]。在西非地区主要是多乳鼠[28-32]，该鼠繁殖能力较强，常出没于食物储藏地及住房环境拥挤、卫生条件差的乡村地区。McCormick等的早期研究显示，在拉沙热流行地区约30%多乳鼠自然携带病毒[9]。人群主要因密切接触带有病毒的啮齿类动物而感染。感染方式包括吸入带病毒的气溶胶、接触被感染动物的分泌物(血液、尿液及粪便)或食入被污染的食物及带病毒的鼠肉等[33-34]。在西非部分经济落后地区，当地居民一直保持捕鼠的游戏活动和食鼠肉的风俗习惯[33,35]。相关研究表明，在食鼠肉感染者中神经性耳聋症状更常见，约为无此饮食习惯感染者的3.7倍[35]。因此，与鼠类密切接触且食用鼠肉的风俗是拉沙热在西非地区流行不可忽视的潜在危险因素。

2.2 病毒传播方式

拉沙病毒可在人与人之间传播，主要通过接触被感染者的血液、尿液、粪便及分泌液(如精液等)[34,36]。有研究显示，可从感染者血、尿、咽部、呕吐物、分泌物及精液中分离到拉沙病毒[31,33,36-38]，该病毒从感染者尿液中排出可持续3～9周，在精液中甚至长达3个月[1,39]。此外，接触被污染的医疗器械和反复利用针具等是造成医院内感染的主要因素[32]。虽然早期研究显示通过简单防护措施能明显减少病毒通过人传人的方式传播[40-42]，但Lo Iacono等通过建立模型对塞拉利昂凯内马公立医院(Kenema Government Hospital，KGH)出现的拉沙热患者进行综合分析时发现，在住院患者中病毒以人传人的方式传播，5%拉沙热患者引起的二代发病率高达20%[34]。目前，性传播方式感染虽有报道，但尚不明确。此外，实验室研究表明该病毒在气溶胶中稳定存在，啮齿类动物之间可通过空气传播方式感染[28,43]。

2.3 发病年龄

多项研究结果显示，拉沙热总体病死率高达1%～2%，住院患者病死率高达15%，疾病暴发期间住院患者病死率高达50%[1,3,9,13,44-46]。各年龄段人群均可感染拉沙病毒。西非利比里亚地区2008—2012年以医院为基础的监测结果表明，拉沙热病例主要为20～39岁群体，女性较男性多(56.2% *vs*. 43.8%)；且病例主要在8月下旬至9月出现[47]。同期，塞拉利昂2002—2012年监测结果表明，患者($Ag^+/IgM^\pm$)发病年龄呈双峰分布，分别为0～9岁和15～39岁；实验室检测发现$Ag^+/IgM^\pm$患者的发病高峰主要在3月，而$Ag^-/IgM^\pm$患者具有两段高峰时期，分别是旱季的3月和雨季的10月[48]。此外，对感染期孕妇的调查显示，流产是拉沙热的严重并发症，特别是妊娠晚期，孕妇和胎

儿死亡率较高[9,49-50]。医疗工作者往往在护理拉沙热患者期间因缺乏适当的个人防护用品(personal protective equipment,PPE)及医院传染病管理规范和防控措施不健全而被感染[3,36,51]。

2.4 病毒感染的扩大趋势

随着全球各国之间人员往来越来越密切,拉沙热也随着旅游人群向其他地区播散。目前,美国、德国、英国、日本、以色列、加拿大均有拉沙热输入性病例的报道[14,17,52-54]。早期,输入性病例主要来自西非高发区(塞拉利昂、尼日利亚、利比里亚和几内亚等)[54],随着病毒在西非广大地区出现,已有来自加纳、马里、布基纳法索或科特迪瓦等原拉沙热低发地区的输入性病例报道[14,54-55]。Branco 等对 1 例拉沙热孕妇体内毒株进行分离,发现该毒株与原型株(Josiah strain)的核苷酸同源性仅为 89%,提示塞拉利昂分离的新病毒流行株的基因出现明显变异,表明此变异株的地理分布范围具有潜在扩大的可能性[50]。

3 致病性与免疫

3.1 发病机制

目前拉沙病毒的免疫发病机制尚不完全清楚[56],但基本认为病毒主要通过呼吸道、消化道和皮肤及黏膜等途径侵入机体,在单核-巨噬细胞和内皮细胞中生长和繁殖,暂时不引起细胞损伤。病毒直接侵犯细胞,在细胞内复制时能抑制某些促炎症因子的作用,因此拉沙热患者中很少见到炎症反应。但由于拉沙病毒的受体 α dystroglycan(α-DG)广泛分布于机体各组织[57],病毒可侵入多种器官,引起肺部疾病、消化道出血、心肌炎、肝脾细胞坏死、肾脏疾病等,从而导致机体多器官功能衰竭而引发死亡。

3.2 病毒抗体

拉沙热血症期达 20 d 左右,由于中和抗体出现晚,且抗体效价低,T 细胞在病毒感染早期发挥重要抵抗作用。若细胞免疫受损或延迟,血液中高病毒血症将导致病情恶性发展[58-59],一般 4～9 d 后病毒血症达高峰[21]。对于幸存者,体内病毒滴度在症状出现 3 周后开始逐渐降低,最终从血循环中清除,患者开始恢复[44,60-62]。中和抗体一般在急性感染后几个月才产生,且抗体效价持续上升,甚至有研究显示在感染后 40 年人体内仍有较高效价的 IgG 抗体[63]。目前,中和抗体在急性恢复中的作用尚不明确,而在被动免疫中则显示保护作用与中和抗体效价相关。

3.3 流行区域

尼日利亚、几内亚和塞拉利昂地区的人群中,拉沙病毒抗体阳性率分别为 21%、4%～55%和8%～52%。据此估计约有5 900万人处于拉沙病毒感染的威胁之中,年发病人数可达 300 万,年死亡人数可达6.7万[8,39,64]。2009 年 Fichet-Calvet 等通过模型估计拉沙热可能覆盖塞拉利昂和利比里亚近 80%的地区,几内亚和利比里亚地区分别达 50%和40%,贝宁、科迪瓦特和多哥均达 30%,加纳约10%[6]。最近,Mylne 等根据研究结果预计,西非地区约 14 个国家中,共计3 700万人生活在适宜拉沙病毒传播的区域[65]。提示如果未能采取适当防控措施,可能会引起疾病的大规模暴发,严重威胁周边国家和地区人群的健康。

4 临床症状和体征

新生乳鼠感染拉沙病毒后,体内可明显检测到病毒滴度,但多为持续性无症状感染[66]。人体感染病毒后,潜伏期一般为 6～21 d[10,44,46]。疾病初期,80%感染者处于亚临床症状,无明显临床症状或症状轻微(轻度发热、无力),因此诊断困难[2,44,67];其余 20%感染者可最终发展为严重的多系统疾病[68]。潜伏后期,患者病情逐渐加重,出现头痛、咽痛、胸痛及肌肉痛[8,62,67,69-70],并伴有恶心、呕吐、腹泻、咳嗽、腹痛和耳鸣等症状[27],常出现面颈部肿胀,胸腔积液,口、鼻、胃肠道、阴道出血,蛋白尿等[2,71-73],甚至发展为低血压,有时可出现皮肤斑丘疹。疾病后期,一般在症状出现后第 10～14 天,患者出现休克、癫痫、震颤、定向障碍和昏迷等严重症状[55]。最终,因肝、肺及心脏等多器官受损而死亡[74]。拉沙热患者很少出现神经系统症状,但神经性耳聋是其并发症之一,常见于疾病后期和恢复早期[75-76],约 20%感染者出现短暂性或永久性耳聋[8]。儿童与成人的病程相似,婴儿则表现为"水肿婴儿综合征",出现全身水肿、腹部肿胀、出血等症状。

5 诊断与鉴别诊断

5.1 诊断

目前,主要采用酶联免疫吸附试验(enzyme-linked immunosorbent assay,ELISA)检测拉沙病毒 IgM 和 IgG 抗体及抗原来确诊疾病,也可采用反转录聚合酶链反应(reverse transcriptase-polymerase chain reaction,RT-PCR)针对拉沙病毒基因进行检测,但由于病毒分离培养时间较长,一

般不用于临床诊断。作为拉沙热筛检指标，检测血清中 IgM 抗体效果并不显著，灵敏度和特异度分别为 55%和 57%[77]。虽然 RT-PCR 的灵敏度和特异度较高，且可用于早期诊断，但西非地区经济欠发达，基本不具备先进实验设备和技术，因此需研发适用于当地的更简易便捷且可操作的快速筛检方法。快速可行的实验室诊断方法有利于早期发现潜在的病毒携带者，给予及时抗病毒治疗，从而提高治疗效果。与埃博拉病毒类似，拉沙病毒病原学检测需在生物安全 4 级（biosafety level 4，BSL-4）实验室中完成。这意味着，由于实验条件限制，常规的病毒分离、培养、检测等方法不能广泛应用。

5.2 鉴别诊断

拉沙热的临床症状缺乏特异性，往往易与穿孔性伤寒回肠炎[11,67]、咽炎、疟疾及其他出血性疾病（如埃博拉病毒病）等混淆[39]。因此，临床诊断时应慎重，避免延误疾病治疗的最佳时间。

6 药物与疫苗

目前尚未有经许可的药物或疫苗用于治疗拉沙热。

6.1 药物

核苷酸类似物利巴韦林被认为是治疗拉沙热的有效抗病毒药物，但对其抗病毒机制尚存在一定争议[78-81]。有研究指出，利巴韦林可用于疾病发展各期[82]，但仅在疾病早期使用时效果明显，能降低患者包括高危患者的病死率[83-84]。McCormick 等研究表明，如果在出现症状后的前 6 d 内静脉注射利巴韦林，病死率将大幅下降（55% *vs*. 5%，P = 0.000 2）[9,83,85]，与 Dahmane 等的研究结果相符（50% *vs*. 29%）[86]。而 Asogun 等研究显示，即使对感染者采用利巴韦林进行抗病毒治疗，仍有近1/3的感染者不能避免死亡[87]。因此，需寻找更有效的治疗药物。目前具有广谱抗病毒作用的法匹拉韦被认为是理想的候选药物[88]。最近一项致死性小鼠实验发现，法匹拉韦与利巴韦林对抗拉沙病毒具有协同作用[89]，提示两者联用有望降低感染者的病死率。

6.2 疫苗

研究表明，灭活拉沙热疫苗安全性较好，但缺乏有效免疫保护作用[90]。Mopeia 病毒和 ML29 毒株是减毒疫苗的良好候选者[91-96]，但仍需更多临床试验支持。重组活载体疫苗（牛痘病毒载体、水疱性口炎病毒载体、黄热病毒 YF17D 载体、委内瑞拉马脑炎病毒复制子、病毒样颗粒）和 DNA 疫苗等新型疫苗尚处于实验阶段[96-101]。研究显示，重组黄热病毒载体疫苗接种的豚鼠虽能避免死亡，但不能防止感染拉沙病毒[97]。此外，考虑到拉沙病毒在不同地理环境中基因的高度多样性[92]，开展抵抗不同基因型拉沙病毒疫苗的研究具有重要意义。Safronetz 等用水疱性口炎病毒载体疫苗 VSV-LASV 免疫近交系 13 的豚鼠及猕猴，证实该疫苗对不同地区（马里、尼日利亚及利比里亚等）的分离株均能产生保护作用[99]，提示理想的候选疫苗应对不同血清型拉沙病毒具有交叉保护作用和良好的成本效益。目前，由于实验动物需求量大、实验条件要求严格（BSL-4 实验室）等限制因素，拉沙热疫苗研发存在一定局限性[96]。

7 预防和控制措施

7.1 控制传染源

在西非地区，主要加强居室周围生活环境中的灭鼠工作。隔离感染者（疑似及确诊患者），防止在医院内引发二次感染，严格处理患者体液和排泄物，对使用后的医疗设备进行消毒杀菌及暴露后预防（post-exposure prophylaxis，PEP）等。鉴于已从拉沙热恢复期患者的尿液或精液中分离到病毒，但尚不清楚排毒时间，故应保证尿液消毒且采取安全的性行为。此外，对密切接触者应开展 20 d 的医学观察。

7.2 切断传播途径

在广泛灭鼠的基础上，加强在西非某些食鼠肉地区进行宣传教育，改变不健康的风俗习惯，减少与多乳鼠接触的机会。保护食物及水源免受鼠类污染，保持良好的环境卫生，及时清理食物垃圾并保存好未食用的食物。与患者密切接触者应使用特定防护用品，如防护服、口罩、手套等。

7.3 保护易感人群

目前尚无主动免疫的方法，因此加强自我防护是重中之重。高危人群可口服利巴韦林开展预防。

7.4 加强出入境检测检疫及病例监测

随着人与动物之间接触日益频繁与密切、居民城镇化水平的范围扩大、全球化水平加剧，任一地区的健康威胁均可能发展至全球性。对于输入性病例的管理，第一时间发现病例是疾病整体预防和控制的关键，也是预防工作的重中之重。

8 结语

目前，拉沙热不仅仅是西非传统流行地区及周

边国家面临的公共卫生问题。随着全球多个国家相继出现输入性病例，且病例原发地已不限于传统高发地区，同时引发疾病的毒株也出现变化，拉沙热的传播与流行已成为潜在的世界性公共卫生问题。

拉沙热的病死率高，无有效疫苗预防，抗病毒药物效果有限。因此，针对拉沙热，早发现、早诊断、早治疗仍是最有效的手段。就疾病防控而言，首先，应建立灵敏、快捷且能广泛应用的检测方法，第一时间发现病例；其次，发现疫情国家应及时进行疫情通报，由世界卫生组织（World Health Organization，WHO）及时发布疫情通报；第三，在出现潜在的世界性流行前，应由 WHO 建立规范的国际性联防联控防治策略和措施，避免潜在感染者将病毒带入其他国家并控制疫源地发展趋势。

随着我国“一带一路”新经济战略的引导，国外居民及旅客人数持续增长，特别是在交流频繁及经济发展快速的地区，各种传染病的输入风险显著增加。针对拉沙热的防控，应借鉴埃博拉病毒病、寨卡病毒病和黄热病的防控策略；同时，应充分利用我国援建塞拉利昂的 BSL-3 实验室，在当地开展拉沙热监测，包括病例监测、毒株毒力和型别监测等，将防控关口前移，真正做到防患于未然，避免引发类似埃博拉病毒病等严重危害人类健康的全球性公共卫生问题。

综上所述，建议在全球经济一体化的大形势下，加强对拉沙热国际防控的关注度，建立国际联防联控防治策略和措施，将其纳入全球防控体系。

参考文献

[1] Ogbu O, Ajuluchukwu E, Uneke CJ. Lassa fever in West African sub-region: an overview [J]. J Vector Borne Dis, 2007, 44(1): 1-11.

[2] Frame JD, Baldwin JM, Gocke DJ, Troup JM. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings [J]. Am J Trop Med Hyg, 1970, 19(4): 670-676.

[3] Fisher-Hoch SP, Tomori O, Nasidi A, Perez-Oronoz GI, Fakile Y, Hutwagner L, McCormick JB. Review of cases of nosocomial Lassa fever in Nigeria: the high price of poor medical practice [J]. BMJ, 1995, 311(79): 857-859.

[4] Inegbenebor U, Okosun J, Inegbenebor J. Prevention of Lassa fever in Nigeria [J]. Trans R Soc Trop Med Hyg, 2010, 104(1): 51-54.

[5] Omilabu SA, Badaru SO, Okokhere P, Asogun D, Drosten C, Emmerich P, Becker-Ziaja B, Schmitz H, Gunther S. Lassa fever, Nigeria, 2003 and 2004 [J]. Emerg Infect Dis, 2005, 11(10): 1642-1644.

[6] Fichet-Calvet E, Rogers DJ. Risk maps of Lassa fever in West Africa [J]. PLoS Negl Trop Dis, 2009, 3(3): e388.

[7] McCormick JB. Epidemiology and control of Lassa fever [J]. Curr Top Microbiol Immunol, 1987, 134: 69-78.

[8] McCormick JB, Fisher-Hoch SP. Lassa fever [J]. Curr Top Microbiol Immunol, 2002, 262: 75-109.

[9] McCormick JB, Webb PA, Krebs JW, Johnson KM, Smith ES. A prospective study of the epidemiology and ecology of Lassa fever [J]. J Infect Dis, 1987, 155(3): 437-444.

[10] Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of High Consequence Pathogens and Pathology (DHCPP), Viral Special Pathogens Branch (VSPB). Lassa fever [EB/OL]. http://www.cdc.gov/vhf/lassa/pdf/factsheet.pdf.

[11] Khan SH, Goba A, Chu M, Roth C, Healing T, Marx A, Fair J, Guttieri MC, Ferro P, Imes T, Monagin C, Garry RF, Bausch DG; Mano River Union Lassa Fever Network. New opportunities for field research on the pathogenesis and treatment of Lassa fever [J]. Antiviral Res, 2008, 78(1): 103-115.

[12] Dzotsi EK, Ohene SA, Asiedu-Bekoe F, Amankwa J, Sarkodie B, Adjabeng M, Thouphique AM, Ofei A, Oduro J, Atitogo D, Bonney JH, Paintsil SC, Ampofo W. The first cases of Lassa fever in Ghana [J]. Ghana Med J, 2012, 46(3): 166-170.

[13] Kyei NA, Abilba MM, Kwawu FK, Agbenohevi PG, Bonney JK, Agbemaple TK, Nimo-Paintsil SC, Ampofo W, Ohene SA, Nyarko EO. Imported Lassa fever: a report of 2 cases in Ghana [J]. BMC Infect Dis, 2015, 15(1): 1-5.

[14] Atkin S, Anaraki S, Gothard P, Walsh A, Brown D, Gopal R, Hand J, Morgan D. The first case of Lassa fever imported from Mali to the United Kingdom, February 2009 [J]. Euro Surveill, 2009, 14(10): pii:19145.

[15] Akoua-Koffi C, Ter Meulen J, Legros D, Akran V, Aïdara M, Nahounou N, Dogbo P, Ehouman A. Detection of anti-Lassa antibodies in the Western Forest area of the Ivory Coast [J]. Med Trop (Mars), 2006, 66(5): 465-468.

[16] Swaan CM, van den Broek PJ, Wijnands S, van Steenbergen JE. Management of viral haemorrhagic fever in the Netherlands [J]. Euro Surveill, 2002, 7(3): 48-50.

[17] Günther S, Emmerich P, Laue T, Kühle O, Asper M, Jung A, Grewing T, Ter Meulen J, Schmitz H. Imported Lassa fever in Germany: molecular characterization of a new Lassa virus strain [J]. Emerg Infect Dis, 2000, 6(5): 466-476.

[18] Emmerich P, Thome-Bolduan C, Drosten C, Gunther S, Ban E, Sawinsky I, Schmitz H. Reverse ELISA for IgG and IgM antibodies to detect Lassa virus infections in Africa [J]. J Clin Virol, 2006, 37(4): 277-281.

[19] Emmerich P, Günther S, Schmitz H. Strain-specific antibody response to Lassa virus in the local population of

West Africa [J]. J Clin Virol, 2008, 42(1): 40-44.

[20] Lukashevich IS, Salvato MS. Lassa virus genome [J]. Curr Genomics, 2006, 7(6): 351-379.

[21] Yun NE, Walker DH. Pathogenesis of Lassa fever [J]. Viruses, 2012, 4(10): 2031-2048.

[22] Buchmeier MJ, Peters CJ, de la Torre JC. Arenaviridae: The viruses and their replication [M]. In: Knipe DL, Holey PM. eds. Fields Virology. 4th ed. Philadelphia: Lippincott-Raven Publisher, 2007: 1791-1828.

[23] Capul AA, de la Torre JC, Buchmeier MJ. Conserved residues in Lassa fever virus Z protein modulate viral infectivity at the level of the ribonucleoprotein [J]. J Virol, 2011, 85(7): 3172-3178.

[24] Buchmeier MJ, Parekh BS. Protein structure and expression among arenaviruses [J]. Curr Top Microbiol Immunol, 1987, 133: 41-57.

[25] Andersen KG, Shylakhter I, Tabrizi S, Grossman SR, Happi CT, Sabeti PC. Genome-wide scans provide evidence for positive selection of genes implicated in Lassa fever [J]. Philos Trans R Soc Lond B Biol Sci, 2012, 367(1590): 868-877.

[26] Kentsis A, Dwyer EC, Perez JM, Sharma M, Chen A, Pan ZQ, Borden KL. The RING domains of the promyelocytic leukemia protein PML and the arenaviral protein Z repress translation by directly inhibiting translation initiation factor eIF4E [J]. J Mol Biol, 2001, 312(4): 609-623.

[27] El-Bahnasawy MM, Megahed LA, Abdalla Saleh HA, Morsy TA. Lassa fever or Lassa hemorrhagic fever risk to humans from rodent-borne zoonoses [J]. J Egypt Soc Parasitol, 2015, 45(1): 61-70.

[28] Monath TP, Newhouse VF, Kemp GE, Setzer HW, Cacciapuoti A. Lassa virus isolation from Mastomys natalensis rodents during an epidemic in Sierra Leone [J]. Science, 1974, 185(4147): 263-265.

[29] Healing T, Gopal R. Report on an assessment visit to Sierra Leone, April 12th-30th 2001 [C]. London: Merlin, 2001.

[30] Demby AH, Inapogui A, Kargbo K, Koninga J, Kourouma K, Kanu J, Coulibaly M, Wagoner KD, Ksiazek TG, Peters CJ, Rollin PE, Bausch DG. Lassa fever in Guinea: II. Distribution and prevalence of Lassa virus infection in small mammals [J]. Vector Borne Zoonotic Dis, 2001, 1(4): 283-297.

[31] Lecompte E, Fichet-Calvet E, Daffis S, Koulémou K, Sylla O, Kourouma F, Doré A, Soropogui B, Aniskin V, Allali B, Kouassi Kan S, Lalis A, Koivogui L, Günther S, Denys C, Ter Meulen J. Mastomys natalensis and Lassa fever, West Africa [J]. Emerg Infect Dis, 2006, 12(12): 1971-1974.

[32] Fisher-Hoch SP. Lessons from nosocomial viral haemorrhagic fever outbreaks [J]. Br Med Bull, 2005, 73-74: 123-137.

[33] Bonwitt J, Kelly AH, Ansumana R, Agbla S, Sahr F, Saez AM, Borchert M, Kock R, Fichet-Calvet E. Rat-atouille: a mixed method study to characterize rodent hunting and consumption in the context of Lassa fever [J/OL]. Ecohealth, 2016. http://link.springer.com/article/10.1007%2Fs10393-016-1098-8.

[34] Lo Iacono G, Cunningham AA, Fichet-Calvet E, Garry RF, Grant DS, Khan SH, Leach M, Moses LM, Schieffelin JS, Shaffer JG, Webb CT, Wood JL. Using modelling to disentangle the relative contributions of zoonotic and anthroponotic transmission: the case of Lassa fever [J]. PLoS Negl Trop Dis, 2015, 9(1): e3398.

[35] Ter Meulen J, Lukashevich I, Sidibe K, Inapogui A, Marx M, Dorlemann A, Yansane ML, Koulemou K, Chang-Claude J, Schmitz H. Hunting of peridomestic rodents and consumption of their meat as possible risk factors for rodent-to-human transmission of Lassa virus in the Republic of Guinea [J]. Am J Trop Med Hyg, 1996, 55(6): 661-666.

[36] Haas WH, Breuer T, Pfaff G, Schmitz H, Köhler P, Asper M, Emmerich P, Drosten C, Gölnitz U, Fleischer K, Günther S. Imported Lassa fever in Germany: surveillance and management of contact persons [J]. Clin Infect Dis, 2003, 36(10): 1254-1258.

[37] World Health Organization. WHO Lassa fever fact sheet No 179 [EB/OL]. http://www.who.int/mediacentre/factsheets/fs179/en/.

[38] Enria D, Mills J N, Flick R. Arenavirus infections [M]. In: Guerrant RL, Walker DH, Weller PF. eds. Tropical Infectious Diseases: Principles, Pathogens, and Practice. 2nd ed. Philadelphia, PA: Elsevier, 2006: 734-755.

[39] Richmond JK, Baglole DJ. Lassa fever: epidemiology, clinical features, and social consequences [J]. BMJ, 2003, 327(7426): 1271-1275.

[40] Cooper CB, Gransden WR, Webster M, King M, O'Mahony M, Young S, Banatvala JE. A case of Lassa fever: experience at St Thomas's Hospital [J]. Br Med J (Clin Res Ed), 1982, 285(6347): 1003-1005.

[41] Fisher-Hoch SP, Price ME, Craven RB, Price FM, Forthall DN, Sasso DR, Scott SM, McCormick JB. Safe intensive-care management of a severe case of Lassa fever with simple barrier nursing techniques [J]. Lancet, 1985, 2(8466): 1227-1229.

[42] Helmick CG, Webb PA, Scribner CL, Krebs JW, McCormick JB. No evidence for increased risk of Lassa fever infection in hospital staff [J]. Lancet, 1986, 2(8517): 1202-1205.

[43] Stephenson EH, Larson EW, Dominik JW. Effect of environmental factors on aerosol-induced Lassa virus infection [J]. J Med Virol, 1984, 14(4): 295-303.

[44] Monath TP, Mertens PE, Patton R, Moser CR, Baum JJ, Pinneo L, Gary GW, Kissling RE. A hospital epidemic of Lassa fever in Zorzor, Liberia, March-April 1972 [J]. Am

J Trop Med Hyg, 1973, 22(6): 773-779.

[45] Carey DE, Kemp GE, White HA, Pinneo L, Addy RF, Fom AL, Stroh G, Casals J, Henderson BE. Lassa fever. Epidemiological aspects of the 1970 epidemic, Jos, Nigeria [J]. Trans R Soc Trop Med Hyg, 1972, 66(3): 402-408.

[46] McCormick JB, King IJ, Webb PA, Johnson KM, O'Sullivan R, Smith ES, Trippel S, Tong TC. A case-control study of the clinical diagnosis and course of Lassa fever [J]. J Infect Dis, 1987, 155(3): 445-455.

[47] Olugasa BO, Dogba JB. Mapping of Lassa fever cases in post-conflict Liberia, 2008-2012: a descriptive and categorical analysis of age, gender and seasonal pattern [J]. Ann Afr Med, 2015, 14(2): 120-122.

[48] Shaffer JG, Grant DS, Schieffelin JS, Boisen ML, Goba A, Hartnett JN, Levy DC, Yenni RE, Moses LM, Fullah M, Momoh M, Fonnie M, Fonnie R, Kanneh L, Koroma VJ, Kargbo K, Ottomassathien D, Muncy IJ, Jones AB, Illick MM, Kulakosky PC, Haislip AM, Bishop CM, Elliot DH, Brown BL, Zhu H, Hastie KM, Andersen KG, Gire SK, Tabrizi S, Tariyal R, Stremlau M, Matschiner A, Sampey DB, Spence JS, Cross RW, Geisbert JB, Folarin OA, Happi CT, Pitts KR, Geske FJ, Geisbert TW, Saphire EO, Robinson JE, Wilson RB, Sabeti PC, Henderson LA, Khan SH, Bausch DG, Branco LM, Garry RF; Viral Hemorrhagic Fever Consortium. Lassa fever in post-conflict Sierra Leone [J]. PLoS Negl Trop Dis, 2014, 8(3): e2748.

[49] Price ME, Fisher-Hoch SP, Craven RB, McCormick JB. A prospective study of maternal and fetal outcome in acute Lassa fever infection during pregnancy [J]. BMJ, 1988, 297 (6648): 584-587.

[50] Branco LM, Boisen ML, Andersen KG, Grove JN, Moses LM, Muncy IJ, Henderson LA, Schieffelin JS, Robinson JE, Bangura JJ, Grant DS, Raabe VN, Fonnie M, Zaitsev EM, Sabeti PC, Garry RF. Lassa hemorrhagic fever in a late term pregnancy from northern Sierra Leone with a positive maternal outcome: case report [J/OL]. Virol J, 2011. http://virologyj. biomedcentral. com/articles/10. 1186/1743-422X-8-404.

[51] Ehichioya DU, Hass M, Olschläger S, Becker-Ziaja B, Onyebuchi Chukwu CO, Coker J, Nasidi A, Ogugua OO, Günther S, Omilabu SA. Lassa fever, Nigeria, 2005-2008 [J]. Emerg Infect Dis, 2010, 16(6): 1040-1041.

[52] Grove JN, Branco LM, Boisen ML, Muncy IJ, Henderson LA, Schieffellin JS, Robinson JE, Bangura JJ, Fonnie M, Schoepp RJ, Hensley LE, Seisay A, Fair JN, Garry RF. Capacity building permitting comprehensive monitoring of a severe case of Lassa hemorrhagic fever in Sierra Leone with a positive outcome: case report [J/OL]. Virol J, 2011. http://virologyj. biomedcentral. com/articles/10. 1186/1743-422X-8-314.

[53] Amorosa V, Macneil A, Mcconnell R, Patel A, Dillon KE, Hamilton K, Erickson BR, Campbell S, Knust B, Cannon D, Miller D, Manning C, Rollin PE, Nichol ST. Imported Lassa fever, Pennsylvania, USA, 2010 [J]. Emerg Infect Dis, 2010, 16(10): 1598-1600.

[54] Macher AM, Wolfe MS. Historical Lassa fever reports and 30-year clinical update [J]. Emerg Infect Dis, 2006, 12(5): 835-837.

[55] Sogoba N, Feldmann H, Safronetz D. Lassa fever in West Africa: evidence for an expanded region of endemicity [J]. Zoonoses Public Health, 2012, 59(Suppl 2): 43-47.

[56] Flatz L, Rieger T, Merkler D, Bergthaler A, Regen T, Schedensack M, Bestmann L, Verschoor A, Kreutzfeldt M, Brück W, Hanisch UK, Günther S, Pinschewer DD. T cell-dependence of Lassa fever pathogenesis [J]. PLoS Pathog, 2010, 6(3): e1000836.

[57] Dylla DE, Michele DE, Campbell KP, Mccray PB. Basolateral entry and release of New and Old World arenaviruses from human airway epithelia [J]. J Virol, 2008, 82(12): 6034-6038.

[58] Jahrling PB, Frame JD, Rhoderick JB, Monson MH. Endemic Lassa fever in Liberia. IV. Selection of optimally effective plasma for treatment by passive immunization [J]. Trans R Soc Trop Med Hyg, 1985, 79(3): 380-384.

[59] Chen JP, Cosgriff TM. Hemorrhagic fever virus-induced changes in hemostasis and vascular biology [J]. Blood Coagul Fibrinolysis, 2000, 11(5): 461-483.

[60] Demby AH, Chamberlain J, Brown DW, Clegg CS. Early diagnosis of Lassa fever by reverse transcription-PCR [J]. J Clin Microbiol, 1994, 32(12): 2898-2903.

[61] Trappier SG, Conaty AL, Farrar BB, Auperin DD, McCormick JB, Fisher-Hoch SP. Evaluation of the polymerase chain reaction for diagnosis of Lassa virus infection [J]. Am J Trop Med Hyg, 1993, 49(2): 214-221.

[62] Johnson KM, McCormick JB, Webb PA, Smith ES, Elliott LH, King IJ. Clinical virology of Lassa fever in hospitalized patients [J]. J Infect Dis, 1987, 155(3): 456-464.

[63] Bond N, Schieffelin JS, Moses LM, Bennett AJ, Bausch DG. A historical look at the first reported cases of Lassa fever: IgG antibodies 40 years after acute infection [J]. Am J Trop Med Hyg, 2012, 88(2): 241-244.

[64] WHO. Update on Lassa fever in West Africa [J]. Wkly Epidemiol Rec, 2005, 80(10): 86-88.

[65] Mylne AQ, Pigott DM, Longbottom JA, Duda KA, Messina JP, Weiss DJ, Moyes CL, Golding N, Hay SI. Mapping the zoonotic niche of Lassa fever in Africa [J]. Trans R Soc Trop Med Hyg, 2015, 109(8): 483-492.

[66] Walker DH, Wulff H, Lange JV, Murphy FA. Comparative pathology of Lassa virus infection in monkeys, guinea-pigs, and Mastomys natalensis [J]. Bull World Health Organ, 1975, 52(4/6): 523-534.

[67] Bausch DG, Demby AH, Coulibaly M, Kanu J, Goba A, Bah A, Condé N, Wurtzel HL, Cavallaro KF, Lloyd E, Baldet FB, Cissé SD, Fofona D, Savané IK, Tolno RT,

Mahy B, Wagoner KD, Ksiazek TG, Peters CJ, Rollin PE. Lassa fever in Guinea: I. Epidemiology of human disease and clinical observations [J]. Vector Borne Zoonotic Dis, 2001, 1(4): 269-281.

[68] Viral Haemorrhagic Fevers Consortium. Lassa fever [EB/OL]. [2013-11-03]. http://www.vhfc.org/lassa_fever.

[69] Knobloch J, McCormick JB, Webb PA, Dietrich M, Schumacher HH, Dennis E. Clinical observations in 42 patients with Lassa fever [J]. Tropenmed Parasitol, 1980, 31(4): 389-398.

[70] Monath TP, Maher M, Casals J, Kissling RE, Cacciapuoti A. Lassa fever in the Eastern Province of Sierra Leone, 1970-1972. II. Clinical observations and virological studies on selected hospital cases [J]. Am J Trop Med Hyg, 1974, 23(6): 1140-1149.

[71] Edington GM, White HA. The pathology of Lassa fever [J]. Trans R Soc Trop Med Hyg, 1972, 66(3): 381-389.

[72] Mccormick JB, Walker DH, King IJ, Webb PA, Elliott LH, Whitfield SG, Johnson KM. Lassa virus hepatitis: a study of fatal Lassa fever in humans [J]. Am J Trop Med Hyg, 1986, 35(2): 401-407.

[73] Walker DH, McCormick JB, Johnson KM, Webb PA, Komba-Kono G, Elliott LH, Gardner JJ. Pathologic and virologic study of fatal Lassa fever in man [J]. Am J Pathol, 1982, 107(3): 349-356.

[74] Peters CJ, Liu CT, Anderson GW, Morrill JC, Jahrling PB. Pathogenesis of viral hemorrhagic fevers: Rift Valley fever and Lassa fever contrasted [J]. Rev Infect Dis, 1989, 11 (Suppl 4): S743-S749.

[75] Cummins D, McCormick JB, Bennett D, Samba JA, Farrar B, Machin SJ, Fisher-Hoch SP. Acute sensorineural deafness in Lassa fever [J]. JAMA, 1990, 264(16): 2093-2096.

[76] Liao BS, Byl FM, Adour KK. Audiometric comparison of Lassa fever hearing loss and idiopathic sudden hearing loss: evidence for viral cause [J]. Otolaryngol Head Neck Surg, 1992, 106(3): 226-229.

[77] Ibekwe TS, Nwegbu MM, Asogun D, Adomeh DI, Okokhere PO. The sensitivity and specificity of Lassa virus IgM by ELISA as screening tool at early phase of Lassa fever infection [J]. Niger Med J, 2012, 53(4): 196-199.

[78] Tam RC, Lau JY, Hong Z. Mechanisms of action of ribavirin in antiviral therapies [J]. Antivir Chem Chemother, 2001, 12(5): 261-272.

[79] Cameron CE, Castro C. The mechanism of action of ribavirin: lethal mutagenesis of RNA virus genomes mediated by the viral RNA-dependent RNA polymerase [J]. Curr Opin Infect Dis, 2001, 14(6): 757-764.

[80] Crotty S, Maag D, Arnold JJ, Zhong W, Lau JY, Hong Z, Andino R, Cameron CE. The broad-spectrum antiviral ribonucleoside ribavirin is an RNA virus mutagen [J]. Nat Med, 2000, 6(12): 1375-1379.

[81] Patterson JL, Fernandez-Larsson R. Molecular mechanisms of action of ribavirin [J]. Rev Infect Dis, 1991, 12(6): 1139-1146.

[82] Crotty S, Cameron CE, Andino R. RNA virus error catastrophe: direct molecular test by using ribavirin [J]. Proc Natl Acad Sci USA, 2001, 98(12): 6895-6900.

[83] McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, Elliott LH, Belmont-Williams R. Lassa fever. Effective therapy with ribavirin [J]. N Engl J Med, 1986, 314(1): 20-26.

[84] Hadi CM, Goba A, Khan SH, Bangura J, Sankoh M, Koroma S, Juana B, Bah A, Coulibaly M, Bausch DG. Ribavirin for Lassa fever postexposure prophylaxis [J]. Emerg Infect Dis, 2010, 16(12): 2009-2011.

[85] McCormick JB. Clinical, epidemiologic, and therapeutic aspects of Lassa fever [J]. Med Microbiol Immunol, 1986, 175(2/3): 153-155.

[86] Dahmane A, van Griensven J, van Herp M, van den Bergh R, Nzomukunda Y, Prior J, Alders P, Jambai A, Zachariah R. Constraints in the diagnosis and treatment of Lassa fever and the effect on mortality in hospitalized children and women with obstetric conditions in a rural district hospital in Sierra Leone [J]. Trans R Soc Trop Med Hyg, 2014, 108(3): 126-132.

[87] Asogun DA, Adomeh DI, Ehimuan J, Odia I, Hass M, Gabriel M, Olschläger S, Becker-Ziaja B, Folarin O, Phelan E, Ehiane PE, Ifeh VE, Uyigue EA, Oladapo YT, Muoebonam EB, Osunde O, Dongo A, Okokhere PO, Okogbenin SA, Momoh M, Alikah SO, Akhuemokhan OC, Imomeh P, Odike MA, Gire S, Andersen K, Sabeti PC, Happi CT, Akpede GO, Günther S. Molecular diagnostics for Lassa fever at Irrua Specialist Teaching Hospital, Nigeria: lessons learnt from two years of laboratory operation [J]. PLoS Negl Trop Dis, 2012, 6(9): e1839.

[88] Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor [J]. Antiviral Res, 2013, 100(2): 446-454.

[89] Oestereich L, Rieger T, Lüdtke A, Ruibal P, Wurr S, Pallasch E, Bockholt S, Krasemann S, Muñoz-Fontela C, Günther S. Efficacy of favipiravir alone and in combination with ribavirin in a lethal, immunocompetent mouse model of Lassa fever [J]. J Infect Dis, 2016, 213(6): 934-938.

[90] Mitchell SW, McCormick JB. Physicochemical inactivation of Lassa, Ebola, and Marburg viruses and effect on clinical laboratory analyses [J]. J Clin Microbiol, 1984, 20(3): 486-489.

[91] Fisher-Hoch SP, Hutwagner L, Brown B, McCormick JB. Effective vaccine for Lassa fever [J]. J Virol, 2000, 74 (15): 6777-6783.

[92] Fisher-Hoch SP, McCormick JB, Auperin D, Brown BG, Castor M, Perez G, Ruo S, Conaty A, Brammer L, Bauer

S. Protection of rhesus monkeys from fatal Lassa fever by vaccination with a recombinant vaccinia virus containing the Lassa virus glycoprotein gene [J]. Proc Natl Acad Sci USA, 1989, 86(1): 317-321.

[93] Zapata JC, Goicochea M, Nadai Y, Eyzaguirre LM, Carr JK, Tallon LJ, Sadzewicz L, Myers G, Fraser CM, Su Q, Djavani M, Lukashevich IS, Salvato MS. Genetic variation in vitro and in vivo of an attenuated Lassa vaccine candidate [J]. J Virol, 2014, 88(6): 3058-3066.

[94] Lukashevich IS, Carrion R Jr, Salvato MS, Mansfield K, Brasky K, Zapata J, Cairo C, Goicochea M, Hoosien GE, Ticer A, Bryant J, Davis H, Hammamieh R, Mayda M, Jett M, Patterson J. Safety, immunogenicity, and efficacy of the ML29 reassortant vaccine for Lassa fever in small non-human primates [J]. Vaccine, 2008, 26(41): 5246-5254.

[95] Lukashevich IS, Patterson J, Carrion R, Moshkoff D, Ticer A, Zapata J, Brasky K, Geiger R, Hubbard GB, Bryant J, Salvato MS. A live attenuated vaccine for Lassa fever made by reassortment of Lassa and Mopeia viruses [J]. J Virol, 2005, 79(22): 13934-13942.

[96] Lukashevich IS. The search for animal models for Lassa fever vaccine development [J]. Expert Rev Vaccines, 2013, 12(1): 71-86.

[97] Jiang X, Dalebout TJ, Bredenbeek PJ, Carrion R, Brasky K, Patterson J, Goicochea M, Bryant J, Salvato MS, Lukashevich IS. Yellow fever 17D-vectored vaccines expressing Lassa virus GP1 and GP2 glycoproteins provide protection against fatal disease in guinea pigs [J]. Vaccine, 2011, 29(6): 1248-1257.

[98] Lukashevich IS. Advanced vaccine candidates for Lassa fever [J]. Viruses, 2012, 4(11): 2514-2557.

[99] Safronetz D, Mire C, Rosenke K, Feldmann F, Haddock E, Geisbert T, Feldmann H. A recombinant vesicular stomatitis virus-based Lassa fever vaccine protects guinea pigs and macaques against challenge with geographically and genetically distinct Lassa viruses [J]. PLoS Negl Trop Dis, 2015, 9(4): e0003736.

[100] Pushko P, Geisbert J, Parker M, Jahrling P, Smith J. Individual and bivalent vaccines based on alphavirus replicons protect guinea pigs against infection with Lassa and Ebola viruses [J]. J Virol, 2001, 75(23): 11677-11685.

[101] Branco LM, Grove JN, Geske FJ, Boisen ML, Muncy IJ, Magliato SA, Henderson LA, Schoepp RJ, Cashman KA, Hensley LE, Garry RF. Lassa virus-like particles displaying all major immunological determinants as a vaccine candidate for Lassa hemorrhagic fever [J/OL]. Virol J, 2010. http://virologyj. biomedcentral. com/articles/10. 1186/1743-422X-7-279.

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