中国科学: 生命科学 2024 年 第 54 卷 第 12 期: 2311 ~ 2320
SCIENTIA SINICA Vitae lifecn.scichina.com
《中国科学》杂志社 SCIENCE CHINA PRESS
评 述 EB病毒发现60周年: 回顾与展望专题

传染性单核细胞增多症的流行病学、免疫机制及临床管理

刘梦佳, 王然*, 谢正德*

国家儿童医学中心, 首都医科大学附属北京儿童医院, 北京市儿科研究所感染与病毒研究室, 中国医学科学院儿童危重感染诊治创新单元, 国家呼吸系统疾病临床医学研究中心, 儿科重大疾病研究教育部重点实验室, 北京 100045
* 联系人, E-mail: xiezhengde@bch.com.cn; randall@mail.ccmu.edu.cn

收稿日期: 2024-09-13; 接受日期: 2024-11-15; 网络版发表日期: 2024-12-09
首都卫生发展科研专项(批准号: 2024-4-1142)、北京市自然科学基金(批准号: L242117)和中国医学科学院医学与健康科技创新工程(批准号: 2019-I2M-5-026)资助

摘要 传染性单核细胞增多症(infectious mononucleosis, IM)是由原发性EBV感染引起的一种良性自限性疾病, 在全球范围内具有较高的发病率. IM具有较长的潜伏期, 其典型的临床"三联征"包括发热、咽峡炎和颈部淋巴结肿大, 同时可伴有肝功能损害、肝脾肿大、皮疹等临床表现. IM的诊断需要结合临床表现和原发性EBV感染的实验室证据. 目前, 对于临床IM的治疗以对症支持为主, 抗病毒治疗并不能获得显著临床效果. 本文系统总结了IM的流行病学特征、发病机制、临床表现、诊断与鉴别诊断以及治疗与预后等方面的进展, 以期为IM的临床诊治和管理提供参考.

关键词 传染性单核细胞增多症, EB病毒, 流行病学特征, 临床特征, 诊断

传染性单核细胞增多症(infectious mononucleosis, IM)是由原发性EB病毒(Epstein-Barr virus, EBV)感染所引起的急性单核-巨噬细胞系统增殖性疾病, 临床主要表现为发热、咽峡炎和颈部淋巴结肿大, 同时伴有外周血中淋巴细胞及异型淋巴细胞比例的升高[1,2]. 19世纪80年代, 俄罗斯儿科医生Nil Filatov首次报道此种疾病, 并命名为特发性腺性热[3]. 1920年, Sprunt和Evans将伴有外周血异型淋巴细胞增加的急性传染病命名为IM. 1923年, Downey和McKinlay证实这些异型淋巴细胞本质是$CD8^+$ T细胞[4]. 随后在1968年, 美国科学家证实IM是由原发性EBV感染引起的[5]. 最近有研究报道, EBV与多发性硬化症(multiple sclerosis, MS)的发生相关[6], IM被认为是远期发展为MS和霍奇金淋巴瘤等多种EBV相关疾病的重要危险因素[7].

1 EBV入侵宿主细胞的机制

EBV, 又名人类疱疹病毒4型, 属于疱疹病毒科, γ亚科, 淋巴潜隐病毒属. EBV感染宿主的靶细胞是B淋巴细胞和口咽部的上皮细胞[3,8]. EBV包膜糖蛋白gp350/220与表达在初始B淋巴细胞表面的C3d补体受

引用格式: 刘梦佳, 王然, 谢正德. 传染性单核细胞增多症的流行病学、免疫机制及临床管理. 中国科学: 生命科学, 2024, 54: 2311–2320
Liu M J, Wang R, Xie Z D. Epidemiology, immune response and clinical management of infectious mononucleosis (in Chinese). Sci Sin Vitae, 2024, 54: 2311–2320, doi: 10.1360/SSV-2024-0187

体CD21结合实现病毒附着，EBV编码糖蛋白gH-gL异二聚体与gp42糖蛋白形成复合物，人白细胞抗原-II作为病毒感染B淋巴细胞的辅助因子，与gp42糖蛋白结合，从而介导gH-gL引起融合蛋白gB构象改变，介导病毒粒子进入宿主细胞[9~11]．在不表达CD21的上皮细胞表面，EBV借助BMRF2与上皮细胞表面的整合素结合后触发病毒粒子的内吞作用[4,9,10,12]，异二聚体gH-gL与整合素αVβ5，αVβ6，αVβ8和Ephrin A型受体2(Ephrin type A receptor 2, EphA2)结合[13]，从而引起融合蛋白gB构象改变，介导EBV与宿主细胞膜融合[12,14,15]．EBV感染宿主细胞后，可呈裂解型感染或潜伏型感染状态，分别表达不同的抗原蛋白，裂解型抗原蛋白参与病毒基因组的复制以及病毒颗粒的组装，在产生子代病毒粒子的过程中发挥重要的作用．潜伏型抗原蛋白促进B细胞分化，参与免疫逃逸，建立并维持EBV阳性细胞的潜伏型感染状态．

2 IM的流行病学特征

2.1 传染源

IM的传染源是原发性EBV感染急性期的患者或者既往感染EBV后经历再激活的健康携带者．EBV感染宿主的靶细胞为B细胞和上皮细胞．原发性EBV感染的潜伏期大约是4~7周，在此期间，EBV经裂解型复制产生大量子代病毒，并经唾液排泌出体外，患者成为传染源[16,17]．在恢复期，子代EBV产生逐渐减少，感染EBV的记忆B淋巴细胞变为终身携带病毒的储备库，宿主成为终身携带者[16,18]．当宿主免疫功能受到抑制或体内再激活信号被诱导时，记忆B淋巴细胞中潜伏的EBV被再激活产生子代病毒，可继续感染初始B细胞以及上皮细胞，并经唾液不定时排泌到体外，使宿主成为重要的传染源[19]．

2.2 传播途径

在青少年和青年中，EBV主要通过亲密接触经唾液传播[8,20]．患者的家庭成员若为原发性EBV感染者或处于再激活阶段的EBV健康携带者，口腔分泌物中含有EBV，患者可因与他们共享食物，共用餐具或玩具等感染EBV[3,18,21]．此外，EBV也可以通过输注血液制品进行传播，但经此途径传播的致病率较低[17,18]．

2.3 易感人群

人群对于EBV普遍易感，但由于发展中国家和发达国家的社会经济水平与生活习惯不同，IM的好发年龄差异较大[16]．在发达国家，IM大多发生在青壮年中[1,17]，Dunmire等人[1,6]的研究数据提示，美国儿童血清中抗EBV抗体的阳性率要低于青壮年，此外，原发性EBV感染发生的年龄逐渐增大，增加了IM的发生风险[22]，在英国和日本也观察到此现象[23,24]．在发展中国家，IM大多发生于学龄期儿童或者青少年中，在低年龄儿童中通常为无症状感染或表现为非典型性IM，部分儿童在3~4岁时血清EBV抗体已阳性，成为EBV健康携带者[2,18,25]．我国IM的发病年龄高峰主要集中在学龄前期和学龄期，以4~6岁多见，且男性患儿多于女性患儿[26~28]．由于卫生条件改善以及生活习惯的改变，我国儿童原发性EBV感染的年龄逐渐增大，10岁时约有90%的儿童完成了血清学转换，具有EBV抗体．2022年的一项研究数据显示，2016~2020年间因IM住院的患儿数逐年上升[2,26,29,30]．原发性EBV感染的年龄与IM、EBV相关肿瘤以及MS的风险相关，也影响疫苗接种时机．因此，需要关注原发性EBV感染的年龄变化趋势．

2.4 IM的季节特点

IM全年均可发生，不同国家和地区IM发病的季节性存在差异[16]．以色列的研究结果显示，IM的发病率在夏季最高[31,32]．美国的研究结果提示IM主要在冬末春初高发[33]．英国伦敦和中国香港的研究数据提示，在15岁以下的儿童中IM的发病时间没有明显的季节性[34]．然而，我国一项多中心研究结果显示，夏秋季是患者因IM住院的高峰时期[26]，在全国多个地区也观察到了相似的流行趋势[25,35,36]．

3 IM的发病机制

3.1 IM受累器官的病理形态学特点

IM的受累器官包括淋巴结、脾脏及肝脏等，其组织学改变随病程呈动态变化．淋巴结组织学改变常表现为淋巴结滤泡增多增大，生发中心增大，其核心可见单核样B淋巴细胞增生以及上皮细胞积聚，随病程进展可观察到淋巴窦内幼稚淋巴细胞增多，以及$CD8^+$

T淋巴细胞增生, 增生的细胞中等偏大, 核形状不规则, 可见核分裂象[37,38]. 脾脏的大体改变通常为较正常2~3倍增大, 充血, 病理学改变包括脾包膜和脾小梁水肿、增厚伴淋巴样细胞浸润, 脾血窦轻度开放. 肝脏表现为细胞轻微肿胀和空泡形成, 门脉区可见淋巴细胞和单核细胞浸润[2,39].

3.2 机体免疫反应

3.2.1 固有免疫应答

原发性EBV感染发生后, 固有免疫反应是机体发挥抗病毒作用的第一道防线. 此前有研究报道, 在体外, EBV的DNA和抗原蛋白可被模式识别受体识别, 促进自然杀伤(natural killer, NK)细胞激活, 发挥抗感染作用[18,40]. IM急性期患者外周血单个核细胞(peripheral blood mononuclear cells, PBMC)中检测到$CD3^{-}CD56^{+}$ NK细胞的数量和比例均有增加[41~43], 尤其是$CD56^{dim}CD16^{-}$ NK细胞亚群, 该亚群在急性感染期增殖, 并对EBV感染细胞具有较强识别能力, 是抗病毒的主要NK细胞亚群[44]. 此外, 该亚群比例和绝对数在婴儿期至学龄前逐渐减少, 可能导致随着年龄增长, NK细胞介导的EBV感染控制能力降低, 而$CD8^{+}$ T细胞扩增代偿性发挥作用, 最终促使IM发生[45]. 在人源化小鼠模型中, 扩增的NK细胞可直接靶向EBV阳性细胞, 早期控制感染[46]. 此外, 炎性细胞因子, 如肿瘤坏死因子-α、白介素6、白介素1β在IM患者的扁桃体组织中增加, 可能在早期控制EBV感染以及促进适应性免疫应答的细胞成熟及分化的过程中发挥了重要作用[47].

3.2.2 适应性免疫应答

原发性EBV感染会诱导机体产生体液和细胞免疫反应. 原发性EBV感染发生后, 机体首先产生针对病毒衣壳抗原(viral capsid antigen, VCA)的IgM和IgG抗体. IM临床症状出现10天后[30,48], 90%的患者可以检测到低亲和力的抗VCA-IgG抗体, 此后2~4月间抗体滴度较高, 之后逐渐转变为高亲和力的抗VCA-IgG抗体, 并持续终身[49,50]. 在IM的恢复期, 可检测到针对早期抗原(early antigen, EA)的IgG抗体, 少部分患者可长期检出[30,51,52]. 针对潜伏型抗原蛋白1(Epstein-Barr nuclear antigen protein-1, EBNA1)的IgG抗体存在延迟产生效应, 通常在EBV感染3个月之后才开始产生, 并持续终身[53]. 此外, 针对糖蛋白350(glycoprotein350, gp350)的抗体也可被检出[54].

细胞免疫反应有助于清除感染细胞、控制病毒复制, 在宿主抗病毒的过程中发挥重要作用. Jayasooriya等人[55]的研究提示, 尽管14~18月龄的非洲无症状EBV感染婴幼儿的血浆EBV-DNA载量与IM患者相似, 但PBMC中未检测到$CD8^{+}$ T细胞的扩增. Abbott等人[56]也报道了类似的结果: 无症状感染的青少年的EBV-DNA载量与IM患者相当, 但其细胞免疫反应程度低于IM患者. 因此, IM的发生与抗原驱动的特异性$CD8^{+}$ T细胞扩增密切相关, 是一种以免疫病理为主的疾病. 基于这一特点, 大量扩增的$CD8^{+}$ T细胞可作为IM的重要辅助诊断指标.

在IM急性期, EBV特异性$CD8^{+}$ T细胞和$CD4^{+}$ T细胞表面均检测到细胞激活标志物的共表达, 提示抗原刺激诱导T细胞呈高度活化状态[57~59]. 活化的T细胞后通过识别潜伏型和裂解型感染状态的细胞, 发挥细胞毒性作用. 其中, 不同抗原蛋白诱导的T细胞免疫应答有所差异[40]. Steven等人[60,61]的研究指出, EBV特异性$CD8^{+}$ T细胞的免疫反应主要集中在裂解型抗原蛋白(如BZLF1/BRLF1), 而对潜伏型抗原蛋白(如EBNA3)的免疫反应较弱[7,62~64].

此外, Chatterjee等人[65]在IM患儿外周血中检测到$PD\text{-}1^{+}CD8^{+}$ T细胞的增殖, 并伴随TIM-3, KLRG1和2B4的高表达. Rühl等人[63]进一步报道, 针对裂解型抗原的$CD8^{+}$ T细胞具有特定的表型(如$PD\text{-}1^{+}TIM\text{-}3^{+}KLRG1^{+}CXCR5^{+}TCF1^{+}$和$BATF3^{+}$), 并可能在生发中心参与控制EBV感染. 因此, PD-1的表达可能在维持EBV特异性T细胞功能中起重要作用, 而阻断PD-1通路可能会干扰T细胞的免疫效应 .

3.2.3 免疫逃逸

免疫逃逸在IM中有助于防止免疫病理损伤的过度发生. EBV通过裂解型和潜伏型抗原蛋白下调MHC-I分子的表达, 阻断抗原递呈, 避免$CD8^{+}$ T细胞的识别, 从而实现免疫逃逸[66]. 此外, 潜伏型抗原蛋白EBNA1蛋白的甘氨酸-丙氨酸(Gly-Ala)重复结构域能够抑制蛋白酶体对EBNA1的降解, 干扰其抗原表位被分解为短肽的过程, 进而使EBNA1逃避$CD8^{+}$ T细胞的识别[67~69]. 这一机制有助于EBNA1在感染细胞中的稳定表达, 维持EBV基因组的存在形式. 与此同时, EBV

通过表达病毒性IL-10(BCRF1)抑制宿主免疫系统的过度炎症反应, 减少组织损伤, 为病毒的持续感染提供条件. 这些免疫逃逸机制共同作用, 有效调节IM中的免疫反应平衡[70,71].

4 IM的临床表现

原发性EBV感染的潜伏期一般为4~7周, 在年幼儿童中可缩短. 婴幼儿可呈无症状感染或表现为不典型的IM, 临床症状较轻, 可仅表现为一过性类上呼吸道感染症状, 或在幼儿体检时发现肝功能异常, 后经血清学抗体检测确认患者为原发性EBV感染. 少数患者仅表现为单一脏器受累的不典型IM症状, 如EBV感染性肝炎, 间质性肺炎等[1,2].

原发性EBV感染在年长儿及青少年中, 则更易表现为典型的IM临床症状和体征, 包括"三联征", 即发热、咽峡炎和颈部淋巴结肿大; 几乎所有的患者均有发热, 体温最高可达40℃, 热程约1周, 少数患者可长达2周或更久; 约95%的患者有咽峡炎, 50%的患者伴有扁桃体部位灰白色膜状渗出物, 25%的患者上颚有淤点出现, 约1周后消失; 80%~95%的患者在疾病初期出现浅表淋巴结肿大, 全身淋巴结均可肿大, 以颈部、耳后、颌下多见, 肿大的淋巴结消退需要数周, 部分可持续数月. 由于EBV感染后易出现肝脾的淋巴细胞浸润, 大部分患者会出现肝功能异常和肝脾肿大等表现, 肝功能异常可在2周~2个月内恢复正常, 一般不会导致慢性肝疾病. 此外, 部分患者可出现眼睑水肿、鼻塞、夜间打鼾等症状, 另有15%的患者可出现多形性皮疹, 部分青少年患者会出现长期乏力的症状[2,25,72].

由于EBV感染及其导致的淋巴细胞浸润以及免疫系统激活后导致继发性炎症损伤, 少部分患者可出现上气道梗阻、脑炎、脑膜炎、心肌炎、溶血性贫血、血小板减少性紫癜和脾破裂等合并症或并发症, 极少数患者可出现继发性噬血细胞综合征(hemophagocytic lymphohistiocytosis, HLH)等严重的并发症[2,18,40,73]. 同时, 需警惕X连锁淋巴组织增殖综合征(X-linked lymphoproliferative syndrome, XLP)患者感染EBV. XLP是一种以贫血、低丙种球蛋白血症和淋巴组织细胞增多症为特征的原发性免疫缺陷疾病. 患有XLP的男孩因不能有效控制原发性EBV感染导致免疫细胞快速扩增, 释放大量细胞因子, 发生HLH, 病情进展迅速, 若不能及时识别并有效控制EBV感染, 严重者可致患者死亡[74,75].

5 IM的诊断与鉴别诊断

IM的诊断需要结合临床表现以及辅助检查进行综合研判, 具体的诊断标准可参考《儿童EB病毒感染相关疾病的诊断和治疗原则专家共识》[2].

外周血象改变是IM的重要特征, 表现为淋巴细胞大量扩增. 若6岁以上儿童发热伴颈淋巴结肿大, 外周血常规检测显示淋巴细胞比例大于50%或淋巴细胞绝对值大于5×10^9/L并检测出异型淋巴细胞比例大于10%, 则提示IM[2], 需完善EBV感染特异性实验室检查. 利用酶联免疫法或化学发光法检测抗VCA-IgM和IgG抗体、抗EBNA-IgG抗体, 及抗VCA-IgG抗体的亲和力. 抗VCA-IgG和IgM抗体阳性而抗EBNA-IgG抗体阴性, 或单一的低亲和力抗VCA-IgG抗体阳性提示原发性EBV感染[30,76]. 对于不典型IM, 还可通过EBV编码的小RNA原位杂交检测, 明确疾病与EBV感染的关系[30,77].

IM急性期患者扁桃体可见灰白色膜状分泌物, 且5%的患者合并链球菌感染, 因此, 应结合其他临床表现以及实验室检查与链球菌导致的化脓性扁桃体炎进行鉴别[2,78]. 人巨细胞病毒、弓形虫以及风疹病毒等也可引起外周血中异型淋巴细胞比例升高且表现为类传染性单核细胞增多综合征[79~81], 可结合临床表现以及病原学检查进行鉴别. 此外, 部分患者可继发川崎病或噬血细胞综合征, 需结合临床表现, 及时诊断和治疗[20,82].

6 IM的治疗与预后

IM大多属于良性自限性疾病, 以对症支持治疗为主. 患者在急性期应注意休息, 肝功能异常明显者建议卧床休息, 给予护肝降酶治疗. 病情较重、有并发症者可服用阿昔洛韦等抗病毒药物降低病毒复制水平, 减少咽部病毒的排泌, 但该药对于缩短病程, 缓解临床表现尚无明显疗效[27,83,84], 一般不推荐常规使用, 热退后可考虑停药. 若患者合并细菌感染, 可考虑应用敏感抗菌药物, 由于氨苄西林和阿莫西林可导致超敏反应,

应禁止使用[2]. 肝脾肿大的患者需限制运动, 以免挤压或撞击脾脏, 出现脾破裂等危急情况. 合并上气道梗阻或血小板减少等并发症的重症患者可短时应用糖皮质激素[2,3].

IM一般预后良好, 大部分患者在病程1个月左右时临床症状缓解, 病程3个月内完全康复, 成为健康携带者. 若3个月后患者仍有反复发热、肝脾肿大、肝功能异常等表现, 需要进一步诊治, 除外慢性活动性EBV感染等情况[85]. 因此, 需要对IM患者病情进行全面的系统评估、精准诊治和随诊管理(图1).

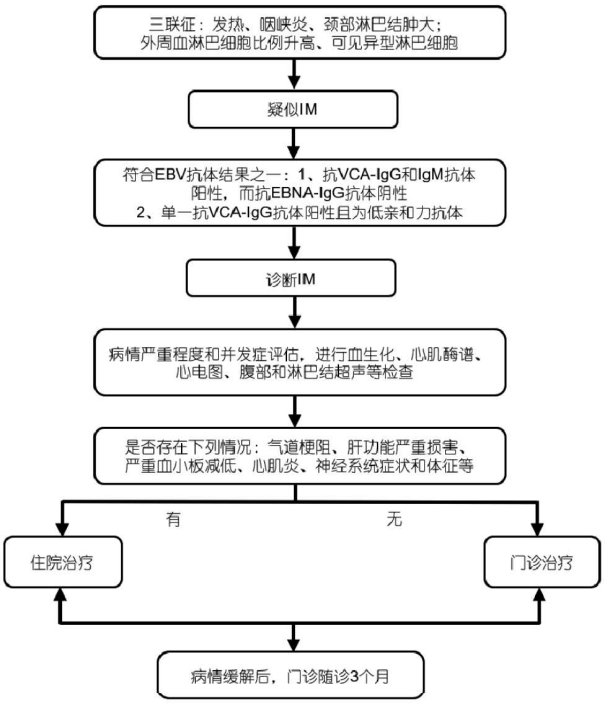

图 1　IM的临床诊断与管理路径图
Figure 1　Diagnosis and clinical management workflow of IM

7　预防EBV感染

EBV的主要传染源为原发性EBV感染急性期的患者以及经历病毒再激活过程的健康携带者. 因此, 应重视对传染源的管理, 通过高风险人群的核酸检测和早期干预减少传播风险. EBV主要通过唾液传播, 亲密接触是其主要传播途径. 为切断传播途径, 可通过保持手卫生、分餐制进食、避免共用餐具和个人生活用品等措施, 有效降低感染几率. 针对易感人群, 研发安全有效的疫苗是关键. 然而, 目前尚无广泛应用的EBV疫苗, Sokal等人[86]的研究显示, gp350亚单位疫苗可降低IM的发病率. Elliott等人[87]则表明, EBNA3A表位疫苗能够诱导特异性$CD8^+$ T细胞应答, 但尚不能完全预防EBV感染.

近年来, 预防EBV感染的新型疫苗的研究取得了重要进展, Wei等人[88]报道, gH/gL+gp350D123和gH/gL/gp42+gp350D12自组装纳米颗粒候选疫苗在小鼠、雪貂和非人类灵长类动物均能诱导免疫反应, 并在人源化小鼠模型中有效抑制EBV感染. Malhi等人[89]发现, gH/gL自组装纳米颗粒候选疫苗在小鼠中具有较好的免疫原性, 可保护人源化小鼠免受EBV感染. Sun等人[90]研究表明, gB-I53-50纳米颗粒候选疫苗在小鼠和非人类灵长类动物模型中表现出良好的免疫原性, 其血清过继转移在人源化小鼠模型中显示出强大的中和抗体保护作用. Kanekiyo等人[91]开发的靶向gp350的铁蛋白纳米颗粒疫苗在小鼠模型中诱导产生高达10~100倍的中和抗体水平, 目前该疫苗已进入临床试验阶段.

此外, Moderna公司开发的针对gH/gL, gp42和gp220糖蛋白抗原的mRNA疫苗也正在进行临床试验[92]. 这些研究为EBV疫苗的开发提供了新的思路. 未来, 应进一步加强针对EBV的特异性抗病毒药物和疫苗的研发, 以更有效地保护易感人群并降低EBV相关疾病的负担.

8　展望

未来的IM研究应聚焦于发病机制、长期风险、防控策略和精准医学等方面. 首先, 需要解析宿主免疫系统在疾病发生与控制中的核心作用, 特别是调控免疫反应强度和防止免疫病理损伤的关键机制. 需重点关注病毒感染过程中免疫细胞的活化与耗竭平衡, 以及这些过程对疾病严重程度和长期转归的影响. 其次, IM与MS和霍奇金淋巴瘤等EBV相关疾病的长期联系仍需纵向研究以明确演变规律, 同时探索宿主基因的遗传易感性. 再次, 在疫苗研发方面, 需优化多抗原组合策略并明确不同年龄段接种时机对IM和EBV相关疾病的保护效果. 此外, 针对EBV再激活的传播动力学及诱因的研究有助于建立精准的传播风险预测模型. 最后, 通过筛选生物标志物和动态监测病毒载量, 可推

动IM的个体化诊疗策略, 并对严重并发症(如EBV-HLH)进行早期预警和干预. 这些研究方向将为优化IM的诊疗手段、提升疫苗接种策略和减轻相关疾病负担提供科学依据和实践指导.

参考文献

1 Dunmire S K, Hogquist K A, Balfour H H. Infectious mononucleosis. In: Münz C, ed. Epstein Barr Virus Volume 1. Current Topics in Microbiology and Immunology. Cham: Springer, 2015. 211–240

2 The Subspecialty Group of Infectious Diseases, the Society of Pediatrics, Chinese Medical, Association, National Children's Epstein-Barr Virus Infection Cooperative Group. Experts consensus on diagnosis and treatment of Epstein-Barr virus infection-related diseases in children (in Chinese). Chin J Pediatr, 2021, 59: 905–911 [中华医学会儿科学分会感染学组, 全国儿童EB病毒感染协作组. 儿童EB病毒感染相关疾病的诊断和治疗原则专家共识. 中华儿科杂志, 2021, 59: 905–911]

3 Balfour H H Jr, Dunmire S K, Hogquist K A. Infectious mononucleosis. Clin Trans Imm, 2015, 4: e33

4 Cohen J I. Epstein-Barr virus infection. N Engl J Med, 2000, 343: 481–492

5 Henle W, Henle G. Epstein-Barr virus and infectious mononucleosis. N Engl J Med, 1973, 288: 263–264

6 Sheik-Ali S. Infectious mononucleosis and multiple sclerosis—updated review on associated risk. Mult Scler Relat Disord, 2017, 14: 56–59

7 Balfour H H Jr, Schmeling D O, Grimm-Geris J M. The promise of a prophylactic Epstein-Barr virus vaccine. Pediatr Res, 2020, 87: 345–352

8 Cruchley A T, Williams D M, Niedobitek G, et al. Epstein-Barr virus: biology and disease. Oral Dis, 1997, 3: S156–S163

9 Molesworth S J, Lake C M, Borza C M, et al. Epstein-Barr virus gH is essential for penetration of B cells but also plays a role in attachment of virus to epithelial cells. J Virol, 2000, 74: 6324–6332

10 Borza C M, Hutt-Fletcher L M. Alternate replication in B cells and epithelial cells switches tropism of Epstein-Barr virus. Nat Med, 2002, 8: 594–599

11 Li Q, Spriggs M K, Kovats S, et al. Epstein-Barr virus uses HLA class II as a cofactor for infection of B lymphocytes. J Virol, 1997, 71: 4657–4662

12 Chen J, Sathiyamoorthy K, Zhang X, et al. Ephrin receptor A2 is a functional entry receptor for Epstein-Barr virus. Nat Microbiol, 2018, 3: 172–180

13 Chesnokova L S, Hutt-Fletcher L M. Fusion of Epstein-Barr virus with epithelial cells can be triggered by αvβ5 in addition to αvβ6 and αvβ8, and integrin binding triggers a conformational change in glycoproteins gHgL. J Virol, 2011, 85: 13214–13223

14 Connolly S A, Jardetzky T S, Longnecker R. The structural basis of herpesvirus entry. Nat Rev Microbiol, 2021, 19: 110–121

15 Bu W, Joyce M G, Nguyen H, et al. Immunization with components of the viral fusion apparatus elicits antibodies that neutralize Epstein-Barr virus in B cells and epithelial cells. Immunity, 2019, 50: 1305–1316.e6

16 Luzuriaga K, Sullivan J L. Infectious mononucleosis. N Engl J Med, 2010, 362: 1993–2000

17 Dunmire S K, Verghese P S, Balfour H H Jr. Primary Epstein-Barr virus infection. J Clin Virol, 2018, 102: 84–92

18 Odumade O A, Hogquist K A, Balfour H H Jr. Progress and problems in understanding and managing primary Epstein-Barr virus infections. Clin Microbiol Rev, 2011, 24: 193–209

19 Liu M, Wang R, Xie Z. T cell-mediated immunity during Epstein-Barr virus infections in children. Infect Genet Evol, 2023, 112: 105443

20 Tsuchiya S. Diagnosis of Epstein-Barr virus-associated diseases. Crit Rev Oncol Hematol, 2002, 44: 227–238

21 Lang D J, Garruto R M, Gajdusek D C. Early acquisition of cytomegalovirus and Epstein-Barr virus antibody in several isolated melanesian populations. Am J Epidemiol, 1977, 105: 480–487

22 Balfour H H Jr, Odumade O A, Schmeling D O, et al. Behavioral, virologic, and immunologic factors associated with acquisition and severity of primary Epstein-Barr virus infection in university students. J Infect Dis, 2013, 207: 80–88

23 Morris M C, Edmunds W J. The changing epidemiology of infectious mononucleosis? J Infect, 2002, 45: 107–109

24 Takeuchi K, Tanaka-Taya K, Kazuyama Y, et al. Prevalence of Epstein-Barr virus in Japan: Trends and future prediction. Pathol Int, 2006, 56: 112–116

25 Gao L W, Xie Z D, Yao Y, et al.Clinical characteristics of infectious mononucleosis associated with Epstein-Barr virus infection in children (in Chinese). Chin J Appl Clin Pediatr, 2010, 25: 725–727 [高立伟, 谢正德, 幺远, 等. 儿童EB病毒感染传染性单核细胞增多症的临床特征. 实用

儿科临床杂志, 2010, 25: 725–727]
26 Liu M, Wang X, Zhang L, et al. Epidemiological characteristics and disease burden of infectious mononucleosis in hospitalized children in China: a nationwide retrospective study. Virol Sin, 2022, 37: 637–645
27 Ouyang W X, Zhang H, Liu J, et al. A single center study on the clinical features and treatment of infectious mononucleosis in children (in Chinese). Chin J Exp Clin Virol, 2018, 32: 12–16 [欧阳文献, 张慧, 刘静, 等. 儿童传染性单核细胞增多症临床特征及治疗的单中心研究. 中华实验和临床病毒学杂志, 2018, 32: 12–16]
28 Guan X L, Yan J, Zhao Q H, et al. Analysis of serum anti-EB virus antibody in children with infectious mononucleosis (in Chinese). Chin J Appl Clin Pediatr, 2021, 36: 1004–1006 [关晓蕾, 闫静, 赵秋红, 等. 传染性单核细胞增多症患儿血清抗EB病毒抗体检测结果分析. 中华实用儿科临床杂志, 2021, 36: 1004–1006]
29 Liu C Y, Yan J, Liu Y Y, et al. Study on the serological diagnosis of Epstein-Barr virus among patients with mononucleosis (in Chinese). Chin J Epidemiol, 2007, 28: 898–900 [刘春艳, 闫静, 刘亚谊, 等. EB病毒相关性传染性单核细胞增多症的血清学诊断. 中华流行病学杂志, 2007, 28: 898–900]
30 National Children's Epstein-Barr Virus Infection Cooperative Group, Editorial Board of Chinese Journal of Experimental and Clinical Virology. Expert consensus on laboratory diagnosis and clinical application of Epstein Barr virus infection (in Chinese). Chin J Exp Clin Virol, 2018, 32: 2–8 [全国儿童EB病毒感染协作组, 中华实验和临床病毒学杂志编辑委员会. EB病毒感染实验室诊断及临床应用专家共识. 中华实验和临床病毒学杂志, 2018, 32: 2–8]
31 Grotto I, Mimouni D, Huerta M, et al. Clinical and laboratory presentation of EBV positive infectious mononucleosis in young adults. Epidemiol Infect, 2003, 131: 683–689
32 Levine H, Mimouni D, Grotto I, et al. Secular and seasonal trends of infectious mononucleosis among young adults in Israel: 1978–2009. Eur J Clin Microbiol Infect Dis, 2012, 31: 757–760
33 Heath C W Jr, Brodsky A L, Potolsky A I. Infectious mononucleosis in a general population. Am J Epidemiol, 1972, 95: 46–52
34 Newell K W. The reported incidence of glandular fever. J Clin Pathol, 1957, 10: 20–22
35 Guo H X, Hu Y J, Yin F R, et al. Clinical and laboratory results of 270 children with infectious mononucleosis (in Chinese). Chin J Appl Clin Pediatr, 2022, 19: 1478–1481 [郭红仙, 胡玉杰, 尹凤蕊, 等. 传染性单核细胞增多症270例临床和实验室检查分析. 中华实用儿科临床杂志, 2022, 19: 1478–1481]
36 Su H P, Xu H R, Zhang L H. Clinical analysis of 362 children infected with Epstein-Barr virus (in Chinese). Chin J Pract Med, 2012, 39: 58–59 [苏华平, 徐会荣, 张连红. 儿童EB病毒感染362例临床分析. 中国实用医刊, 2012, 39: 58–59]
37 Ye D M, Zhang Z W, Liu Y. Pathological staging and differential diagnosis of infectious mononucleosis (in Chinese). Chin J Pathol, 2019, 48: 421–424 [叶东梅, 张志伟, 刘勇. 传染性单核细胞增多症的病理分期与鉴别诊断. 中华病理学杂志, 2019, 48: 421–424]
38 Anagnostopoulos I, Hummel M, Kreschel C, et al. Morphology, immunophenotype, and distribution of latently and/or productively Epstein-Barr virus-infected cells in acute infectious mononucleosis: implications for the interindividual infection route of Epstein-Barr virus. Blood, 1995, 85: 744–750
39 Chen Y Z, Zhou X G, Jin Y, et al. Study of clinical and morphological features, immunophenotype and Epstein-Bar virus infection in situ of infectious mononucleosis (in Chinese). Chin J Pathol, 2008, 37: 440–444 [陈云昭, 周小鸽, 金妍, 等. 传染性单核细胞增多症的临床病理及EB病毒定位性研究. 中华病理学杂志, 2008, 37: 440–444]
40 Taylor G S, Long H M, Brooks J M, et al. The immunology of Epstein-Barr virus-induced disease. Annu Rev Immunol, 2015, 33: 787–821
41 Tomkinson B E, Wagner D K, Nelson D L, et al. Activated lymphocytes during acute Epstein-Barr virus infection. J Immunol, 1987, 139: 3802–3807
42 Chijioke O, Landtwing V, Münz C. NK cell influence on the outcome of primary Epstein-Barr virus infection. Front Immunol, 2016, 7: 323
43 Williams H, McAulay K, Macsween K F, et al. The immune response to primary EBV infection: a role for natural killer cells. Br J Haematol, 2005, 129: 266–274
44 Azzi T, Lünemann A, Murer A, et al. Role for early-differentiated natural killer cells in infectious mononucleosis. Blood, 2014, 124: 2533–2543
45 Strowig T, Brilot F, Arrey F, et al. Tonsilar NK cells restrict B cell transformation by the Epstein-Barr virus via IFN-gamma. PLoS Pathog, 2008, 4: e27
46 Chijioke O, Müller A, Feederle R, et al. Human natural killer cells prevent infectious mononucleosis features by targeting lytic Epstein-Barr virus infection. Cell Rep, 2013, 5: 1489–1498

47 Foss H D, Herbst H, Hummel M, et al. Patterns of cytokine gene expression in infectious mononucleosis. Blood, 1994, 83: 707–712
48 Andersson A, Vetter V, Kreutzer L, et al. Avidities of IgG directed against viral capsid antigen or early antigen: useful markers for significant Epstein-Barr virus serology. J Med Virol, 1994, 43: 238–244
49 Rea T D, Ashley R L, Russo J E, et al. A systematic study of Epstein-Barr virus serologic assays following acute infection. Am J Clin Pathol, 2002, 117: 156–161
50 Robertson P, Beynon S, Whybin R, et al. Measurement of EBV-IgG anti-VCA avidity aids the early and reliable diagnosis of primary EBV infection. J Med Virol, 2003, 70: 617–623
51 Kaschka W P, Hilgers R, Skvaril F. Humoral immune response in Epstein-Barr virus infections. I. Elevated serum concentration of the IgG1 subclass in infectious mononucleosis and nasopharyngeal carcinoma. Clin Exp Immunol, 1982, 49: 149–156
52 Fleisher G R, Collins M, Fager S. Humoral immune response in infectious mononucleosis. J Adolesc Health Care, 1985, 6: 424–428
53 Yin Y, Manoury B, Fåhraeus R. Self-inhibition of synthesis and antigen presentation by Epstein-Barr virus-encoded EBNA1. Science, 2003, 301: 1371–1374
54 Moutschen M, Léonard P, Sokal E M, et al. Phase I/II studies to evaluate safety and immunogenicity of a recombinant gp350 Epstein-Barr virus vaccine in healthy adults. Vaccine, 2007, 25: 4697–4705
55 Jayasooriya S, De Silva T I, Njie-Jobe J, et al. Early virological and immunological events in asymptomatic Epstein-Barr virus infection in African children. PLoS Pathog, 2015, 11: e1004746
56 Abbott R J, Pachnio A, Pedroza-Pacheco I, et al. Asymptomatic primary infection with Epstein-Barr virus: observations on young adult cases. J Virol, 2017, 91: e00382-17
57 Callan M F C, Tan L, Annels N, et al. Direct visualization of antigen-specific $CD8^+$ T cells during the primary immune response to Epstein-Barr virus *in vivo*. J Exp Med, 1998, 187: 1395–1402
58 Fedyanina O S, Filippova A E, Demina O I, et al. The nature and clinical significance of atypical mononuclear cells in infectious mononucleosis caused by the Epstein-Barr virus in children. J Infect Dis, 2021, 223: 1699–1706
59 Wang Y, Luo Y, Tang G, et al. HLA-DR expression level in $CD8^+$ T cells correlates with the severity of children with acute infectious mononucleosis. Front Immunol, 2021, 12: 753290
60 Steven N M, Annels N E, Kumar A, et al. Immediate early and early lytic cycle proteins are frequent targets of the Epstein-Barr virus-induced cytotoxic T cell response. J Exp Med, 1997, 185: 1605–1618
61 Steven N M, Leese A M, Annels N E, et al. Epitope focusing in the primary cytotoxic T cell response to Epstein-Barr virus and its relationship to T cell memory. J Exp Med, 1996, 184: 1801–1813
62 Precopio M L, Sullivan J L, Willard C, et al. Differential kinetics and specificity of EBV-specific $CD4^+$ and $CD8^+$ T cells during primary infection. J Immunol, 2003, 170: 2590–2598
63 Rühl J, Leung C S, Münz C. Vaccination against the Epstein-Barr virus. Cell Mol Life Sci, 2020, 77: 4315–4324
64 COHEN J I. Vaccine Development for Epstein-Barr virus. In: Kawaguchi Y, Mori Y, Kimura H, eds. Human Herpesviruses. Advances in Experimental Medicine and Biology. Singapore: Springer, 2018. 477–793
65 Chatterjee B, Deng Y, Holler A, et al. $CD8^+$ T cells retain protective functions despite sustained inhibitory receptor expression during Epstein-Barr virus infection *in vivo*. PLoS Pathog, 2019, 15: e1007748
66 van Gent M, Gram A M, Boer I G J, et al. Silencing the shutoff protein of Epstein-Barr virus in productively infected B cells points to (innate) targets for immune evasion. J Gen Virol, 2015, 96: 858–865
67 Levitskaya J, Sharipo A, Leonchiks A, et al. Inhibition of ubiquitin/proteasome-dependent protein degradation by the Gly-Ala repeat domain of the Epstein-Barr virus nuclear antigen 1. Proc Natl Acad Sci USA, 1997, 94: 12616–12621
68 Farrell P J. Epstein-Barr virus and cancer. Annu Rev Pathol Mech Dis, 2019, 14: 29–53
69 Apcher S, Komarova A, Daskalogianni C, et al. mRNA translation regulation by the Gly-Ala repeat of Epstein-Barr virus nuclear antigen 1. J Virol, 2009, 83: 1289–1298
70 Mckenzie J, Lopez-Giraldez F, Delecluse H J, et al. The Epstein-Barr virus immunoevasins BCRF1 and BPLF1 are expressed by a mechanism independent of the canonical late pre-initiation complex. PLoS Pathog, 2016, 12: e1006008
71 Kanegane H, Wakiguchi H, Kanegane C, et al. Viral interleukin-10 in chronic active Epstein-Barr virus infection. J Infect Dis, 1997, 176: 254–257

72 Naughton P, Healy M, Enright F, et al. Infectious Mononucleosis: diagnosis and clinical interpretation. Br J Biomed Sci, 2021, 78: 107–116

73 Kimura H, Ito Y, Kawabe S, et al. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. Blood, 2012, 119: 673–686

74 Nagy N, Klein E. Deficiency of the proapoptotic SAP function in X-linked lymphoproliferative disease aggravates Epstein-Barr virus (EBV) induced mononucleosis and promotes lymphoma development. Immunol Lett, 2010, 130: 13–18

75 MacGinnitie A J, Geha R. X-linked lymphoproliferative disease: Genetic lesions and clinical consequences. Curr Allergy Asthma Rep, 2002, 2: 361–367

76 Bailey R E. Diagnosis and treatment of infectious mononucleosis. Am Fam Physician, 1994, 49: 879–888

77 Abusalah M A H, Gan S H, Al-Hatamleh M A I, et al. Recent advances in diagnostic approaches for Epstein-Barr virus. Pathogens, 2020, 9: 226

78 Danstrup C S, Klug T E. Low rate of co-infection in complicated infectious mononucleosis. Dan Med J, 2019, 66: A5564

79 Fiala M, Heiner D C, Turner J A, et al. Infectious mononucleosis and mononucleosis syndromes. West J Med, 1977, 126: 445–459

80 Escobar M R, Allison M J, Dalton H P. Etiology and laboratory diagnosis of infectious mononucleosis: II. Cytomegalovirus (CMV) mononucleosis. Va Med Mon (1918), 1970, 97: 191–192

81 Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. Am J Med, 2007, 120: 911.e1–911.e8

82 Melekian B. Kawasaki-like infectious mononucleosis. Acta Paediatr Scand, 1982, 71: 843–844

83 Hu H, Deng H, Bi J, et al. Clinical characteristics and effectiveness of antiviral agents in hospitalized children with infectious mononucleosis in China: a multicenter retrospective study. Pediatr Invest, 2021, 5: 188–194

84 De Paor M, O'Brien K, Fahey T, et al. Antiviral agents for infectious mononucleosis (glandular fever). Cochrane Database Syst Rev, 2016, 12: CD011487

85 Bollard C M, Cohen J I. How I treat T-cell chronic active Epstein-Barr virus disease. Blood, 2018, 131: 2899–2905

86 Sokal E M, Hoppenbrouwers K, Vandermeulen C, et al. Recombinant gp350 vaccine for infectious mononucleosis: a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of an Epstein-Barr virus vaccine in healthy young adults. J Infect Dis, 2007, 196: 1749–1753

87 Elliott S L, Suhrbier A, Miles J J, et al. Phase I trial of a $CD8^+$ T-cell peptide epitope-based vaccine for infectious mononucleosis. J Virol, 2008, 82: 1448–1457

88 Wei C J, Bu W, Nguyen L A, et al. A bivalent Epstein-Barr virus vaccine induces neutralizing antibodies that block infection and confer immunity in humanized mice. Sci Transl Med, 2022, 14: eabf3685

89 Malhi H, Homad L J, Wan Y H, et al. Immunization with a self-assembling nanoparticle vaccine displaying EBV gH/gL protects humanized mice against lethal viral challenge. Cell Rep Med, 2022, 3: 100658

90 Sun C, Kang Y F, Fang X Y, et al. A gB nanoparticle vaccine elicits a protective neutralizing antibody response against EBV. Cell Host Microbe, 2023, 31: 1882–1897.e10

91 Kanekiyo M, Bu W, Joyce M G, et al. Rational design of an Epstein-Barr virus vaccine targeting the receptor-binding site. Cell, 2015, 162: 1090–1100

92 Zhao G, Bu G, Liu G, et al. mRNA-based vaccines targeting the T-cell Epitope-rich domain of Epstein Barr virus latent proteins elicit robust anti-tumor immunity in mice. Adv Sci, 2023, 10: e2302116

Epidemiology, immune response and clinical management of infectious mononucleosis

LIU MengJia, WANG Ran & XIE ZhengDe

Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Key Laboratory of Major Diseases in Children, Ministry of Education, National Clinical Research Center for Respiratory Diseases, Research Unit of Critical Infection in Children, Chinese Academy of Medical Sciences, 2019RU016, Laboratory of Infection and Virology, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China

Infectious mononucleosis (IM) is a benign, self-limiting disease caused by primary EBV infection, with a high incidence worldwide. IM has a relatively long incubation period, and its typical clinical "triad" includes fever, pharyngitis, and cervical lymphadenopathy, often accompanied by symptoms such as liver dysfunction, hepatosplenomegaly, and rash. The diagnosis of IM requires a combination of clinical presentation and laboratory evidence of primary EBV infection. Currently, the treatment of clinical IM primarily focuses on symptomatic support, as antiviral therapy does not yield significant clinical effects. This article systematically summarizes the epidemiological characteristics, pathogenesis, clinical manifestations, diagnosis, and differential diagnosis, as well as treatment and prognosis of IM, and provides guidance for the clinical diagnosis, treatment, and management of IM.

infectious mononucleosis, **EBV**, **epidemiological features**, **clinical characteristics**, **diagnosis**

doi: 10.1360/SSV-2024-0187