·综述·

儿童恙虫病临床特点及诊治研究进展

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【摘要】恙虫病（TD）是由恙虫病东方体（Ot）感染而引起的自然疫源性疾病，人群对Ot普遍易感。因对儿童TD关注不够，导致我国TD儿童患者误诊、误治发生率较高。本文对儿童TD的临床特点进行综述，以提高对儿童TD的临床认知。TD特征性体征焦痂在儿童TD发生率为34.6%～70.5%，皮疹发生率仅为10%～20%，是导致误诊误治的主要原因。儿童TD神经系统感染发生率高，肝功能损伤发生率高，血小板减少、贫血、心肌炎发生率高，儿童高热伴多系统受累应怀疑TD。儿童TD病死率高达4.8%～12.2%，致死原因为多器官功能衰竭（MSOF）、急性呼吸窘迫综合征（ARDS）和嗜血细胞综合征（HPS）。儿童TD需要与发热伴血小板减少综合征（SFTS）、登革热、伤寒、钩端螺旋体病、流行性出血热、黑热病等相鉴别。运用聚合酶链式反应（PCR）检测血液和（或）焦痂Ot，酶联免疫吸附测定（ELISA）检测血液Ot抗体IgM是TD病原学诊断的成熟技术，也有应用宏基因二代测序技术（mNGS）诊断TD的报道。Ot为细胞内寄生菌，应用能进入细胞内的抗菌药物，如多西环素、阿奇霉素、氯霉素和克拉霉素均可取得显著疗效。

【关键词】恙虫病；儿童；临床特点；诊断；鉴别诊断；抗菌药物

Research progress on clinical characteristics, diagnosis and treatment of tsutsugamushi disease in children

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【Abstract】Tsutsutsugamushi disease (TD) is a natural epidemic disease caused by orientia tsutsugamushi (Ot) infection, and all people are generally susceptible to Ot. Insufficient attention to children with TD in China leads to a high incidence of misdiagnosis and mistreatment. This article reviews the clinical features of children with TD, in order to improve the clinical understanding of children's TD. The incidence of characteristic signs of TD eschar in children with TD was 34.6%-70.5%, and the incidence of rash was only 10%-20%, which was the main cause of the misdiagnosis and mistreatment. TD has a high incidence of nervous system infection, liver damage, thrombocytopenia, anemia and myocarditis in children. TD should be suspected in children with high fever and multiple system involvement. The mortality rate of TD in children was as high as 4.8%-12.2%. The causes of death are multiple organ failure, acute respiratory distress syndrome and hemophagocytic syndrome. TD should be differentiated from severe fever with thrombocytopenia syndrome (SFTS), dengue fever, typhoid fever, leptospirosis, epidemic hemorrhagic fever and kala-azar. Detection of Ot in blood and/or eschar by polymerase chain reaction (PCR), detection of Ot antibody IgM in blood by enzyme-linked immunosorbent assay (ELISA) was a mature technology for TD etiological diagnosis, and there were also reports using macro gene second-generation sequencing technology to diagnose TD. Ot was an intracellular parasite, and the application of antibiotics doxycycline, azithromycin, chloramphenicol and clarithromycin, which could enter the cell and could achieve

DOI：10.3877/cma.j.issn.1674-1358. 2022. 05. 001

基金项目：国家自然科学基金青年科学基金资助项目（No. 82002149）；2014年度湖北省教育厅科学研究计划（No. Q20142106）；2021年十堰市科学技术研究与攻关项目（No. 2021K65）；2022年十堰市科技局引导性科研项目（No. 22Y78）；2022年湖北医药学院研究生科技创新项目（No. 2022HBUMY066）

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remarkable curative effect.

【**Key words**】Tsutsugamushi disease; Children; Clinical characteristics; Diagnosis; Differential diagnosis; Antimicrobial drugs

恙虫病（tsutsugamushi disease，TD）是由恙虫病东方体（Orientia tsutsugamsushi，Ot）感染所致的自然疫源性传染病，典型临床表现高热、焦痂、皮疹伴多器官功能损害（multiple organ dysfunction，MOD）。因TD为全身感染性疾病，当以某一个系统症状为主要表现、或以脓毒血症为主要表现、医务人员对该病临床特点和流行病学特点认知不足时，易致误诊和误治[1-2]。TD是引起急性发热的重要疾病，中国近年患病数快速增加、流行区域急剧上升（图1和2）[3-5]。通过建立TD“积分诊断量表”和学术推广，TD误诊误治得到一定的抑制[1, 6-7]。由于人群对TD普遍易感，患者年龄跨度大，儿童在生理上与成人有较大差别，临床特点与成人有较大差别，本文对儿童TD临床特点及诊治进展作一综述。

一、TD临床特征研究进展

TD是恙虫病三角地区（东亚、东南亚、澳大利亚）由恙螨传播的螨类传染病，是南亚次大陆最常见的传染病之一，WHO认定TD是东南亚再发传染病，中国是TD发病率增长最快的地区[8]。TD特征性表现为“高热、焦痂、皮疹”。但TD患儿焦痂发生率为34.6%～70.5%；皮疹发生率仅为10%～20%[9-13]。TD以非特征性临床症状和体征如头痛、呕吐、恶心、肌痛、癫痫发作、腹痛、咳嗽、呼吸困难、淋巴结肿大、关节痛、肝脾肿大、面部浮肿、脸色苍白、肝肿大、脾肿大、低血压、水肿、少尿、脑膜体征、结膜炎等就诊为误诊误治发生率高的原因。TD患儿神经系统感染如脑炎、脑膜炎发生率高，血小板（platelet，PLT）减少、贫血和心肌炎发生率高[14-20]，肾脏损害发生率较低，高热患儿多系统受累应怀疑TD。南亚地区TD病死率为4.8%～12.2%，原因是多器官功能衰竭（multiple system organ failure，MSOF）、急性呼吸窘迫综合征（acute respiratory distress syndrome，ARDS）、嗜血细胞综合征（haemophilus syndrome，HPS）。目前国内尚无儿童TD病死率的相关数据。

1. 神经系统表现：TD神经系统病变可以为中枢性或周围性，脑膜脑炎、无菌性脑膜炎、小脑炎、颅神经麻痹、横贯性脊髓炎、急性播散性脑脊髓炎（acute disseminated encephalomyelitis，ADEM）、吉兰-巴雷综合征、臂神经炎、动眼神经麻痹、外展神经麻痹、舌咽神经麻痹、迷走神经麻痹、感音神经性耳聋等发生率达7.4%～34.4%。头痛、恶心、呕吐是TD患儿发生中枢神经系统感染的重要预测因素，可有脑膜刺激征、视乳头水肿、癫痫以及其他神经受损的症状和体征。脑脊液检测常显示轻度蛋白升高、细胞数轻微升高（以淋巴细胞为主）、葡萄糖含量基本正常。天门冬氨酸氨基转移酶（aspartate amino transferase，

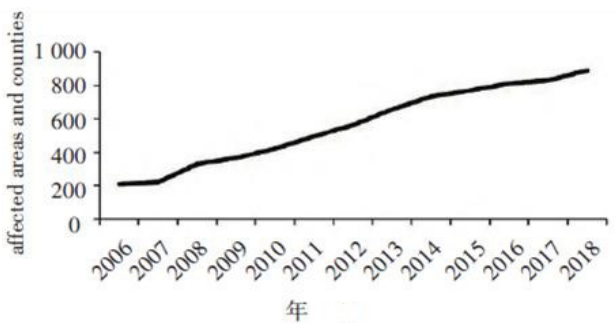

图1 我国2006至2018年TD发病县区数

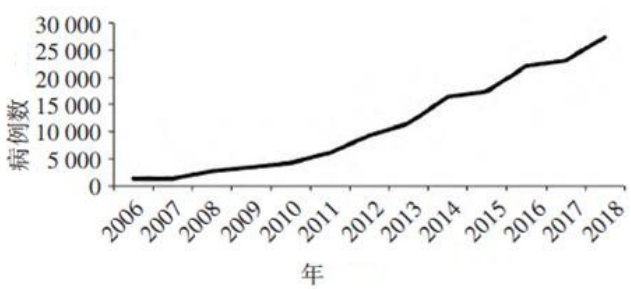

图2 我国2006至2018年TD发病例数化

AST）升高2倍以上提示神经系统感染；TD相关脑出血、脑血栓形成等神经病变可能遗留后遗症[21-30]。导致神经系统病变的原因是由于Ot侵入血管内皮细胞（endothelial cell，EC）和血管内膜引起血管炎和血管周围炎、淋巴细胞侵润，病变可进展为脑出血、脑血栓形成、脑炎以及脑膜脑炎等。

2. 消化系统损伤：儿童TD消化系统症状、体征多种多样如呕吐、腹痛、腹胀、肝脏肿大、脾脏肿大等。肝脏肿大、脾脏肿大、AST、丙氨酸氨基转移酶（alanine aminotransferase，ALT）在TD诊治和预后判断中具有重要意义，呕吐、腹痛、腹胀不具有特异性。国内文献报道TD患儿AST、ALT水平升高发生率达77.0%～96.7%[31]，但尚无肝脏肿大、脾脏肿大的发生率相关数据。TD在东南亚发病率高，有多篇关于TD患儿AST、ALT、肝脏肿大、脾脏肿大、肝脾肿大的文献研究。肝脏肿大发生率为29%～70%，脾肿大发生率为38.7%～70.0%，肝脾肿大发生率为32.2%～56.0%。AST升高发生率为36.9%～84.0%，ALT升高发生率为51%～77%[11, 15-17, 32-37]。肝脏损害的原因与Ot损害肝脏血管EC和血管内膜，引起肝血管炎和血管周围炎，导致肝细胞损害所致。临床研究发现，AST升高不仅在TD患者中常见，而且还是TD发生严重器官损伤的预警指标：AST升高3倍以上且PLT减少的患者发生并发症的风险增加[12]，AST升高2.5倍以上发生脑膜脑炎的风险增加[25]，AST升高和低蛋白血症是预测发生急性肾损伤（acute kidney injury，AKI）的有效指标[38]。

3. 血液系统损伤：血常规在成人TD临床诊治中具有重要意义，表现为白细胞（white blood cell，WBC）正常或下降，嗜酸性粒细胞（eosinophilic granulocyte，EOS）下降[1-2, 6-7]、甚至降为“0”等成人TD特征性改变，但在TD患儿未见报道。对PLT在儿童TD的临床表现研究较多，20.0%～72.6%患儿发生血小板减少[15-16, 30, 34-37, 39]，严重PLT减少症发生率约为22.4%。AST升高3倍以上和PLT减少症（＜ 10万/ml）具有发生并发症的风险[12]。PLT下降与感染和免疫介导共同作用导致[40]。AST升高和低白蛋白血症可预测AKI。

4. 心血管系统损伤：心肌炎是TD患儿常见心脏损害之一[14]，处理不当可能导致患儿死亡、遗留心血管后遗症。心肌炎发生率文献报道差异较大，为7.0%～72.4%[17, 36]，有全心心肌炎报道[41]，全心炎易导致循环衰竭，病情凶险。TD患儿高休克发生率可能与由心肌炎、脓毒血症、MSOF导致，发生休克时要仔细寻找病因，针对病因和休克治疗。

5. 呼吸系统损伤：TD患儿呼吸系统症状发生率高，异常体征发生率高，易因ATDS危及生命，咳嗽发生率为35.5%～90.0%，咯痰发生率为10%～45%，呼吸急促发生率为22.4%～40.0%，肺炎发生率为14%，胸腔积液发生率为23%～40%，ARDS发生率为2.5%～12.0%。儿童急性发热伴呼吸系统病变时要注意TD，并进行相应检测[9-10, 14-15, 17, 20, 33, 36-37, 39]，以明确病因，对因治疗，控制病情，预防ARDS发生，并改善患儿预后。

5. 环境对感染的影响、特殊部位焦痂、特殊临床表现：印度学者对导致TD感染的环境因素研究发现，野外工作生活史、室内储存木柴、处理牛饲料、露天排便或树上晾衣等均为TD发病的危险因素[41-42]，在TD防控中要关注以上细节。

焦痂对TD的确诊具有重要意义，成人TD焦痂特殊部位、特殊表现已有文献总结[2]，儿童TD焦痂发现率远低于成人。文献报道1例长期高热患儿，在外耳道发现焦痂后，给予针对TD的抗菌药物，病情得到控制，经病原体检测确定为TD[29]。肾功能异常为TD常见的实验室检查异常，AKI发生率高达18.7%～30.0%[38, 43]、儿童AKI发生率为3.7%，但有症状者少见、需透析治疗的病例少见。文献报道[44] 1例TD患儿治疗过程中发生水肿，后经肾组织病理学确定为TD致AKI成为患儿“局灶节段性肾小球硬化（focal segmental glomerulosclerosis，FSGS）”发病诱因，提示儿童TD发生肾功能异常一方面要注意TD所造成AKI的诊治，另一方面要注意进行肾脏原发疾病的筛查。焦痂缺失，临床表现特殊的TD患者更需引起临床注意，注意排查。文献报道1例高热、小关节多发性关节炎、肝脾肿大患儿，病原学诊断确定为TD，病原学治疗达到治愈的病例[45]。因此，在TD流行区持续高热患者不管有无焦痂均应警惕TD，仔细寻找病原学诊断证据。从感染和免疫角度看，关节炎发生与Ot感染后免疫反应有关，直接感染可能性不大，应该引起临床重视，故特殊临床表现的识别对TD科学诊治具有重要意义。

6. ARDS、MSOF和HPS等致死并发症：TD患儿病死率报道差距较大，为0.8%～12.2%，可能与病情严重程度、就诊时间、医疗水平等有关。死亡原因包括MSOF、HPS或称噬血细胞性淋巴组织细胞增多症（hemophagocytic lymphohistiocytosis，HLH）以及ARDS等并发症[11-12, 33, 36, 38-39, 43, 46-47]。早诊断，及时使用有效的抗菌药物行病原学治疗，及时处理器官功能损伤是防止发生致死并发症的关键。

二、TD与发热伴血小板减少综合征（severe fever with thrombocytopenia syndrome，SFTS）、登革热、伤寒、钩端螺旋体病、流行性出血热和黑热病的鉴别

文献认为TD需要与登革热、斑疹伤寒、伤寒、钩端螺旋体病、流行性出血热和皮肤炭疽相鉴别[48]。TD和SFTS、黑热病临床特点更为相似[2, 49-50]。SFTS、登革热致病微生物为病毒，钩端螺旋体病致病微生物为螺旋体，伤寒致病微生物为伤寒杆菌，皮肤炭疽致病微生物为炭疽芽孢杆菌，黑热病致病微生物为原虫。由于疫区扩大和交通便利导致的输入性感染，要注意鉴别诊断和重叠感染问题。流行性出血热典型“三红三热”特点，常有少尿、无尿，WBC

升高；钩端螺旋体病腓肠肌疼痛；皮肤炭疽病变位于外露部位，病灶周围红肿、水泡，中度发热或无发热；提高警惕，及时病原学检查，鉴别并不困难。登革热、斑疹伤寒、伤寒、SFTS、黑热病高热、肝脾肿大、WBC下降、MOD相似。一是流行病学史在鉴别诊断中具有重要作用，如黑热病有特殊疫区逗留和生活史，斑疹伤寒发病于冬春季，与TD不同。二是仔细寻找TD焦痂、皮疹，伤寒玫瑰疹、胃肠道（腹部）症状，SFTS的瘀点。三是常规实验室检查TD患者EOS常下降、甚至降为“0”；伤寒患者EOS下降、但TD更为显著；TD患者肝功能、肾功能损伤常无症状性，而SFTS、登革热患者肝功能、肾功能损伤临床表现较重；在TD诊断和鉴别诊断中，应用TD“积分诊断量表”具有重要价值[7-8]。四是病原学在病因诊断中具有定性作用，在临床诊断和鉴别诊断的基础上，病原学诊断极为重要。

三、病原学诊断技术研究进展

儿童TD致残、致死并发症发生率均较高，诊断延迟导致治疗延误是其重要原因[39]。早诊断、早治疗可有效降低致死、致残率，降低抗菌药物的滥用[51]。但中国11年持续研究证实，TD病原学确诊率仅为4.7%，乡镇卫生院确诊率远低于三级医院；自2006年至2016年实验室确诊率持续下降[52]，主要原因是用于诊断TD的外斐实验（Weil-Felix test，W-F）阳性率太低，且为回顾性诊断[1-2, 7-8, 53]。近几年运用医学进展，在发病的不同时间点PCR法检测血液Ot，PCR法检测焦痂Ot，酶联免疫吸附试验（enzyme linked immunosorbent assay，ELISA）检测血液Ot抗体IgM，可提高TD病原学诊断的敏感性和特异性[2, 8, 54-56]。Ot抗体检查方法包括ELISA、免疫荧光试验（immunofluorescence assay，IFA）、免疫层析快速诊断试验（immunochromatographic rapid diagnostic test，RDT），Ot病原体检查有常规聚合酶链反应（conventional polymerase chain reaction，cPCR）、定量聚合酶链反应（quantitative polymerase chain reaction，qPCR）和环介导等温扩增（loop-mediated isothermal amplification assay，LAMP），研究发现，qPCR为病原学诊断的首选方法，特别是病程少于7 d的患者（表1）[57]。应用宏基因二代测序技术（metagenomics next-generation sequencing，mNGS）诊断TD因价格或技术原因尚未成为常规检查方法。

四、TD治疗技术研究进展

Ot为细胞内寄生菌，尽早、足疗程应用能够进入细胞内的敏感抗菌药物为提高疗效、降低致残、致死率的主要措施，研究证实阿奇霉素、多西环素、氯霉素和克拉霉素均为可选择的抗菌药物。研究发现多西环素、阿奇霉素、氯霉素和克拉霉素疗效相似，TD患儿给予多西环素退热效果更好[34]，也有文献报道应用阿奇霉素治疗儿童TD，可降低危重病例发生率[12]。

五、小结与展望

儿童TD焦痂发生率极低，致残、致死率较高；提高临床和病原学诊断技术、早诊断、早治疗、科学诊治是提高治愈率、降低致死和致残率的关键。应用现有研究成果，实现快速诊断试纸条化，结合抗体检查为未来TD科学防治的方向之一。

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表 1 各种病原学检查方法敏感性和特异性

检查方法	敏感性（%）	特异性（%）	文献来源
ELISA法检测Ot-Ab-IgM	92.0	92.0	参考文献[62]
RDT法检测Ot-Ab-IgM	94.0	92.0	参考文献[62]
IFA法检测Ot-Ab-IgM	95.0	74.0	参考文献[62]
cPCR法检测Ot	76.0	97.0	参考文献[62]
qPCR法检测Ot	97.0	97.0	参考文献[62]
LAMP法检测Ot	91.7	91.7	参考文献[62]
W-F试验	17.6	96.0	参考文献[58]

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（收稿日期：2022-04-16）
（本文编辑：孙荣华）

李凤霞，毛静，杨军杰，等. 儿童恙虫病临床特点及诊治研究进展[J/CD]. 中华实验和临床感染病杂志（电子版），2022,16(5):289-294.

·综述·

儿童副流感病毒感染研究进展

孟一星　邓莉

【摘要】人副流感病毒（HPIVs）是引起儿童急性上、下呼吸道感染的一种重要病毒，属于副黏病毒科，分为4个亚型（HPIV1～4），其中HPIV1、2多在秋季流行，是导致儿童喉炎的主要病原体；HPIV3于春季、秋季均可流行，可导致新生儿及婴儿毛细支气管炎、肺炎；HPIV4感染多症状轻微，占比较低，相关数据较少。在全球范围内，HPIV是引起儿童喉炎、气管支气管炎、毛细支气管炎和肺炎等急性呼吸道感染疾病的常见病原，因其感染就诊、住院人数众多，且导致免疫功能低下人群病重、病死率增加，造成了沉重的疾病负担。HPIV感染的确诊依赖病原学检测，其中核酸检测灵敏度、特异度高，目前在临床应用范围越来越广。虽然目前尚无针对该病毒的特效药物，但重组神经氨酸酶融合蛋白DAS181，以及神经氨酸酶抑制剂BCX2798和BCX2855的相关研究不断进展。另外，针对HPIV的多种疫苗目前已进入了临床试验阶段。本综述总结HPIV感染的病毒学特征、流行病学特征、临床表现、诊断及治疗，以及疫苗方面的相关内容及研究进展，以供临床医师参考。

【关键词】人副流感病毒；儿科

Research progress on human parainfluenza viruses infection in children

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【**Abstract**】Human parainfluenza viruses (HPIVs) are important viruses which cause acute upper and lower respiratory tract infections in children. They belong to the Paramyxoviridae family and are divided into four subtypes (HPIV1-4). HPIV1 and HPIV2, which are mainly prevalent in autumn, are the main cause of laryngitis in children. HPIV3 causes epidemic in spring and autumn, often causing neonatal and infant bronchiolitis and pneumonia. Symptoms of HPIV4 infection are mostly mild, accounting for a relatively low proportion of the relevant data. Globally, HPIVs are common causes of acute respiratory tract infections in children, such as laryngitis, tracheobronchitis, bronchiolitis, pneumonia and so on. Heavy disease burden was resulted from the large numbers of outpatients and inpatients, as well as the high rates of severity and fatality among immunocompromised. The diagnosis depends on the pathogen detection, among which nupopulationcleic acid detection has high sensitivity and specificity, and is now being used more and more widely in clinical applications. Although there is no specific drug for the virus at present, studies on recombinant neuraminidase fusion protein DAS181, and neuraminidase inhibitors BCX2798 and BCX2855 are progressing. Breakthroughs on the treatment of the virus will be completed in the near future. In addition, several vaccines against HPIVs are currently in clinical trials. In this review, the virology, epidemiology, clinical manifestations, diagnosis, treatment, and vaccines of human parainfluenza viruses are summarized for clinical reference.

【**Key words**】Human parainfluenza viruses; Pediatrics

副流感病毒是人类和动物均可感染的重要病原体，是一种有包膜的单股负链RNA病毒，属副黏病毒科，与正黏病毒科的流感病毒抗原性、生物学特性均不同。人副流感病毒（human parainfluenza viruses，HPIVs）可分为4种血清型，即HPIVl、HPIV2、HPIV3和HPIV4，其中4型又可分为HPIV4a和HPIV4b两个亚型。虽然各型病毒在结构上相似，但其流行病学特点和临床特征均存在差异。HPIVs是引起儿童急性呼吸道感染的主要病毒之一，可造成沉重的疾病负担。本文就HPIVs的病毒学、流行病学、临床表现、诊

DOI：DOI：10.3877/cma.j.issn.1674-1358. 2022. 05. 002

基金项目：北京市医院管理中心儿科学协同发展中心专项（No. XTCX201822）

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