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# 血行播散型结核的临床研究进展

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## 摘　要

**血行播散型结核作为一种罕见的结核病，重症死亡率高。患者的临床表现不典型，传统的血培养耗时长、敏感性低，常导致诊断和治疗的延误。mMGS (metagenomic next-generation sequencing)作为一种新兴的微生物检测手段，已经越来越多被用于结核病的诊断。本文对血行播散型结核的临床症状、实验室及影像学检查、病理学特点、发病机制、诊断方法、治疗方案进行回顾，分析了mMGS在血行播散型结核中的应用价值，为该病在临床实践中的早期识别和诊断提供方向。**

## 关键词

**血行播散型结核，结核病，宏基因组二代测序，诊断**

# Clinical Research Progress on Hematogenous Disseminated Tuberculosis

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## Abstract

**Hematogenous disseminated tuberculosis is a rare form of tuberculosis with a high mortality rate. The clinical manifestations of the patients are not typical, and the traditional blood culture is time-consuming and low sensitivity, which often leads to the delay of diagnosis and treatment.**

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**mMGS (metagenomic next-generation sequencing), as an emerging means of microbial detection, has been increasingly used for the diagnosis of tuberculosis. In this paper, the clinical symptom, laboratory and imaging examinations, pathological features, pathogenesis, diagnostic methods and treatment of hematogenous disseminated tuberculosis were reviewed, and the application value of mMGS in hematogenous disseminated tuberculosis was analyzed, providing directions for the early recognition and diagnosis of this disease in clinical practice.**

## Keywords

**Hematogenous Disseminated Tuberculosis, Tuberculosis, mNGS, Diagnosis**



## 1. 引言

结核作为一种常见的传染性疾病，其病原体结核分枝杆菌可以通过呼吸道、消化道、皮肤等途径侵入人体，造成肺内或胸膜、脑膜、淋巴结等肺外部位的感染[1]。结核分枝杆菌可通过血液或淋巴液进行传播，当结核菌从血液中被分离或来自单个患者的两个或多个不连续的器官时，结核被认为是播散性的[2] [3]。血行播散型结核是结核菌在血液中播散引起的一种血流感染，可以由结核原发感染播散所致，也可以通过潜伏病灶再激活、播散所致[4]。播散性结核占所有结核病病例的 1%~5%，常见于人类免疫缺陷病毒(Human Immunodeficiency Virus, HIV)感染患者[5] [6]，部分可见于因恶性肿瘤、血液系统疾病、免疫抑制药物使用等因素导致免疫下降的患者，很少出现在免疫功能正常的个体中[7] [8] [9]。血行播散型结核作为播散性结核的一员，约占结核病的 1%~2% [4]，但这一数据因为诊断受限存在被低估的可能[10] [11]，因此其真实患病率尚不十分清楚。血行播散型结核的重症率及死亡率高，患者的中位生存期很短[12]，半数病人在研究入组后 36 天内死亡[13]。早期识别及治疗对于增加生存者的比例非常重要[14]。然而，血行播散型结核的临床表现缺乏特异性，加上传统的诊断金标准——血培养耗时长、阳性率低[15]，常常导致疾病的诊断及治疗延误，患者预后不佳[11]，因此急需引入满足临床快速诊断要求的新型检测方法。目前，针对血行播散型结核尚缺乏比较全面的概述文章，结核相关指南也只是提到了播散性结核，并未直接针对结核的血流感染展开详细论述。本文拟对近年来血行播散型结核的研究进展进行综述，以期加强对血行播散型结核的疾病认知，寻找切实可行的诊断措施，为帮助临床医生在实践工作中早期识别、诊断结核菌的血流感染并及时开展针对性治疗作出指引。

## 2. 血行播散型结核的临床表现

### 2.1. 症状

播散性结核可累及全身各脏器，其临床表现主要因受累器官系统的不同而多样，也与患者的基础疾病、免疫状态、营养状态等因素相关。疲倦、厌食、体重减轻和咳嗽是常常出现的症状[16]。在 HIV 感染者中，发热和咳嗽更为常见[17]。呼吸道症状的多见可能与肺部最常受累有关[18]。但当其他脏器受累，没有肺部症状、首发表现为非特异性肺外症状时，诊断常较为困难[19]。有研究表明，持续 ＞1 个月的慢性咳嗽和发热、体重减轻 ＞10%、淋巴结肿大和 HIV 感染史有助于识别播散性结核病患者[12] [20] [21]。

### 2.2. 实验室检查

在播散性结核患者中，CD4+T 淋巴细胞计数降低是常见的，中位计数约为 100~200 个细胞/μL，较低的计数水平已被证明为疾病预测因子和死亡预测因子[13]。部分患者可出现低蛋白血症[3]。贫血非常普遍，尤其是在重症患者中[22]。在极少的情况下，患者可能出现全血细胞减少[23]。炎症指标方面，C反应蛋白的明显升高和降钙素原超过临界值(0.5 ng/mL)在部分患者中被观测到，且其升高水平被发现可能与疾病的严重程度存在关联[24] [25]。

### 2.3. 影像学检查

胸部影像学检查提示粟粒样结节是播散性结核累及肺部的一种常见表现，在疾病的早期发现中具有重要的提示作用。经典的粟粒样改变见于 85%~90%的病例，但可能与结节病、尘肺、肺癌转移、支气管肺泡癌的表现相似[26] [27]，因此不具有特异性。对于肺外的器官，影像学检查可以提示感染部位及器官受累的程度，对于诊断播散性结核具有一定的辅助作用。临床实践中，可结合患者的影像学结果选择合适的部位取样进行病原学或组织学检测以明确诊断。

### 2.4. 病理学表现

当结核分枝杆菌急性大量播散入血，脾脏、肝脏、肺、骨髓等血流量大的器官可出现粟粒性结节改变。在大体检查中表现为大小均匀的点状、灰色至红褐色的圆形病变[28]。脉络膜作为兼具高血流量、氧含量及低流速的血管被膜，可为结核菌留滞提供理想环境。脉络膜结节是一种边缘模糊的灰黄色小结节病变，已被证明是粟粒性结核的特征性结节。脉络膜结节主要位于后极，可发生在单眼或双眼，结节可以是单个或多个，大多数病灶少于 5 个[29]。但在临床实践中，结核病人的眼科检查常被忽略，应在易感人群中检测脉络膜结节以作为播散性结核病的眼科证据[30]。

## 3. 血行播散型结核的发病机制

关于播散性结核的机制，有两种可以独立也可以并存的方式。一种是结核菌通过侵蚀肺泡细胞上皮扩散到肺静脉，进而到达心脏并进入体循环，一种是结核菌通过攻击肺泡内壁细胞进入淋巴结，通过淋巴管大量进入全身静脉血[31]。入血的结核分枝杆菌沿血流播散并栓塞至各个器官的血管床，从而激活多个病灶[4]。结核病作为传染性疾病的同时，也是一种免疫性疾病。从免疫反应的角度来看，细胞因子在结核感染免疫应答的过程中发挥着重要作用。肿瘤坏死因子 $\alpha$ 是机体控制结核感染的枢纽因子，不仅可以通过直接激活和刺激 T 细胞释放 $\gamma$-干扰素间接激活巨噬细胞，加强对结核菌的杀灭，还能与其诱导释放的 $\gamma$-干扰素发挥协同作用，促进保护性肉芽肿的形成以封闭结核感染病灶[32]。但另一方面，肿瘤坏死因子 $\alpha$ 具有双重生物学效应，过量的分泌及释放会破坏机体的免疫平衡，引发组织病理损伤和不良全身效应，甚至导致病情恶化。为了抑制过度的炎症反应，机体会分泌白细胞介素 10、白细胞介素 4 和转化生长因子 $\beta$ 等细胞因子下调抗结核免疫，但如果这一调节过程失衡，细胞因子过量产生，则会反过来抑制感染的控制，导致结核的广泛播散[33]。

## 4. 血行播散型结核的诊断

### 4.1. 诊断标准

播散性结核病的临床诊断，满足以下任何一种情况即可[5] [9] [31] [34]：

(1) 从血液、骨髓、肝活检样本或至少两个非相邻器官中分离出结核分枝杆菌或结核分子生物学检测阳性；(2) 在一个器官中分离结核分枝杆菌，并在骨髓、肝活检样品或另一个不相邻部位中对干酪样肉芽

肿进行组织学确认；(3) 一个器官干酪样肉芽肿的组织病理学鉴定伴有粟粒性肺结核的放射学发现。基于此，血行播散型结核的诊断，满足从血液样本中分离出结核分枝杆菌或结核分子生物学检测阳性即可。

### 4.2. 传统病原学检测

在过去的几十年，血行播散型结核的诊断主要依赖的是金标准血培养，但其敏感性不高且培养时间较长的局限性常导致诊断延迟，进而加剧疾病的重症化，因此无法满足血行播散型结核快速诊断的临床需求[15]。虽然有研究表明播散性结核的菌血症是持续的[17]，但血培养的阳性率不高，即便通过持续的检测，部分患者仍无法得到识别[14]。在培养阳性的患者中，结核分枝杆菌阳性的中位时间超过 3 周[35]。血行播散型结核的早期死亡率高，明确诊断的时间可能长于患者的在院生存时间[11]，这就导致血培养的诊断价值有限。既往有研究表明为提高阳性率可将单次取血 20 ml 作为血培养检测结核分枝杆菌的最佳剂量[17]，但却没有得到后续研究的进一步验证。此外，由于播散性结核常累及肺部[18]，痰涂片找抗酸杆菌和痰培养对辅助明确结核诊断也具有一定作用。但涂片灵敏度低，常出现假阴性结果，而传统培养非常耗时，大约需要 4~8 周[36]。

### 4.3. 新型检测手段

#### 4.3.1. Xpert

结核分枝杆菌具有厚壁、生长周期长的特性，常规的病原学检测效果有限[37]。分子生物学技术在结核病诊断中的应用已经较为常见。聚合酶链式反应作为分子生物技术的基础，能在短时间内将模板 DNA 扩增至足够数量并进行结构分析，可临床上快速诊断病原微生物感染[38]。Xpert MTB/RIF，一种自动的半嵌套实时聚合酶链反应测定，基于一个独立的试剂盒系统，既可以避免交叉污染，又能大大减少人工技术时间[39]，可在 2 小时内同时检测结核分枝杆菌和利福平耐药性[40]。目前，Xpert MTB/RIF 和在此基础上开发的 Xpert MTB/RIF Ultra 已经被世卫组织推荐用于活动性结核病的诊断[41]，也被认可用于在 HIV 阳性患者中诊断结核分枝杆菌的血流感染[42]。但对于 HIV 阴性患者的血液样本和少菌样本，Xpert 表现却出较低的敏感性[43] [44]。

#### 4.3.2. mNGS

mNGS 作为一种不依赖培养的新兴高通量测序技术，能够在短时间内同时对临床样本中的核酸直接进行无偏倚检测，并通过序列对比确定微生物的组成，可检测的种类广泛、覆盖面广[45]，在诊断罕见感染和混合感染方面具有显著优势[46] [47]。mNGS 在结核病的诊断中，对肺内样本的敏感性为 62%~87.5%，对肺外样本的敏感性为 47.4%~60%，对各种样本的特异性接近 100% [48]。有研究显示 mNGS 诊断结核病的敏感性高于传统检测方法，且不劣于 Xpert MTB/RIF，具有出色的诊断性能，二者的联合使用甚至可以显著改善结核分枝杆菌和其他病原体的病因诊断[49]。mNGS 检测通常需要 2~3 天，部分实验室甚至可以缩短至 1 天[50]。比起传统的病原学方法，mNGS 能够大大缩短时间的同时保证全面、准确的检测，有助于临床医生快速诊断疾病及指导针对性用药。目前，mNGS 已经越来越多地被用于肺结核、结核性胸膜炎、结核性脑膜炎等单器官结核病的诊断[51] [52] [53]，在播散性结核中的应用也已有研究报道[54] [55]。比如，一例免疫功能正常的男性，无任何症状，检查发现肺、肝、脊柱、纵隔和前列腺病灶，最初考虑恶性肿瘤或转移性肿瘤，但最终通过 mNGS 明确了播散性结核的诊断[48]。mNGS 与传统病原学检测方法相比具有显著优势，有助于早期快速锁定病原体，可能在血行播散型结核的诊断中发挥重要作用。但值得注意的是，因为 mNGS 全覆盖检测的特性，存在微生物定植或被污染的标本不太适合采用 mNGS 进行耐药性检测[56]，与 Xpert 联合使用可能是一个不错的选择[49]。此外，mNGS 作为一种新兴的微生物检测技术，无法在医疗水平落后的地区实施。从经济成本的

角度来看，mNGS 的检测费用也相对较高，因此不会在疑诊结核的病例中常规开展，是否送检还需根据患者的具体情况进行综合考量。

关于结核菌 mNGS 结果的判读，考虑到结核分枝杆菌为胞内菌，破壁相对困难，DNA 提取不易，且并非实验室常见背景菌，发生污染的可能性小，如果满足：(1) 其属是标准化特定读取数(SDSMRN)最高的前 20 名，(2) 在其属中排名第一，以及(3) 其 SDSMRN 为>1 [57]，即判定为检测到结核分枝杆菌。对于结核分枝杆菌这种对临床具有重要意义且检测较难的病原菌，即使只检出 1 条特异性序列，也应该高度怀疑它的致病性[58]。此外，mNGS 阴性对排除感染有较好的预测价值，但对于结核菌这种核酸提取难度大的微生物，阴性的结果也不能完全除外结核感染的可能[59]。

## 5. 血行播散型结核的治疗

播散性结核的死亡率高，确诊后需尽早开启抗结核治疗。甚至有共识声明主张：

在结核病流行国家，因 HIV 感染和长期发热、咳嗽住院的患者应在等待血培养和痰培养结果的同时，进行播散性结核的经验性治疗[60]。然而，在标准抗结核方案的基础上，播散性结核患者的最佳治疗时长尚未达成共识。美国胸科学会、美国疾病控制与预防中心、美国传染病学会和英国胸科学会的指南建议对无脑膜受累患者进行 6 个月治疗，包括异烟肼、利福平、吡嗪酰胺、乙胺丁醇或链霉素治疗的 2 个月强化期，以及异烟肼、利福平治疗的 4 个月持续期[61] [62]。针对存在结核性脑膜炎的患者，美国儿科学会传染病委员建议应用异烟肼、利福平、吡嗪酰胺、乙硫异烟胺或氨基糖苷类抗生素进行 2 个月的强化治疗及应用异烟肼、利福平进行 7~10 个月的持续治疗[63]。除抗结核治疗外，有研究提到皮质类固醇可能对伴有结核性脑膜炎、大量心包或胸腔积液的患者有益[4]，但目前尚未出现皮质类固醇治疗播散性结核疗效的针对性研究，还需要更多临床证据以进一步评估。

## 6. 总结与展望

血行播散型结核的临床表现不典型。HIV 感染、发热、咳嗽、体重减轻可能对疾病存在提示。部分患者可出现高炎症、低免疫水平指标，影像学、病理学提示粟粒样结节。传统的血培养无法满足临床快速诊断的需求。分子生物学手段 Xpert 可用于诊断 HIV 阳性患者的结核分枝杆菌血流感染，但对 HIV 阴性患者敏感性较低。mNGS 可快速进行全面、无偏倚的微生物检测，对明确结核感染具有独特优势，有望在血行播散型结核的诊断中发挥重要作用。血行播散型结核的治疗尚未完全达成共识，可根据指南在标准抗结核方案基础上根据患者情况进行调整。目前血行播散型结核的相关研究主要涉及 HIV 感染患者，HIV 阴性患者的结核血流感染仍存在较大空白，未来还需要开展更多相关研究进一步探寻。

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