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五种传染病的即时检测研究进展

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摘　要

新型冠状病毒感染大流行，给全球经济造成巨大的损失。发展即时快速的病原体检测方法，对传染病的预防及治疗具有非常重要的意义。科技水平的提高以及人民对健康的重视，极大推动即时检测(POCT)技术的发展。本文综述了近年来POCT技术应用于疟疾、HBV、艾滋病、埃博拉病毒、SARS-CoV-2五种疾病的进展，突出利用等温扩增技术、CRISPR/Cas技术、侧向流动分析技术等多种技术的联合使用在不同传染病的检测优势。可穿戴设备、人工智能的引入使得POCT诊断更为方便。

关键词

传染病，即时检测，CRISPR/Cas技术，等温扩增，侧向流动分析技术

Research Progress in the Point-of-Care Testing of Five Infectious Diseases

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Abstract

The global economic impact caused by the ongoing SARS-CoV-2 pandemic emphasizes the urgent need for the development of rapid and real-time pathogen detection methods. Such advancements are crucial for the prevention and treatment of infectious diseases. The continuous improvement of technology, coupled with increased public awareness of health, has greatly accelerated the progress of Point-of-Care Testing (POCT) techniques. This review article provides an overview of the recent

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advancements in POCT technology applied to five diseases: malaria, hepatitis B, HIV/AIDS, Ebola virus, and SARS-CoV-2. The article highlights the advantages of combining various techniques such as isothermal amplification, CRISPR/Cas technology, and lateral flow analysis for the detection of different infectious diseases. Furthermore, the integration of wearable devices and artificial intelligence has facilitated the convenience of POCT diagnostics.

Keywords

Infectious Diseases, Point-of-Care Testing, CRISPR/Cas Technology, Isothermal Amplification, Lateral Flow Technology

1. 引言

传染病是机体感染病原体(如细菌、病毒、真菌或寄生虫等)导致机体免疫反应和病理损伤，引发各种症状和并发症，严重情况下会危及生命。2019 年底爆发的新型冠状病毒感染大流行对全球的公共卫生安全造成了重大威胁，截至 2022 年 5 月导致全球 600 多万人死亡[1]。快速、准确地检测病原体可以有效隔离感染患者，指导患者合理用药，避免疾病的传播。目前传染病的诊断方法包括免疫学分析、逆转录实时荧光定量 PCR 技术(RT-qPCR)和基因测序技术等。然而，这些技术都需要将样本运输到临床实验室集中检测。较长时间的运输都可能会影响检测结果。抗原－抗体检测结果的灵敏度和准确度不够高。核酸检测和基因测序较为复杂，需要专业的技术人员、昂贵的仪器和试剂耗材和较长时间的操作过程。上述这些诊断方法不足以在传染病大流行爆发期间，尤其是在医疗资源相对贫乏的地区，实现快速、准确的现场诊断。

近年来，即时检测(point-of-care testing, POCT)技术为传染病的检测提供快速、准确、灵敏、廉价、可行的诊断结果，为患者随时随地检测，是预防疾病传播、指导有效治疗最有效的方法之一[2]-[4]。世界卫生组织(WHO)推荐的 POCT 诊断提出的 ASSURED 标准应具备价格合理、敏感性高、特异性强、易于使用、快速、无设备以及可供最终用户使用等特性[5]。这项标准为开发实用的 POCT 设备提供了指导。

本文简单介绍了 POCT 常用的检测技术，以疟疾、HBV、艾滋病、埃博拉病毒、SARS-CoV-2 为例，综述了近年来 POCT 在诊断 5 种传染病方面的研究进展，为 POCT 在传染病进一步检测提供指南。

2. 传染病 POCT 的常见技术

2.1. 等温核酸扩增技术

等温核酸扩增技术是 POCT 诊断平台常用的技术。该技术无需仪器，简化了扩增程序，提高检测灵敏度。目前，POCT 诊断平台上实现的各种等温扩增技术主要有环介导等温扩增(loop-mediated isothermal amplification, LAMP) [6]-[8]、重组酶聚合酶扩增(recombinase polymerase amplification, RPA) [9] [10]、滚环扩增(rolling circle amplification, RCA) [11] [12]、切割酶恒温扩增(nicking enzyme-assisted reaction, NEAR) [13] [14]等。其中以 LAMP 和 RPA 最为常用。LAMP 的独特优势是扩增产物可以通过多种方式进行检测，包括比色法、实时荧光法和浊度法，并且可以实现结果的可视化。RPA 的反应温度低于 LAMP，具有反应温度低、引物设计简单、扩增效率高、灵敏度高、易于与电化学生物传感器等其他技术相结合的优点，

适合于各种场景的 POCT。

2.2. CRISPR/Cas 技术

CRISPR/Cas 技术是一种常用的基因编辑工具，由成簇规则间隔的短回文重复序列(Clustered Regularly Interspaced Short Palindromic Repeats, CRISPR)和 CRISPR 相关蛋白(CRISPR-associated proteins, Cas)组成。因其识别和切割特定 DNA 或 RNA 序列，可用于核酸检测领域。目前，该技术在分子诊断中取得重大进展[15]-[17]。其中基于 Cas13a 或 Cas12a 开发的超灵敏新平台 SHERLOCK (specific highsensitivity enzymatic reporter unlocking) [18] [19]和 DETECTR (DNA endonuclease-targeted CRISPR trans reporter) [20]为感染病的诊断如寨卡病毒、巨细胞病毒、BK 病毒和疟原虫等[18] [21] [22]提供新的契机。在 POCT 诊断中，CRISPR/Cas 技术往往与等温扩增技术[23] [24]、侧向流动分析技术[19] [21] [22] [25]等结合使用使检测平台更加灵敏高效。

2.3. 侧向流动分析技术

在 POCT 平台中，另一项值得关注的技术是基于纸张的侧向流动分析技术(Lateral flow assays, LFA)。LFA 技术已被广泛用于检测各种分析物，包括蛋白质[26] [27]、核酸[28] [29]、感染性病毒[30] [31]等。它具有检测快速、检测成本低、在几分钟内通过肉眼得到结果等优点。纳米金颗粒(AuNPs)是传统 LFA 中最常用的抗体标记材料。但它在定量检测灵敏度存在局限性。近年来，荧光微球[32]、量子点[33]、铕纳米颗粒[34]、碳纳米颗粒[35]、上转换纳米颗粒[36]和等离子体纳米颗粒[37]、表面增强拉曼散射(SERS) [38]等新型标记材料使检测性能大幅度提升。此外，开发多重侧向流动分析可以实现多个分析物的同时检测[39]。

3. POCT 在 5 种传染病的研究进展

3.1. POCT 在疟疾诊断中的研究进展

疟疾是一种急性发热性疾病，主要通过感染疟原虫的蚊子叮咬传播给人类。根据世界卫生组织推荐的《疟疾病例管理：操作手册》，早期即时诊断和青蒿素联合治疗(ACT)能减少疟疾耐药性和抑制疟疾传播[40]。

在抗原检测中，恶性疟原虫乳酸脱氢酶(PfLDH)和恶性疟原虫富组氨酸蛋白 2 (PfHRP2)是目前疟疾各项 POCT 中占主导地位的标志物[41] [42]。LFA 技术结合其他技术用于疟疾种类的检测，并且检测灵敏度较高[43]。Li 等开发一种新型微流控免疫分析平台快速定量全血中 PfHRP2 [44]。该平台该装置通过两种诊断模式，即低浓度(100 pg/mL)和高浓度(1000 ng/mL)下检测 PfHRP2，使其应用于多个场景，并且检测结果与超灵敏 ELISA 结果基本一致，在 15 分钟可完成检测。但是该平台不能对多种疟疾同时检测。为此，Kim 等开发一种基于颜色编码的双色多路免疫分析方法，允许在单个检测线上识别疟疾种类，并且可同时检测 PfHRP2 和 PfLDH [45]。其中检测线的颜色和颜色强度分别表示疟疾种类和抗原浓度水平。

LFA 技术跟核酸扩增技术相结合用于疟疾的诊断。Cooper 团队开发一种基于纸张的微流控装置，用于疟疾种类特异性诊断[46]。该装置包含样本的处理、LAMP 等温扩增和基于侧向流动的结果检测。虽然该设备可在50分钟得到结果，但检测结果仍具有一定主观性，也不能及时反馈给中央实验室。为此，Cooper团队进一步研发一种新平台，用于疟疾的 DNA 诊断[47]。该装置由移动加热器，智能手机 APP、基于纸张的微流控芯片技术以及后端引擎组成。该平台利用提供决策支持的深度学习算法，客观收集结果，并运用区块链技术将数据传到中心实验室，以实现远程诊断。

目前，疟疾的物种特异性检测主要是区分恶性疟原虫和非恶性疟原虫，而非恶性疟原虫的特异性诊断仍然是疟疾诊断方面的一个弱势。为此，Lai 等开发一种多重 LAMP 反应系统，并结合自制的多重 LFA 同时检测恶性疟原虫、间日疟原虫、卵形疟原虫和诺氏疟原虫[48]。此外，Lee 等开发一种超灵敏的基于 CRISPR/Cas 的新平台 SHERLOCK 检测 4 种疟原虫[21]。临床试验表明这两种方法检测的灵敏度和特异性均达到 97%以上。

此外，无创诊断技术为无症状疟疾患者提供一个理想的平台。Garcia 等开发一种基于近红外光谱技术和机器学习算法在 10 秒通过皮肤获得疟原虫吸收峰[49]。该方法可实现大规模人群的无创筛查，并识别无症状患者。

3.2. POCT 在 HBV 诊断中的研究进展

乙型肝炎病毒(Hepatitis B virus, HBV)是一种引起乙型肝炎的病原体。尽管全球有广泛的疫苗接种计划，全球仍有 2.6 亿慢性乙肝患者，每年有 89 万人死于感染 HBV 所引起的并发症[50]。世卫组织计划提出到 2030 年使 HBV 的感染人数减少 90% [51]，这一任务仍然艰巨。

乙型肝炎表面抗原(HBsAg)是 HBV 感染后出现的第一个血清学标记物，检测的窗口期为 HBV 感染后的 38 天左右。HBsAg 诊断对于监测和治疗 HBV 感染至关重要。目前已报道多种 LFA 技术结合其他技术用于检测 HBsAg 的 POCT 诊断[52] [53]。Lin 等开发一种酶标记的电化学检测方法来检测 HBsAg [52]。该方法结合 LFA 技术和酶标记电化学生物传感器的催化性能的优点，检测限为 0.3 ng/mL。Martiskainen 等开发利用上转换纳米颗粒结合 LFA 技术检测血清中的 HBsAg，可在 30 分钟完成检测[53]。与常规 LFA 的检测线 3.2 IU/mL 相比，该方法的检测限为 0.1 Ig/mL，大大提高检测灵敏度。

乙型肝炎 e 抗原(HBeAg)是 HBV 核衣壳的分泌形式，是病毒复制的标志物。HbeAg 标志着该病毒具有高度复制能力和高度传染。Si 等基于树突状纳米颗粒复合物的信号放大系统提高 LFA 的灵敏度，应用于 HBeAg 的检测，检测限低至 9 ng/mL，比传统 LFA 相比的灵敏度高 27 倍[54]。Zhang 等构建电化学免疫传感器检测 HBeAg [55]。该方法结合辣根过氧化物酶(HRP)和金纳米颗粒提高检测灵敏度，检测限为 0.064 pg/mL。

尽管 HBsAg 对 HBV 诊断很有效，但 HBV DNA 的检测有助于为 HBV 治疗提供决策信息和监测患者治疗情况。RPA 技术和 LAMP 技术用于 HBV DNA 的检测[56] [57]。将两者技术相结合，显著提高 HBV DNA 检测的灵敏度和速度。Chen 等将重交叉位移扩增(MCDA)与基于聚合物纳米颗粒的侧流生物传感器相结合，用于检测血液样本中 HBV 的 e 基因[58]。此外，基于 CRISPR/Cas 系统的新诊断平台用于 HBV DNA 的即时诊断。Ding 等开发一种基于 CRISPR/Cas12 结合 LAMP 技术检测 HBV DNA [59]。该方法结合 LFA 技术，使荧光信号可视化。在短时间内检测到 1 个拷贝/μL 的 HBV DNA，与 qPCR 结果完全一致。Tian 等开发基于 CRISPR/Cas13a 结合 RAA 扩增技术的快速便携式 HBV DNA 检测技术，灵敏度为 101 拷贝/μL，特异性为 100%，在 1 小时内即可得到结果[60]。

在临床治疗中，HBV 感染的功能性治愈是指 HBsAg 持续性消失，完全治愈则定义为 HBV 共价闭合环状 DNA (HBV cccDNA)的根除[61] [62]。HBV cccDNA 是 HBV 检测的一种新的标志物。Zhang 等建立一种基于 CRISPR/Cas13a 的 cccDNA 新的检测方法[63]。将样本经过 RCA 和 PCR 扩增后，通过 CRISPR/Cas13 辅助荧光读数可以检测到 1 拷贝/μL cccDNA。他们使用数字 PCR、qPCR、RCA-qPCR、PCR-CRISPR 和 RCA-PCR-CRISPR 这 5 种方法分别检测 40 名 HBV 相关患者的肝组织样本，发现这些方法与 CRISPR/Cas13a 相比，有 20 份阳性样本完全未检测到 HBV cccDNA。这些结果表明基于 CRISPR/Cas13a 的检测方法对 HBV cccDNA 检测具有高度的敏感性和特异性，为抗病毒治疗 HBV 感染提供了一种很有前途的检测方法。

3.3. POCT 在艾滋病诊断中的研究进展

艾滋病(Acquired Immunodeficiency Syndrome, AIDS)是由人类免疫缺陷病毒(Human Immunodeficiency Virus, HIV)感染引起的一种严重的免疫系统疾病。全世界有 4000 多万人受到艾滋病毒的感染。艾滋病毒感染会造成机体多种免疫系统功能障碍，最终导致患者各种感染和肿瘤并发症。目前，尚无治愈艾滋病的药物，抗逆转录病毒疗法(Antiretroviral Therapy, ART)能有效抑制病毒的复制和繁殖，提高患者的生存率。

艾滋病的早期核酸诊断是启动抗逆转录病毒治疗的关键。LAMP 技术和 RPA 技术应用于 HIV 核酸的即时检测[64] [65]。Kong 等开发一种可穿戴的 RPA 设备[65]。该设备由聚二甲基硅氧烷(PDMS)制备，利用人体热量在 30 分钟内扩增 HIV-1 DNA，通过智能手机实现定量分析。这种可穿戴设备允许无限连接智能手机进行健康监测。Liu 等开发一种基于逆转录 LAMP(RT-LAMP)的集成核酸检测(NAT)设备，由微流控试剂盒和连接 USB 的小型分析仪组成，可对患者的病毒载量实时监测[66]。Li 等基于 CRISPR/Cas13a 平台结合 RT-RAA 技术检测 HIV-1 RNA，灵敏度为 1 拷贝/μL，检测限(LOD)为 112 拷贝/mL [67]。

HIV p24 抗原是 HIV 感染的早期生物学标志物，在病毒感染的第 14 天可检测到[68]。微流控芯片技术结合其他检测方法实现 HIV p24 抗原快速检测，并具有极高的灵敏度，实现多样本检测[69] [70]。然而这些装置需要接通外部电源才可完成检测，在实际操作比较麻烦。Sailapu 等构建 p24 抗原检测的自供电智能传感平台，利用电解质门控场效应晶体管和纸基生物燃料电池从样品中获得能量来解决电源问题，检测线为 1fM [71]。Chen 等通过设计一种基于比色 ELISA 的 3D 纸基微流控分析装置(3DtPADs)，利用酶促反应的纸基比色检测系统来解决外部电源的供应，检测线可达到 0.03 ng/mL [72]。

$CD4^+$细胞计数是用于监测和评估 HIV 患者的免疫状态的一个指标。Sher 等开发基于细胞裂解液电阻率量变化的方法来定量 $CD4^+$细胞[73]。Xiao 等设计一种基于荧光免疫层析系统和阻断技术相结合间接计数 $CD4^+$的方法[74]。此外，Hwang 等开发一种 ImmunoSpin 方法，基于微粒结合图像技术对 $CD4^+$细胞计数[75]。该方法既无微流控装置，也无荧光检测装置。以上方法与临床实验室流式细胞术 FCM 结果高度一致，说明在实际应用中可行。

3.4. POCT 在埃博拉病毒诊断中的研究进展

由埃博拉病毒(Ebola virus, EBOV)感染引起的埃博拉病(Ebola virus disease, EVD)，是一种具有较高致病性、传染性和致死性的人畜共患疾病[76]。患者在传染之初症状并不明显，很容易导致多系统器官衰竭和严重的出血症状，致死率很高。

可溶性糖蛋白(sGP)是埃博拉病毒的一个早期生物学标志物。使用比色－荧光－磁性纳米颗粒结合 LFA 提高检测的灵敏度[77]。Hu 等开发一种双信号可读的新型多功能纳米球(RNs@Au)，结合 LFA 技术对 EBOV 糖蛋白检测[78]。这些含有量子点和金纳米颗粒的纳米球比单量子点或金纳米颗粒具有更强的荧光和比色信号，检测结果可通过比色和荧光模式读取。这种双重模式的信号输出具有更高的灵敏度和特异性，在 20 分钟内完成。Fontes 等开发一种新型超灵敏－抗体微阵列芯片平台(EBOV D4 assay)用于检测 sGP [79]。该技术在非人灵长类动物模型中能比 PCR 技术更早检测到 EBOV 感染。这对 EBOV 的早期诊断是非常有效的。此外，Zang 等构建一种超灵敏的三维等离子体纳米生物传感器，有效识别血浆中接近 220 fg/mL 的 sGP [80]。与现有的 FDA 批准的免疫分析法相比，该传感器装置提高了超过 24 万倍的 EBOV 抗原监测的灵敏度。

核酸检测仍然是 EBOV 病毒早期诊断最有效的指标。为此，Na 等利用 RCA 技术对包括 EBOV 在内的多种病毒进行核酸扩增，在 15 分钟完成检测，满足现场检测的需求[81]。为了区分埃博拉病毒与疫区

的其他发热性疾病，Barnes 等基于 CRISPR/Cas13a 的新平台 SHERLOCK，结合 LFA 技术和荧光检测埃博拉和拉沙病毒(LASV)的 DNA [82]。该检测方法可检测到低至 10 拷贝/mL 的 DNA。并使用这种方法成功测试来自塞拉利昂和尼日利亚地区的临床样本。

3.5. POCT 在 SARS-CoV-2 诊断中的研究进展

严重急性呼吸系统综合征冠状病毒 2 型(Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2)，是 2019 年冠状病毒传染病(COVID-19)的病原体，属于冠状病毒。它会导致严重的急性呼吸系统疾病和一系列并发症[83]。该病毒具有高度传染性，目前在全球仍处于低水平传播，持续的流行给全球经济和公共医疗系统带来了沉重负担[84] [85]。

基于 CRISPR/Cas 系统的诊断新平台 SHERLOCK 和 DETECT，已广泛用于 SARS-CoV-2 的诊断[86]-[89]。Braugton 等介绍一种基于 CRISPR/Cas12 结合 LFA 技术检测 SARS-CoV-2 中 RNA 的 E 和 N 基因。该方法同时利用 RT-LAMP 对 RNA 扩增，可在 40 分钟内完成检测，并且与 qRT-PCR 检测结果具有高度一致性[86]。

随着疫情的进展，SARS-CoV-2 的基因序列不断发生突变，这为其诊断和治疗带来难题[90]。Lin 等基于 CRISPR/Cas12 结合 RAA 技术，开发一种单管基因分型检测方法[91]。他们通过设计一组能够识别目标序列中单核苷酸突变的特异性 CRISPR RNAs (crRNAs)，在 2 小时内实现对 SARS-CoV-2 突变株包括 Alpha 变异株、Beta 变异株、Delta 变异株和奥密克戎 BA.1 和 BA.2 的鉴定和检测。Helena 等基于 CRISPR 原理，开发 miSHERLOCK 平台检测 SARS-CoV-2 的变异区域[89]。该平台利用智能手机应用程序对检测结果量化分析并远程检测。

越来越多学者关注 ACE2 蛋白作为 SARS-CoV-2 的受体，并开发基于 ACE2 的生物传感器用于检测 SARS-CoV-2 及其变异体[92]-[94]。Park 等开发一种基于电化学生物传感器检测 SARS-CoV-2 的 ACE2，并采用双门场效应晶体管来提高灵敏度[95]。这种便携式电生物传感器在 20 分钟内完成检测，检测灵敏度可到达 165 拷贝/mL。

LFA 技术仍是 SARS-CoV-2 抗原检测重要手段[96]。为提高传统 LFA 的灵敏度，Guo 等利用具有介孔二氧化硅封装纳米壳结构的上转换纳米颗粒标记 LFA，通过荧光传感器检测 S 和 N 蛋白质的灵敏度可达到 1.6 ng/mL 和 2.2 ng/mL [97]。该方法通过物联网设备进行大数据分析和远程监控。纳米材料修饰会提高电化学免疫传感技术检测的灵敏度[98]。Zeng 等开发一种金纳米颗粒修饰的丝网印刷碳电极的电化学免疫分析方法，用于检测 SARS-CoV-2 的 N 蛋白[99]。该方法的检测限为 2.6 pg/mL，在 5 分钟内完成检测。

4. 小结与展望

POCT 在以上五种传染病诊断上已取得巨大的进步。基于等温扩增、CRISPR/Cas、LFA 等技术的发展使 POCT 检测设备更加便捷。而这些技术的联合使用又进一步使 POCT 检测更加快速、灵敏、准确。此外，基于智能手机的生物传感器[100]、基于纸张的诊断平台[101]、基于等离子体平台[102]等已被报道用于传染病的快速诊断，并且可以实现多种疾病和多个指标的检测。

尽管针对传染病的 POCT 检测方法和相关的 POCT 设备发展迅速，但实现快速、高灵敏度、准确的传染病 POCT 技术仍然是该领域的一大挑战。可穿戴设备、人工智能和医用物联网技术的引入使得 POCT 实现数据共享和远程实时监测。这将彻底改变医疗诊断，并及时提供个性化的医疗服务。这些方法将有助于更早识别传染病，从而有助于预防大流行疾病爆发。尽管 POCT 诊断还存在一定挑战，比如 POCT 受到人为因素和环境的影响、检测结果的定标问题、质量控制问题等。这些问题将激励更多智能 POCT 技术的发展。

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