·新型冠状病毒肺炎·综述·

新型冠状病毒与严重急性呼吸综合征冠状病毒的比较认知

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【摘要】 新型冠状病毒(SARS-CoV-2)和 SARS 冠状病毒(SARS-CoV),分别是新型冠状病毒肺炎(COVID-19)和 SARS 的病原体,均引发了国内突发公共卫生事件。此文从传播途径、发病机制,临床表现等方面比较两种病毒的不同以及总结两者的相似性,有助于对 SARS-CoV-2 本身有更加清晰的认识。回顾 SARS 诊断及治疗的前期工作,也对 COVID-19 疾病的深入研究有重大意义。

【关键词】 新型冠状病毒;肺炎;呼吸道传播;诊断和治疗
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Comparative understanding of SARS-CoV-2 and SARS-CoV

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【**Abstract**】 SARS-CoV-2 and SARS-CoV are the pathogens for COVID-19 and SARS, which cause emergency public health emergencies. By comparing the differences of the two viruses from the source of infection, pathogenesis, clinical manifestations, and summarizing the similarities between the two viruses, it is helpful to have a clearer understanding of SARS-CoV-2. The review about preliminary work of SARS diagnosis and treatment is of great significance for the in-depth study of COVID-19 caused by SARS-CoV-2.

【**Key words**】 SARS-CoV-2; Pneumonia; Respiratory transmission; Diagnosis and treatment
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冠状病毒能够感染人类和动物,引起呼吸道和肠道疾病。人类约 30%的上呼吸道疾病由冠状病毒引起[1]。比如 229E、OC43、NL63 和 HKU1 这 4 种冠状病毒普遍存在于免疫能力强的个体中,它们通常引起常见的感冒症状[2]。最近报告了一种能够引起急性肺炎疾病流行的新型冠状病毒(SARS-CoV-2),它是冠状病毒新进化的一个分支[3],由该病毒引起的肺炎疾病被 WHO 命名为新型冠状病毒肺炎(COVID-19)[4]。SARS-CoV-2 是继 SARS 冠状病毒(SARS-CoV)和中东呼吸综合征冠状病毒(MERS-CoV)之后,近 20 年来威胁全球公众健康的第三种病毒[5]。然而与 SARS 和 MERS 相比较而言,COVID-19 所导致的疾病严重程度似乎较轻[2],传播性似乎更强[6]。SARS 在全球六大洲 26 个国家传播,累计造成了 8 096 人感染和 774 人死亡(9.6%)[7]。根据 WHO 数据显示,截止到 2020 年 4 月 5 日,COVID-19 波及了全球 200 多个国家或地区,确诊感染人数达 1 133 758 人,死亡 62 784 人(5.5%)[8]。SARS-CoV-2 和 SARS-CoV 诱发的肺炎疾病,都引发了国内突发公共卫生事件。这 2 种病毒和由它们引起的疾病在流行病学和临床特征上既有相似之处,又有不同之处。我们系统地回顾和比较 SARS-CoV 和 SARS-CoV-2 在病毒传播、发病机制、临床特点,诊断和治疗方法等方面的异同点,希望对 SARS-CoV-2 病毒本身以及其引起的肺炎疾病有更加清晰的认识。

一、病毒传播

呼吸道飞沫传播和直接接触传播被认为是这种 2 病毒主要传染途径[9-13]。由于部分 SARS 患者和 COVID-19 患者的粪便中病毒呈阳性[14,15],研究人员也提出可能存在消化道传播途径。相较呼吸道病毒检出时间,粪便中病毒的阳性检出有一定的延迟性。例如,SARS-CoV-2 在 COVID-19 患者的粪便检出时间比痰液中病毒检出晚 2~5 d[16],而且康复期患者咽拭子病毒转阴,粪便中病毒阳性仍能持续 6~10 d[17]。这提示粪口传播的风险是存在的。

SARS-CoV-2 在人际之间的传播主要发生在家庭成员以及与患者密切接触的亲友之间，表现为明显的家庭聚集性[18-19]。而 SARS-CoV 则主要在医院聚集传播[20]。对家庭聚集性病例的追溯研究发现 SARS-CoV-2 在潜伏期内就具有强的传染性和可传播性[21]。这是因为 SARS-CoV-2 的病毒载量在症状发作前就可达到高峰[22]。无症状感染者的病毒载量与有症状者相似,同样具有传染性[23]。相反,SARS-CoV 的病毒载量在症状发生的第 10 天才能达到高峰[24]。离体人肺组织中的实验也证明 SARS-CoV-2 在 48 h 内复制的病毒颗粒是 SARS-CoV 的 3.20 倍[25]。这种传染阶段的差异可能与 SARS-CoV 的医院聚集暴发有关[22]。而且无症状感染者造成 SARS-CoV-2 传播的隐匿性，也可能是其感染人数远超 SARS-CoV 的原因之一。

即便传播途径相似，SARS-CoV-2 和 SARS-CoV 在人群中表现出来的传染能力不同。衡量病毒传染强弱常用的一个指数是基本繁殖数 R_0,即一个感染者在整个感染期内能引起其他个体感染的平均数[26]。据 WHO 报道,SARS-CoV-2 的 R_0 估计值为 2~2.5,而 SARS-CoV 则要偏低一些,R_0 估计值为 1.7~1.9[27]。因此 SARS-CoV-2 较 SARS-CoV 更具传染性,若不加以控制可能引起大流行。

二、发病机制

冠状病毒通过包膜糖蛋白介导的宿主细胞结合和随后的膜融合而进入细胞[28]。S 蛋白是细胞取向和疾病发病机制的主要决定因素 [29]。研究人员对 SARS-CoV-2 和 SARS-CoV 的 S 蛋白受体结合域进行序列比对和结构分析,结果显示这 2 种病毒受体的氨基酸序列有 72%的同源性,而且具有高度相似的三级结构 [30]。即 SARS-CoV-2 进入人体的方式与 SARS-CoV 相似,都可结合 ACE2。

在宿主细胞内,SARS-CoV-2 和 SARS-CoV 利用细胞生产线合成自身基因和蛋白,并且进行组装,实现大量复制[28]。机体抗病毒的第一反应是产生 IFN 并激活先天免疫应答[31]。SARS 中的研究发现高水平的 IFN-α、IFN 刺激基因的表达伴随 SARS 早期后遗症[32]。也有研究表明 SARS-CoV 感染导致延迟的 IFN-Ⅰ表达[33]。延迟的 IFN-Ⅰ信号促进了致病性炎症单核细胞/巨噬细胞的积聚，导致肺细胞因子/趋化因子水平升高、血管渗漏和病毒特异性 T 细胞反应受损。被感染的细胞还可产生其他高水平促炎细胞因子，如:MCP-1、TGF-β1、TNF-α、IL-1β、IL-6 和 RANTES 等[34-35]。细胞因子的大量产生会形成炎症风暴,加重患者的组织损伤[36]。然而中国香港大学研究人员发现,SARS-CoV-2 在离体人肺组织中并未触发明显的干扰素反应,仅激活部分细胞因子,促炎症反应明显较 SARS-CoV 轻[25]。这也许可以解释 COVID-19 患者临床病情普遍较 SARS 患者轻,致死率低的原因。而 SARS-CoV-2 的先天免疫激活不足,可能造成了无症状感染患者的出现。

SARS-CoV-2 和 SARS-CoV 主要靶向肺和免疫器官 [37-38]。SARS-CoV-2 和 SARS-CoV 与 ACE2 结合后会下调 ACE2 在肺泡细胞表面的表达，减少 ACE2 对肺部的保护作用[34,39]。SARS-CoV 感染后,会导致免疫功能下降、支气管上皮剥脱、纤毛丢失和鳞状化生、巨细胞浸润,广泛肺实变和弥漫性肺泡损伤并形成透明膜[1,38]。然而关于 COVID-19 患者的靶细胞病理改变的研究资料还不够丰富。武汉大学中南医院的研究人员对 2 位肺腺癌并且在手术时发现 COVID-19 感染的患者进行回顾分析。病理检查发现,除肿瘤外,肺组织均有水肿、蛋白样渗出物、局灶性反应性肺细胞增生伴斑片状炎性细胞浸润和多核巨细胞。这 2 例患者在手术时都没有表现出肺炎的症状，这些变化可能代表了 COVID-19 肺炎肺部的早期病理改变[40]。

三、临床特点

SARS 的潜伏期为 2~14 d,平均潜伏期 6.4 d[1,41],95%的患者在暴露后的 10 d 以内出现临床症状[42]。与引起流感的冠状病毒主要引起上呼吸道不同,SARS 主要表现为下呼吸道症状[2]。SARS 的典型特征包括持续发热、寒战、肌痛、不适,盗汗和食欲不振[42-43]。SARS 患者的平均年龄为 41.3 岁[44],60 岁以上的老年人的预后较差,死亡率达到 50%[45]。患者常见的血液学特征包括中性粒细胞增多，淋巴细胞减少 [1],C-反应蛋白,天冬氨酸转氨酶、丙氨酸转氨酶、乳酸脱氢酶和上调[46]。SARS 患者发生急性呼吸窘迫综合征的高峰段分别在症状出现的第 11 和 20 天[1]。

COVID-19 潜伏期为 1~14 d，平均潜伏期 5.2 d[47-48]。患者的中位年龄为 47 岁,男女比例为 1.17:1[48]。COVID-19 患者的最初症状包括发热、咳嗽、呼吸困难、肌痛或疲劳、咳痰、头痛,咯血和腹泻[6,49-50]。喉咙痛、鼻塞、流涕等上呼吸道症状少见。值得注意的是,在危重病人病程中,可出现中低热甚至无明显发热[51]。严重患者会发生急性呼吸窘迫综合征,合并肝肾等器官衰竭[49]。COVID-19 患者的住院时间中位数为 12.0 d

(平均 12.8 d)[49]。免疫功能较弱而伴有基础疾病的老年男性最容易感染 COVID-19[50],而且患有 COVID-19 的老年患者更容易发展成重症疾病,死亡率高于中青年[52]。另外,COVID-19 患者的血液较健康者血凝度升高,严重感染者的 D-二聚体和纤维蛋白降解产物值较轻度感染者高[53]。淋巴细胞减少最为常见,小部分患者的血小板和白细胞也减少[49]。丙氨酸氨基转移酶、天冬氨酸氨基转移酶,肌酸激酶水平一般不升高[49]。SARS-CoV-2 和 SARS-CoV 作为 RNA 病毒可以随时间发生变异,这可能部分解释了患者临床表现和疫情持续时间的差异。

四、检测和诊断

实验室检测和临床影像学检查均可为 SARS-CoV-2 和 SARS-CoV 感染提供证据。目前常规利用实时荧光定量聚合酶链反应(RT-PCR)技术来检测呼吸道病毒[54]。广州医科大学第一附属医院实验人员开发了一种快速、简便的免疫分析法,可在 15 min 内同时检测人血中抗 SARS-CoV-2 的 IgM 和 IgG 抗体,总检测灵敏度为 88.66%,特异性为 90.63%[55]。北京大学人民医院的研究人员对武汉同济医院的 60 名恢复期患者进行了 SARS-CoV-2 特异性抗体的检测,发现患者的免疫状态符合临床和体液免疫的一般特征,抗体检测可以作为 COVID-19 进展阶段的指标[56]。SARS 类病毒的分离和培养要在三级生物安全实验室内进行,目前不作为常规和推广的检测手段。

COVID-19 患者的胸部 CT 表现以磨玻璃样阴影和双侧斑片状阴影最常见[49],病灶多为外周分布和双侧受累,以下肺及多灶性为主[57-58],这与 SARS 患者的影像学表现相似[59]。虽然肺部 CT 的灵敏度可以达到 97%[60-61],但是特异性较低,为 56%[60],因此,对于临床高度怀疑 SARS-CoV-2 感染但 RT-PCR 筛查阴性的患者,重复拭子测试以及结合影像学表现可能会对诊断有所帮助[62]。

五、治疗

SARS-CoV-2 和 SARS-CoV 都属于冠状病毒,因此针对 SARS 的治疗方案可以为 COVID-19 提供参考。SARS 主要通过支持护理、激素治疗、抗病毒和对症治疗来救治患者[63]。目前用于治疗 SARS 类病毒感染的药物可以分为 2 种[64]:一种靶向病毒,一种靶向宿主细胞。靶向病毒的有核苷类似物(如法匹拉韦、利巴韦林、瑞德西韦和 galidesivir 等)、蛋白酶抑制剂(如双硫仑、洛匹那韦、利托那韦以及抑制病毒 S 蛋白的 griffithsin 等)。而 Peg-IFNα2a、Peg-IFNα2b、氯喹和硝唑尼特等药物则可杀伤宿主细胞。有研究者将目光集中于积极参与病毒进入宿主的 TNF-α 转化酶,结果发现 TNF-α 转化酶抑制剂能够在体内外抑制病毒的进入[65]。美国约翰霍普金斯医院研究人员提出 ACE 免疫球蛋 Fc 结构域治疗方法,这是以 SARS-CoV-2 的宿主受体为切入点[66]。这种 ACE2-Fc 治疗法除了抗病毒,还能补充肺中 ACE2 水平的降低,从而直接治疗急性呼吸窘迫病理生理学。另外,研究者提出 JAK2 抑制剂 fedratinib,IL-1 和 IL-6 因子抑制剂因为能靶向细胞因子可能作为 COVID-19 患者抗病毒及抗炎的治疗策略[67-68]。复旦大学研究者首次报道了 SARS-CoV 特异性人单克隆抗体 CR3022 与 SARS-CoV-2 的受体结合区域存在潜在结合,CR3022 可能用于预防和抵抗 SARS-CoV-2 的感染[69]。免疫疗法的独特优越性促使此次治法中采用了血浆疗法,通过将含有中和抗体的恢复期血浆转移到 COVID-19 重症患者,来中和病毒和防止进一步感染[70]。另外一种让人瞩目的疗法是传统中国医学的应用,国内有超过 85%的 COVID-19 患者接受了中医治疗[71]。根据报道,山西、河北、黑龙江和陕西省的 214 例患者使用清肺排毒汤治疗,总有效率≥90%[72]。目前,清肺排毒汤已被国家卫健委明确纳入《新型冠状病毒肺炎诊疗方案(试行第六版)》[73]。另外,体外实验也已经证明治疗流感的莲花清瘟,能够明显抑制 SARS-CoV-2 复制及 TNF-α、IL-6、CCL-2/MCP-1 和 CXCL-10/IP-10 细胞因子产生[74]。

与 SARS 治疗相比,此次 COVID-19 患者的推荐治疗较为明显的是“康复者血浆疗法”和中医药的参与[37,75]。糖皮质激素的推荐应用对象是疾病进展迅速、机体炎症过度激活的患者。然而目前还缺乏证据表明 SARS-CoV-2 引起的肺损伤或休克患者可从皮质类固醇中获益[76]。而且针对 SARS 患者的治疗表明,虽然糖皮质激素有抗炎作用,但是激素的大量长期应用可能会在远期导致患者股骨头坏死[77]。

六、总结

目前 SARS-CoV-2 仍在流行,已经对全球的健康造成了威胁。SARS 已有的研究基础对 COVID-19 的防疫及治疗工作开展有极大的参考和指导意义。关于 SARS-CoV-2 的研究仍需要深入,这是确定其传染性、传播性、致病性,开发新型药物,寻找有效治疗方法以及预防部署的必要手段,而且对预防冠状病毒在未来引发流行极其重要。

利益冲突 所有作者均声明不存在利益冲突

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