SARS-CoV-2“后暴发”阶段医院感染控制

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摘要 新型冠状病毒SARS-CoV-2在世界范围内引发了大流行. 在暴发数月后, 病毒在中国内地的传播已基本得到控制, 新发病例数较暴发期间显著减少, 以境外输入病例及局部流行为主, 我们将此阶段称为SARS-CoV-2的“后暴发”阶段. 如何在全球大流行背景下遏制新发病例, 防止中国再次出现大规模暴发, 对卫生系统的所有人员都是巨大挑战. 目前研究公布的 R_0 数据表明, SARS-CoV-2比其他可引起人下呼吸道感染的冠状病毒, 如SARS-CoV和MERS-CoV, 具有更强的传播力. 另外, 最新的病毒传播动力学预测模型显示, SARS-CoV-2可能会周期性暴发, 甚至造成季节或常年性流行, 因此医疗系统需持续保持警惕. 在疫情暴发时期, 我国和许多其他国家医务工作者的感染率相对较高. 因此本文重点分析了几个高危科室如呼吸科、眼科、产科等的病毒传播特点和风险点, 提出了针对性的防控措施. 并总结及分析了在“后暴发”阶段医院防控的共同性举措, 包括防止病毒在患者和医生之间通过气溶胶传播, 研发快速、可靠的诊断方法, 建立有效的远程医疗咨询和实践患者风险分层系统以减少交叉传播等. 本文旨在强调“后暴发”阶段对SARS-CoV-2病毒传播的认识, 并为疫情防控研究提出建议.

关键词 SARS-CoV-2, 医院感染控制, 医务工作者防护, 病毒检测, 后暴发阶段

2019年末出现的SARS-CoV-2病毒是目前构成全球大流行的首个冠状病毒. 截至2020年8月初, 该病毒已累计导致全球超1800万人感染, 超70万人死亡, 并对公共医疗资源的承载能力和医护人员的安全防护造成了严峻的挑战. 在SARS-CoV-2流行早期, 因对该病毒传播特点未掌握, 部分医护人员防护力度不够, 多国出现了较高比例的医护人员感染^[1,2]. 继之世界卫生组织(WHO, https://apps.who.int/iris/bitstream/handle/10665/331498/WHO-2019-nCoV-IPCPPE_use-2020.2-eng.pdf)和中国发布的新型冠状病毒防控指南(<http://www.nhc.gov.cn/xcs/zhengcwj/202003/46c9294a7dfe4cef80dc7-f5912eb1989.shtml>)均对医护人员自我防护及医院感染

的防控作了具体的规定. 中国采用的严格隔离措施, 加上全国医护人员的共同努力, 有效地控制了病毒扩散, 及时救治了感染患者. 目前我国新发病例数较疫情期间显著降低, 已从全国性暴发转变为以输入病例及局部流行为主的阶段, 我们将其称之为“后暴发”阶段. 然而目前全球疫情依然严峻, 一些国家每日新发病例数仍在持续增长, 这给我们的疫情防控带来了巨大的挑战. 目前, 我国医疗系统的威胁仍未结束, 多地间断出现散发或流行情形, 而且面临呼吸道病毒感染高发的秋冬季节. 有学者利用现有的流行数据建立模型预测SARS-CoV-2在未来仍可能有再次流行或散发的风险^[3,4]. 本文根据目前掌握的SARS-CoV-2病毒知识及其

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流行信息,分析“后暴发”阶段医院面临的防控挑战,并提出一些应对的思考和建议。

1 SARS-CoV-2的未来流行趋势

最新发现的SARS-CoV-2,与SARS-CoV、MERS-CoV、HCoV-HKU1及HCoV-OC43等同属于 β 类冠状病毒。全基因检测研究表明,SARS-CoV-2与SARS-CoV的基因序列最为相近,有82%的基因序列与之相同。两者用于识别宿主细胞表面受体的钉突蛋白(spike protein, S蛋白)的氨基酸序列也有76.5%相同,尤其是在受体识别的关键结构区域。因而两种 β 类冠状病毒具有类似的人体易感性^[5,6]。 β 类冠状病毒SARS-CoV及MERS-CoV都曾在局部地区流行,但未造成全球大流行。而SARS-CoV-2造成了世界范围的大暴发,表明SARS-CoV-2具有更强的传播力。流行病学数据估算病毒的基本传染数(basic reproduction number, R_0)显示,SARS-CoV-2的 R_0 在2.0~4.9左右^[7],高于SARS-CoV的1.7~1.9^[8]及MERS-CoV的0.69~0.95^[9,10]。多国流行病学研究显示,SARS-CoV-2的重症率为23.4%,死亡率为0.7%~6.0%^[11~13],数据受到人种、年龄、健康状况等因素影响^[14]。在无保护性疫苗问世之前,群体对SARS-CoV-2仍具有普遍易感性,不能排除在较长时间内仍然有地区性暴发的风险,对公众健康造成持续的威胁。

目前尚未了解SARS-CoV-2是否会像如HCoV-HKU1、HCoV-OC43、HCoV-NL63及HCoV-229E等其

他几种引起上呼吸道感染为主的冠状病毒一样在世界各地反复地季节性流行(表1)^[30]。基于常见冠状病毒的流行病学数据及流行特征,有学者构建了SARS-CoV-2未来流行趋势的预测模型^[3,4]。模型提出,SARS-CoV-2有可能在未来再次暴发,甚至与HCoV-OC43或HCoV-HKU1一样每1~2年即流行一次。流行模拟曲线受多种因素影响,如隔离措施、流行的季节性、 R_0 、人口流动性及中和抗体保护时间等,因此还需要后续数据确证。值得注意的是,对SARS-CoV-2感染者血清抗体的随访研究表明,恢复期血清抗体滴度呈快速下降趋势,40.0%的无症状感染者和12.9%的有症状感染者在恢复期初期血清特异性IgG即转阴,另外部分轻症及抗体峰值较低患者感染后3月内中和抗体消失。这种一过性的血清抗体反应与引起季节性传播的冠状病毒更加相似,也提示了其具有再次暴发的风险^[31,32]。如果SARS-CoV-2感染的暂时控制与严密的隔离措施及疾病的季节性波动有关,这就意味着对SARS-CoV-2的防控措施不可松懈,尤其在有效疫苗研发成功之前。近期,我国的北京、新疆、辽宁等地先后出现了局部的本土暴发病例,进一步提示了持续防控及继续研究病毒流行特点的重要性。

2 “后暴发”阶段医院感染的控制

SARS-CoV-2对于医疗系统的感染控制及医护人员安全防护造成的挑战是多方面的,包括病毒的高传

表1 SARS-CoV-2与其他冠状病毒主要流行病学参数比较^{a)}

Table 1 Major epidemiologic parameters of SARS-CoV-2 and other coronaviruses

病毒名称	属	R_0	潜伏期(d)	重症率/入院率	死亡率	无症状感染者率	流行时间特点
SARS-CoV-2	2B	2.0~4.9 ^[7]	5.2 ^[12]	重症率23.4% ^[12]	4.0%~4.7% ^[12]	17.9%~18.1% ^[15,16]	尚不明确
SARS-CoV	2B	1.7~1.9 ^[8]	4.0 ^[17]	入院率约100%	9.6% ^[17]	11% ^[18]	2002~2003年区域性流行后尚无暴发流行
MERS-CoV	2C	0.69~0.95 ^[9,10]	4.5~5.2 ^[17]	入院率约100%, 46.2%需ICU治疗 ^[19]	35.5% ^[17]	9.8% ^[20]	2014~2016年出现局部区域暴发,其余时间以散发病例为主 ^[21]
HCoV-HKU1	2A	N.A.	2~5** ^[22]	N.A.	0.0036% ^[11]	N.A.	部分年份在部分地区流行,冬季高发 ^[23]
HCoV-OC43	2A	N.A.	2~4 ^[24]	入院率12.6%* ^[25]	0.013% ^[11]	13.6%~23.6% ^[26]	部分年份在部分地区流行,冬季高发 ^[27]
HCoV-NL63	1	N.A.	2~5** ^[22]	入院率21.1%* ^[28]	0.027% ^[11]	N.A.	部分年份在部分地区流行,春夏季高发 ^[29]
HCoV-229E	1	N.A.	2~5**	ICU入住率3%* ^[26]	0.011% ^[11]	33.3%~44.4% ^[26]	部分年份在部分地区流行,冬季高发 ^[27]

a) *,数据来自小样本或地区性报道; **,该研究数据包含HCoV-HKU1、HCoV-OC43、HCoV-NL63及HCoV-229E四种冠状病毒; N.A.,未有相关研究能提供可靠的数据

染性、病毒的长期存在及病毒暴发性传播对医疗资源承载能力的威胁等。日本的研究数据显示,在疫情期间61例聚集性暴发病例中,有22例均发生在医院及疗养中心,其他也均发生在人群高度聚集的封闭场所,提醒我们人流量巨大的医院等公共场所是重点防控对象^[33]。多国针对医务工作者进行了SARS-CoV-2的普查,在英国的研究发现,无症状医护人员核酸检测阳性率为3%,另一项在有疑似症状医护人员中的核酸检测阳性率为18%^[1,2],警示无症状感染的医务人员也是院内传播的隐患。西班牙对一家中心医院医护人员进行血清抗体普查,显示11.2%的调查者感染过SARS-CoV-2,其中40.0%感染者未被诊断,46.2%无相关症状^[34]。在对伦敦抗疫一线医护人员进行的血清流调也显示,高达45.3%的医护人员曾感染过SARS-CoV-2^[35]。这些研究证实,疫情暴发阶段医护人员感染的风险较大。

目前已知SARS-CoV-2的主要传播途径为飞沫传播、气溶胶传播及近距离接触传播,其他方式如粪口传播^[36]、经结膜传播^[37]、血行传播^[38]及性传播^[39]的可能性也正在被评估并存在一些支持证据。SARS-CoV-2的传播方式决定了不同科室的医护人员有不同的危险性。一项纳入武汉抗疫一线医务工作者的回顾性研究表明,在呼吸科、ICU、外科等高危科室的工作人员感染风险显著高于其他科室^[40]。本文以呼吸科、产科及眼科为例,结合各国疫情期间出台的防控指南,对科室面临的挑战和防控措施进行分析。

2.1 呼吸科

呼吸道是SARS-CoV-2感染和复制的主要和首要部位。SARS-CoV-2能够在支气管纤毛上皮、黏液分泌上皮、I型肺泡上皮、鼻咽部上皮等部位广泛增殖。肺泡上皮富含SARS-CoV-2的关键细胞受体ACE-2,是主要的受累部位^[41],感染者可出现包括咳嗽、气短、呼吸困难等多种呼吸道症状^[42]。呼吸科医生可根据症状进一步排查SARS-CoV-2感染。但是,SARS-CoV-2有两个特点:一是较长的潜伏时间,潜伏期中位数是5.2 d^[11];二是有部分病人可以无症状,研究显示无症状感染率可高达18%左右^[17,43]。2020年5月在武汉、牡丹江等地进行的共超过1000万人的全民核酸筛查显示,两市无症状感染者比率分别为每十万人中3.03及2.88名。而无症状感染者及有症状者上呼吸道病毒载量无显著性差异,在发病后早期鼻部、喉部病毒载量即达到高峰^[30]。呼

吸道医生需熟知SARS-CoV-2的流行特点及其变化,警惕疑似感染者,尤其是早期感染者,同时在诊治病人时做好自身防护。

研究显示,下呼吸道样本的病毒载量显著高于上呼吸道,尤其是在病程发展到肺部以后^[44]。因而有专家建议,下呼吸道样本的病毒载量对判断患者病情发展具有预测价值,因此可作为监测指标^[45,46]。需要接触下呼吸道的操作,如吸痰、采集呼吸道标本等,可增加感染冠状病毒的风险^[47],需有严格的防护流程。研究显示,在气管插管、气管镜使用、无创呼吸机使用、气管切开、机械通气等情况下气溶胶暴露及上呼吸道感染风险增加了1.9~6.6倍^[48]。在存在高浓度气溶胶风险的情况下,除了保护医护人员的口鼻、眼部保护也具有必要性^[49]。已有研究清楚地表明,佩戴眼罩可降低冠状病毒感染风险^[50]。

在秋冬呼吸道感染高发季节,如何从大量的具有类似呼吸道症状及体征的患者中早期、准确地筛选出SARS-CoV-2感染者非常重要。意大利疫情暴发期间的一项研究采集了前来医院就诊的具有发热及呼吸道症状的疑似患者的鼻咽拭子并进行病原学分析,发现SARS-CoV-2感染者占比为2.4%,其他常见的病原体包括流感病毒、肠病毒、鼻病毒及其他冠状病毒等^[51]。面对大量的呼吸道感染病例,需要采用创新、高效的手段应对如此大的检测压力并控制感染的继续传播^[52]。有实践证明,面对大量排查案例可采用多名测试者样本混合后检测,尤其是对感染率较低的人群,可大大提高检测的效率^[53,54]。还有研究采用机器深度学习方式对比不同病原体导致下呼吸道感染的患者的肺部影像学,可较准确地从中识别出新冠患者的影像^[55,56]。在SARS-CoV-2疫情防控的压力下,各国都在创新上发力,以提高发现和诊治新病例的效率。

为了减少疑似患者前往医院途中造成传播的风险,四川大学华西医院创新性地借助5G技术搭建了线上远程诊疗平台,对有呼吸道症状的患者进行远程诊疗和指导,并和多家医疗机构开展视频会诊工作,减少了高危患者就诊途中造成的传播扩散。国家利用区块链技术开源数据共享平台,收集个人位置、症状及高危接触信息,并和社交平台合作开发健康码,对个人进行感染风险度评估,也方便就诊时采取分级诊疗。

总之,对有呼吸道感染的患者进行风险分级、呼吸道病毒的快速检测及医护人员的呼吸道保护,是呼

吸科在“后暴发”阶段的重点。

2.2 眼科

SARS-CoV-2是否能经结膜传播目前还存在争议。已有研究表明,在SARS-CoV-2感染者的泪液及结膜分泌物中可检出病毒的RNA,且人的角结膜上皮均表达病毒受体ACE2及辅助受体TMPRSS2,有病毒感染的结构基础^[57,58]。体外实验证实,SARS-CoV-2可感染结膜上皮细胞并能在细胞内复制增殖^[59]。在恒河猴结膜接种感染量的SARS-CoV-2后,病毒可通过鼻泪管通道导致肺部感染及血清抗体转阳^[60]。在SARS-CoV-2确诊感染者中,常见的眼部受累表现包括结膜充血、眼痛、异物感及分泌物增多。另有病例报道,个别患者可出现出血性结膜炎、泪小管炎、急性睑板腺炎等表现^[61,62]。另外,少数患者在出现发热及呼吸道症状之前以眼部表现首发,随后被确诊感染,其中一些病例是医务人员^[63,64]。近期一篇病例报道,一名以双侧结膜炎为首发症状的女性患者在确诊后21 d内泪液持续检测为阳性,且随着病情好转泪液中病毒载量逐渐降低,提示眼表可能是SARS-CoV-2的受累部位之一^[65]。一篇共纳入全球范围内11项研究共252名SARS-CoV-2确诊感染患者的系统回顾显示,具有结膜炎表现的患者比率高达32%,但仅1.2%的患者同时能在泪液中检出病毒RNA^[66]。泪液的低检出率可能与泪液的快速更新相关。也有学者认为,眼表的RNA剪切酶APOBEC3A和ADAR-1表达较高,可使眼表具有一定的防护SARS-CoV-2感染的能力,并降低泪液拭子检测的阳性率^[67]。另外,根据目前数据显示,具有结膜炎表现的SARS-CoV-2感染患者中仅少量能在眼部样本检出病毒,说明其结膜炎表现不一定直接与感染相关,可能是一些常见的引起结膜充血反应的慢性疾病的反应性加重,如过敏性结膜炎、干眼等。眼科医师需要在接诊时仔细鉴别^[68]。尽管目前SARS-CoV-2通过结膜传播还存在争议并缺乏足够实验证据,但少量感染者眼表可检出病毒RNA已是临床事实,因此眼科医护人员在“后暴发”阶段要继续有防护意识,检查病人以后注意洗手,避免造成交叉感染^[69]。

由于病毒传播的特点和眼科近距离检查的特殊性,眼科保护重点需要考虑减少病毒颗粒通过气溶胶及飞沫在医患之间的传播。进行眼科常规检查,如裂隙灯、直接检眼镜、角膜地形图时,医务人员需近距离面对患者,尤其是在直接检眼镜检查时,医生需贴近患者面

部并与之仅相距1~2 cm^[70]。该距离完全在飞沫及气溶胶传播的范围之内^[71]。喷气式眼压计测量眼压时喷射的气流可冲击患者泪膜并形成局部的气溶胶,如泪液中携带病毒颗粒则可能具有传播的风险^[72]。疫情期间,国家有关部门针对眼科门诊、手术工作的开展、眼科器械消毒及医务人员防护发布了具体的专家建议,尤其对于高风险操作如喷气式眼压测量、裂隙灯检查及接触性设备检查提出了操作和防护要求。美国眼科学会(American Academy of Ophthalmology, AAO)也强调了结膜感染的风险,并提倡眼科医生在近距离接触患者时佩戴眼罩进行保护。对于日常使用的接触性检查器械,需按照每人使用后即消毒的原则处理,使用3%过氧化氢、75%乙醇或含氯消毒剂浸泡或擦拭均能有效灭活病毒,但需特别注意再次使用前除去残留消毒剂避免刺激眼表^[73]。在裂隙灯检查时,可将胶片裁剪后安装在裂隙灯上隔离患者及医生面部,减少近距离传播风险^[74]。由于眼科手术多为微创且患者周转快,对于疫情期间眼科手术及随诊治疗的开展,多名专家及眼科学会建议根据疫情风险等级对患者进行分层管理,入院前开展核酸筛查,对高风险区域或高风险患者暂停择期手术,尽量选择局部麻醉避免插管带来的气溶胶传播风险,减少家属陪视、院内停留时间及交谈行为,控制交叉感染的风险^[73,75,76]。对必须进行的手术和治疗,如急诊手术、限期手术、抗VEGF玻璃体注射、激光治疗、葡萄膜炎随诊等,需正常开展,但需做好医护人员的防护^[77]。对激素及免疫抑制药物的使用,在无SARS-CoV-2感染证据情况下,应基于患者眼部疾病治疗需求进行选择^[78]。

在“后暴发”阶段,要继续有防护意识,认识到眼手接触和近距离气溶胶暴露都能增加眼部病毒传播风险。因此,眼科医务人员需佩戴完备的个人防护装置,保持检查室空气流通。另外,一些创新性的方法,如研发和使用局部可拆卸或接触部位采用一次性耗材的检查仪器可减少患者间交叉感染的风险,并提高门诊检查的效率。

2.3 产科

产科在避免孕产妇间的交叉感染、降低垂直传播风险及保护医护人员的安全方面都面临挑战。一项纽约疫情暴发期间在妇产专科医院展开的流行病学研究显示,对前来就诊的孕产妇进行SARS-CoV-2核酸检测,发现有症状感染者及无症状感染者的比例分别为

13.5%及1.9%^[79],说明孕产妇也是高危人群。

妊娠期间机体为了避免对胎儿的排斥反应而下调免疫状态,淋巴细胞的增生和激活受到抑制,使得孕产妇对SARS-CoV-2的抵抗力更低^[80]。而孕产妇在妊娠期间需多次前往医院进行产前检查,增加了交叉感染的危险性。在收治新型冠状病毒感染者的产科病房进行空气采样,发现28%的样本RT-PCR检测为阳性,远高于普通隔离区病房的采样阳性率^[81]。面对如何减少孕产妇暴露的难题,各国都有相应措施。有建议提出,在产前检查阶段,根据孕产妇症状、核酸检测结果及流行病学史进行风险分层和分诊,以避免不同风险的孕产妇互相接触,并配套相应的医护防护装备^[82]。刘兴会等人^[83,84]提出对孕产妇按照有无流行病学接触史及相关症状进行分类管理,并对高风险孕产妇终止妊娠指征、分娩方式、围产期新生儿防护等给出了详细的建议。英国皇家妇产科协会制定了预约制控制产区人数、推行自行在家采集样本进行核酸检测、远程产前指导等措施,降低孕产妇及新生儿感染的风险(<https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/>)。

SARS-CoV-2感染的孕产妇在妊娠和分娩过程中的垂直传播风险也得到大量关注。研究表明,病毒受体ACE2在子宫-胎儿界面的蜕膜、合体滋养层、细胞滋养层及胎儿的肺部、心脏等部位广泛表达。尽管目前还未在脐带血、羊水、乳汁、阴道分泌物等样本中检出SARS-CoV-2的RNA,且大部分确诊感染者经阴道分娩或剖宫产分娩的新生儿均病毒检测为阴性,目前已有数例新生儿在出生后数小时内被确诊SARS-CoV-2感染的报道,部分新生儿出生后血清IgM及IgG检测为阳性,提示宫内感染的可能^[85]。另外,Vivanti等人^[86]报道一例孕晚期感染妇女出现病毒血症后通过胎盘传播导致新生儿感染的病例,为SARS-CoV-2的垂直传播提供了证据支持。国际妇产联合会(International Federation of Gynecology and Obstetrics, IFGO)发布了SARS-CoV-2感染者妊娠期间及围产期临床指导方案。该指南基于现有的临床证据提出了在负压室分娩、佩戴全套个人防护装置、缩短第二产程、分娩困难者早期转剖宫产、尽量避免插管全麻造成气溶胶传播、早期切断脐带、早期分离母婴等措施来减少新生儿及医护人员的感染风险。这对医护人员的安全防护提出了更高的挑战。

以上只列举了在SARS-CoV-2“后暴发”阶段相对

高危或较特殊的部门,医护人员的防护是普遍的。疫情期间我国及WHO(<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/health-workers>)均提出了适用于所有医护人员的个人防护及医院感染控制原则,对医院环境消毒、感染性物品处理、疑似感染者隔离、个人防护品佩戴等进行了规定。在“后暴发”阶段,医院感染的控制不容松懈,研究及应用创新、高效、远程的多元防控体系是该阶段的研发方向之一^[87]。

3 医护人员职业环境暴露风险研究和防护

科学地研究医护人员在不同情境下职业暴露的风险是指导“后暴发”阶段医院感染防控和指导医护人员佩戴适当的自我防护装备的关键。尽管目前已有一些实地或模拟实验能够为医院感染防控提供依据,但仍有大量问题需要更多的研究支撑。

不同医院环境下的病毒存在情况。研究表明,在收治SARS-CoV-2患者的区域中,ICU治疗区的空气中病毒检出率最高,在隔离区病房、产房甚至医务人员工作区域的空气中均能检出病毒的RNA。另外在疑似感染者观察区的护士台、隔离区的鼠标、地板、垃圾桶、门把手等表面也可检出病毒^[88-90]。因此医院要建立有效的消毒流程和检查标准,防止医院成为交叉传染地。

医院传播中最具争议的问题是SARS-CoV-2能否通过气溶胶进行广泛播散。在SARS-CoV暴发期间,香港和多伦多医院均有关于由气溶胶传播所导致的医院内感染扩散的报道^[91,92]。但对于SARS-CoV-2能否以及如何通过气溶胶传播还有很多未知和争议。有研究表明,在距离患者约4 m范围内的空气中可检出SARS-CoV-2病毒的RNA,甚至能在隔离区域的厕所、走廊等远离患者长期活动区域的空气中检测出病毒,提示了院内气溶胶传播的可能性^[88,93]。但也有研究显示,病毒无法在超出患者飞沫可到达的范围外(约2 m)检出^[94]。一项纳入172项关于SARS-CoV-2及其他β类冠状病毒研究的Meta分析显示,近距离接触感染者(距离<1 m)时感染冠状病毒的风险显著增加^[50]。Duan等人^[95]利用3D打印技术根据真实人体面部、呼吸道及肺部制作呼吸模型,将呼出气流模拟装置放置于距模型鼻部20 cm的位置,模拟人与人面对面交流时飞沫传播的情况,以评估近距离检查或问诊的情境下飞沫传播风险,发现在面部80%的飞沫颗粒均沉积于唇部,少量可沉

积于眼部表面. Stadnytskyi等人^[33]利用激光照相机捕捉说话过程中产生的飞沫,发现形成的悬浮飞沫液滴可在周围的静态空气中停留8~14 min,而在流动空气中停留时间大大减少.这些研究提示,与病人近距离接触时需要做好口眼保护并增加环境通风.

口罩是呼吸道疾病的有效防护屏障,其防护作用各国不同看法,口罩的选择标准也存在争议.有学者认为,N95口罩可更好地滤过微小病毒(如流感病毒)及气溶胶颗粒^[96].也有人认为,SARS-CoV-2颗粒直径约120 nm,远大于流感病毒,因此普通外科口罩过滤就已足够^[97].一项纳入超过10000名近距离接触呼吸道感染者的医护人员的研究表明,佩戴普通外科口罩及N95口罩对呼吸道病毒防护效果无差异,但是该研究并未评估门诊及高危气溶胶暴露情境下的感染风险^[98].在疫情期间WHO建议直接接触SARS-CoV-2确诊感染者的医护人员佩戴外科口罩,而在有气溶胶暴露风险的情况下使用N95口罩.

通过增强通风和限制人群密度可以降低空气中的病毒量^[89,99].医院自然开窗通风的换气量是负压机械通风的两倍,是关闭门窗时的18倍,因此保持开窗换气是普通诊室及病房控制病毒经空气传播的首要措施之一^[100].对于多床式隔离病房,增设负压排气扇及空气泵,在病床间及走廊设置散风器均能一定程度上阻断患者间的病毒传播^[91].在收治SARS-CoV-2感染患者的医院中,小而不通风的患者卫生间及员工更衣室等空气中病毒量较高,而通风良好的病房空气中病毒量较低^[89].香港的一项研究显示,在SARS-CoV-2首例病例出现后的72 d内,香港医院无院内交叉感染及医护人员感染病例的报道,其采取的措施包括严格的患者危险分层管理、加强通风和医院消毒、多医院共同分担患者避免单个医院患者拥挤、提前做好医护人员个人防护培训等^[101].这些措施的成功使用对于提高医院环境下病毒防控具有重要的参考价值.

4 “后暴发”阶段病毒检测

“后暴发”阶段医院感染控制也依赖于病毒检测手段的进一步提升,尤其需要成本合理、操作简便、结果准确的检测手段,以保证检测方法的广泛应用及便于医护人员及时作出决策.

4.1 病毒检测方法的提升

现有的SARS-CoV-2检测方法包括,基于核酸的检

测手段(RT-PCR法、环介导逆转录等温扩增技术、基于CRISPR的核酸检测法及基因芯片等)、基于抗体的检测手段(ELISA法、胶体金免疫层析技术、化学发光免疫分析等)及基于病毒感染力的检测手段(噬菌斑试验)^[102](表2).

目前,WHO(<https://www.who.int/publications/item/10665-331501>)、中国、美国CDC (<https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html>)等发布的新型冠状病毒诊疗方案均将呼吸道样本的RT-PCR检测作为标准的诊断方法.该方法根据SARS-CoV-2的核衣壳蛋白、ORF1b或RNA聚合酶(RdRp)等基因序列设计探针,特异性地放大信号及并检测.RT-PCR法具有一些局限性,包括检测时间相对较长、无法判断病毒的感染力与活性、对检测人员操作要求较高、与其他呼吸道病毒和冠状病毒有一定的交叉反应以及较高的假阴性率等^[38].单独使用RT-PCR检测可能有漏诊风险,有研究测算该手段在喉拭子、鼻拭子和痰中的检出阳性率分别为74%~89%、54%~73%及43%~61%^[103].个别患者多次使用RT-PCR法检测结果为阴性但最终确诊感染^[104].而环介导逆转录等温扩增技术和基于CRISPR的核酸检测法的病毒检测灵敏度高于RT-PCR,可便携操作,并能在1 h内出结果,其关键的优势在于操作方法简单,不需要专业人士操作^[105].然而,这些方法的应用还需进一步验证,在不同人群、不同临床样本的检测灵敏度及特异性还需更多数据来支撑^[102].

为了提高样本的检测效率,多国在核酸筛查中采用了样本预先混合的手段,节省了检测时间.研究显示,在总体感染率为10%及以下的人群中采用样本混合检测即具备提高检测效率的可能^[106].Schmid-Burgk等人^[107]对个体独特的DNA序列进行预先标记后将多人的生物样本混合检测,可实现超高通量检测,并对阳性样本快速追踪,从而应对疫情期间爆发性增长的检测需求.另外,基于胶体金免疫层析技术的快速检测试剂盒也被开发,初步临床研究表明,该方法的灵敏度及特异度可达71.1%及96.2%,因其具备延时显示结果的优点,可用作快速初筛^[108,109].

新的检测方法需要考虑“后暴发”阶段病毒流行的特点,在人群流动性大、感染率低、多种病原体感染混杂的情况下,能快速、简便、特异地检出SARS-CoV-2感染患者,同时费用合理,是该阶段检测手段的研发方向.

表 2 SARS-CoV-2 现行常见检测手段的原理及优缺点比较^{a)}

Table 2 Advantages and drawbacks of common diagnostic tools for SARS-CoV-2

检测方法	检测内容	优点	缺点
基于病毒核酸的检测方法			
RT-PCR	检测病毒特异性核酸序列	可定量, 部分方法能够精确区分 SARS-CoV-2 及其他冠状病毒	对设备、人员技术要求高, 假阴性率高, 部分方法有交叉反应
RT-LAMP	检测病毒特异性核酸序列	灵敏度高, 交叉反应少, 检测速度快, 操作便捷	无法多重扩增, 无法判断病毒的活性及感染性
基于CRISPR的核酸检测	检测病毒特异性核酸序列	仪器便携, 检测速度快, 可现场开展检测	灵敏度不及RT-PCR
基因芯片法	检测病毒特异性核酸序列	可同时设计多种检测探针及片段, 高通量检测, 能同时覆盖多种突变型	对设备要求高, 昂贵, 不适用于大规模检测及现场检测
基于蛋白的检测方法			
ELISA	检测特异性IgA、IgM或IgG抗体	检测灵敏度较高, 方法简单, 检测速度快	在发病早期阳性率低, 与其他病毒抗体可能存在交叉免疫反应
CLIA	检测特异性IgA、IgM或IgG抗体	检测灵敏度较高, 操作简便, 检测速度快	在发病早期阳性率低, 与其他病毒抗体可能存在交叉免疫反应
GICA	检测特异性IgA、IgM或IgG抗体	检测灵敏度较高, 操作简便, 检测速度快	在发病早期阳性率低, 只能定性检测, 与其他病毒抗体可能存在交叉免疫反应
基于病毒感染性的检测方法			
噬菌斑试验	检测病毒的感染力	能够定量估算具备感染力的病毒滴度, 是估计病毒活力及感染力最准确的方法	需首先培养病毒, 所需时间长, 灵敏度低

a) RT-PCR, 逆转录聚合酶链式反应(reverse transcription polymerase chain reaction); RT-LAMP, 逆转录等温扩增技术(reverse transcription loop-mediated isothermal amplification); CRISPR, 成簇的规律间隔的短回文重复序列(clustered regularly interspaced short palindromic repeats); ELISA, 酶联免疫吸附检测(enzyme-linked immunosorbent assay); CLIA, 化学发光免疫检测(chemiluminescence immunoassay); GICA, 胶体金免疫层析技术(colloidal gold immunochromatographic assay)

4.2 检测样本的多样化

SARS-CoV-2 感染患者不同生物样本的核酸检测研究表明, 发病早期患者的呼吸道样本(鼻咽拭子、痰、气管吸引物及肺泡灌洗液等)具有最高的检出率, 其中鼻咽拭子是 WHO 推荐的检测 SARS-CoV-2 的方法。而除呼吸道样本外, 在感染者消化道样本(唾液、粪便)、结膜分泌物、尿液、血液、精液、脑脊液等多个生物样本中均有检测出 SARS-CoV-2 的 RNA 的报道^[39,110,111]。各国目前也正在开展 SARS-CoV-2 死亡患者的尸检工作, 已在上、下呼吸道、肾脏、睾丸中检出病毒^[112]。从之前流行的 SARS-CoV 感染患者的尸检结果推断, 病毒可能具有造成全身多器官广泛感染的能力, 因而能在多个生物样本中检出病毒 RNA^[113]。虽然相比于呼吸道样本, 这些生物样本的检出阳性率较低, 但对疾病诊断、感染机制、预防及转归判断等的研究均具有重要的意义。值得注意的是, 样本中检出病毒 RNA 并不意味着该生物样本具有传染性, 也无法说明病毒可以通过该途径进行传

播, 而未来更多的病毒活性研究及尸检结果能为此提供依据^[114]。

在非呼吸道样本中, 粪便具有较高的检出阳性率, 达 15%~55%^[115]。粪便样本中核酸阳性持续时间较长, 部分学者报道在呼吸道样本转阴后 3~14 d 仍可在粪便中检出病毒 RNA^[116]。尤其在儿童中, 粪便中病毒核酸检测时间窗更长^[117,118]。有人提出, 消化道样本阳性率高、阳性持续时间长, 可作为辅助诊断手段, 并在疾病后期感染性监测中发挥作用^[117]。

唾液样本在诊断中的作用也开始得到认识。在喉深部唾液、口腔内唾液及唾液腺开口处分泌物样本中, SARS-CoV-2 的检测阳性率可分别达 92%~100%、50% 及 13%。其中, 喉深部唾液与鼻咽部拭子检测结果具有高度一致性。这种样本可自行采集, 更方便、低价和高效。此检测方法正得到进一步开发和研究^[119]。

在血液样本中, SARS-CoV-2 感染者核酸检测的阳性率为 0~41%, 但在重症患者的血液样本中, 病毒的检出率明显高于普通患者, 可作为预判患者病情严重程度及预后的指标之一。

Sullivan等人^[120]利用远程视频连线指导隔离患者在家收集血液、唾液及口咽样本,并对患者收集样本的可靠性进行评估,发现这些自行采集的样本能够满足核酸及抗体检测的需求。一项研究表明,用医护人员采集的舌部、鼻部及中鼻道拭子样本作为标准参照,患者自行采集的相应样本的诊断灵敏度分别可达90%、98%和96%。这种居家采集样本的方法减少了患者前往核酸检测点或医院过程中造成的交叉感染风险^[121,122]。在“后暴发”阶段,需要建立多样化的样本检测手段,让检测更简便,诊断成本更低。

4.3 血清保护性抗体的研究

对SARS-CoV-2感染者血清抗体的检测及纵向追踪具有重要的意义,目前各国都在进行大规模的血清流行病学调查^[123,124]。我国一项在3~4月间进行的样本总数超17000人的横断面血清流行病学调查显示,武汉居民血清抗体阳性率最高,达3.2%~3.8%。另外,医院血透患者及医务工作者也有相对较高的阳性率,分别为3.3%及1.8%^[125]。血清保护性抗体存在时间长,能够用于疑似或确诊患者传播链的追踪,以明确和发现传染源。通过对医院或社会人群的血清抗体的流行病学调查,还能够明确SARS-CoV-2的无症状感染率,从而协助制定筛查手段和隔离措施^[108]。另外,血清保护性抗体的研究对疫苗研发具有重要参考价值^[126]。

有研究发现,大多数患者在起病3周内能产生中和抗体^[127],但与其他冠状病毒无交叉免疫反应,中老年患者的抗体滴度明显高于年轻患者,但部分患者保护性抗体滴度过低,甚至低于检测极限,可能与机体免疫抑制有关^[128]。目前多国均在医务工作者中广泛开展血清抗体流行病学调查。发表的数据显示,在各国医务工

作者中,SARS-CoV-2抗体的阳性率在1.5%~45.3%,其中相当比例抗体阳性的医务工作者无相关症状或之前RT-PCR检测为阴性^[34,129~133]。

在“后暴发”阶段,血清保护性抗体研究对于医院感染控制和疾病研究均具有重要意义,有学者建议对所有医务工作者定期开展全面的核酸和血清抗体筛查^[19]。对那些收治有基础疾病或免疫抑制病人的大型医疗中心,更要尽早识别并隔离无症状感染的医护人员,降低免疫力低下的病人在院内感染的风险。另外,对于参与重点区域社区防控的一线工作人员及接触发热患者的高危科室的医护人员,需要特别注意定期筛查,避免院内的交叉感染。

一项研究显示,相比直接接触SARS-CoV-2感染患者的高危医护人员,中危医护人员(仅接触非SARS-CoV-2患者)的血清抗体阳性率更高(5.4% vs 1.2%)^[130],这可能与其自我防控意识不够及个人防护措施使用不规范有关。这也提示了我们对所有医护人员感染监测的必要性。我们希望获得更多的数据,如社区医疗机构医护人员的阳性率、不同科室阳性率比较等,以用于了解和指导医护人员风险分层管理。

5 总结与展望

我国已暂时进入“后暴发”阶段,模拟病毒流行趋势的模型提示,SARS-CoV-2在未来可能有再次暴发流行的风险。本文通过总结SARS-CoV-2的现有知识,结合不同科室的临床特点,分析了在“后暴发”阶段医护面临的防控挑战,提出一些应对的思考。希望通过分享相关临床知识,分析“后暴发”阶段疫情防控的关键点,提升医护人员的防护意识和水平,避免医院成为SARS-CoV-2交叉感染的地方。

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Summary for “SARS-CoV-2‘后暴发’阶段医院感染控制”

The challenge and management of nosocomial infection control during the “post-outbreak” period of SARS-CoV-2

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The novel coronavirus SARS-CoV-2 is causing a pandemic worldwide. Several months after the initial outbreak, with the help of tight isolation policy, SARS-CoV-2 transmission in the general population is now under control in China. The number of new cases dramatically decreases compared to the outbreak period. Thus, we name this phase the “post-outbreak” period when China has lived through the pandemic phase while many other countries are still facing fast growing cases. To keep the number of new cases at low level under the consistent pressure of imported cases from other countries and prevent a second outbreak in China are tremendous challenges to all workers in the health care system. Currently available studies of the basic reproduction number (R_0) of SARS-CoV-2 demonstrate that the new virus has a higher transmission capacity than other coronaviruses such as SARS-CoV and MERS-CoV. Besides, longitudinal serological studies illuminate that protective antibodies to SARS-CoV-2 may turn negative at early convalescent phase in certain patients, indicating a relatively short protection time. Recent prediction models of the transmission dynamics suggested a risk of recurrent outbreaks of SARS-CoV-2, even in seasonal or perennial pattern. When autumn and winter are approaching, the number of patients infected with SARS-CoV-2 will be likely to increase if appropriate measures are not taken, which will further challenge the medical system. It has been shown that during the outbreak period, the infection rate of SARS-CoV-2 among medical workers is relatively high. According to the serum specific antibody test, about half of the front-line medical staffs have been infected in some countries. Some cluster cases of SARS-CoV-2 infection in hospital settings have been reported. This indicates that the risk of virus transmission in the hospital environment is high and more intensive infection control is needed. In this article, we particularly focus on several high-risk areas, such as respiratory clinics, eye clinics and obstetrical clinics. We summarize their unique clinical practices and possible risks of virus transmission, and propose some suggestions for the protection of health care workers in daily work during the “post-outbreak” period based on guidelines proposed by international groups and specialists of the fields. The review also discusses some approaches that hospitals can take during the “post-outbreak” period to early detect infected patients and cut nosocomial transmission. We focus on the topics including the prevention of the virus spreading via aerosol between patients and doctors, innovation of fast and reliable diagnostic methods to effectively identify SARS-CoV-2 carriers from large number of suspected patients, implementation of effective remote doctor consultation and establishment of a patient stratification system to reduce cross-infection, etc. This article aims to highlight the awareness of SARS-CoV-2 virus transmission in hospitals and clinics during the “post-outbreak” phase and propose crucial aspects for the research of nosocomial infection control.

SARS-CoV-2, nosocomial infection control, protection of health care workers, viral detection, post-outbreak period

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