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雾化吸入用药在新冠肺炎疫情中的研究现状

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摘　要

新型冠状病毒肺炎(Corona Virus Disease 2019, COVID-19) (以下简称“新冠肺炎”)已经造成了全球大爆发、大流行，新冠肺炎患者的研究和临床观察表明，2019新型冠状病毒(SARS-CoV-2)的主要靶点是肺。雾化吸入作为一种以肺为主要靶器官的直接给药方法，在治疗呼吸系统相关疾病中发挥着重要作用。但是目前，针对于COVID-19的全球大流行态势，雾化吸入用药的优势尚未被有效利用，本文旨在对新冠肺炎疫情中对雾化吸入用药的研究现状进行综述，为新冠肺炎患者治疗期间雾化吸入用药提供参考。

关键词

新型冠状病毒肺炎，2019新型冠状病毒，雾化吸入，给药途径

Research Status of Aerosol Inhalation Drugs in COVID-19 Outbreak

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Abstract

COVID-19 (Corona Virus Disease 2019) (hereinafter referred to as “COVID-19”) has produced a global outbreak, pandemic, COVID-19 patient studies and clinical observations have shown that

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the main target of the Novel Corona virus 2019 (SARS-COV-2) is the lung. Aerosol inhalation, as a direct drug delivery method with the lung as the main target organ, plays an important role in the treatment of respiratory diseases. However, in view of the global pandemic situation of COVID-19, the advantages of aerosol inhalation medication have not been effectively utilized. This paper aims to review the research status of aerosol inhalation medication in COVID-19 epidemic, and provide reference for aerosol inhalation medication during the treatment of COVID-19 patients.

Keywords

Corona Virus Disease 2019, SARS-CoV-2, Aerosol Inhalation, Administration Route

1. 引言

新型冠状病毒肺炎(Corona Virus Disease 2019, COVID-19) (以下简称“新冠肺炎”)已经造成了全球大规模爆发，世界卫生组织已宣布其为大流行[1]。据报道，有症状的新型冠状病毒患者表现为发热、干咳、气短和肌痛。死亡率主要源于急性肺损伤、呼吸衰竭、急性呼吸窘迫综合征(Acute Respiratory Distress Syndrome, ARDS)等关联疾病。死后评估的病理报告描述了双侧弥漫性肺泡损伤，伴有水肿、肺细胞脱落、透明膜形成和大量肺栓塞[2] [3]。它的初期症状常表现为咳嗽和发热，大约 8 天后，20%的患者会出现呼吸困难，大约 10%的患者会出现肺部炎性浸润[4] [5]。大约 25%的住院患者在症状出现后的第 10~12 天出现 ARDS [5]。新冠肺炎患者的研究和临床观察表明，2019 新型冠状病毒(SARS-CoV-2)的主要靶点是肺[6]。雾化吸入作为一种以肺为主要靶器官的给药方式，具有起效快、用药量少、局部药物浓度高、应用方便及全身不良反应少等众多优点，已被作为呼吸系统相关疾病重要的治疗手段[7]。目前，针对于 COVID-19 的全球大流行态势，雾化吸入用药的优势尚未被有效地利用，相关研究大多停留在理论层面，雾化吸入途径也被认为存在着增加 COVID-19 传染的风险[8] [9]，本文旨在对新冠肺炎疫情中对雾化吸入用药的研究现状进行综述，为新冠肺炎患者治疗期间雾化吸入用药提供参考。

2. 新冠肺炎与雾化吸入用药

2.1. 一氧化氮

一氧化氮是一种内皮衍生的舒张因子，在血管信号传导、血流调节和宿主防御中发挥关键作用[10]。当前 SARS-CoV-2 的总核苷酸序列显示出与 SARS-CoV-1 约 79%的相似性[11] [12]，病理学和遗传结构的重叠使得 SARS-CoV-2 与更多关于 SARS-CoV-1 病理生理学的已有文献具有相似性。正常的一氧化氮/活性氧平衡对正常的血管功能至关重要。其在调节炎症级联反应中起关键作用，当在内皮功能下降的情况下过度激活时，炎症级联反应会导致急性肺损伤和急性呼吸窘迫综合征。缺乏一氧化氮的脉管系统受到炎症和氧气输送减弱的影响，清除有毒副产物的能力会大大降低[13] [14] [15]。在宿主细胞中，病毒感染期间 iNOS 通常会升高，而在 SARS-CoV-1 感染中，一氧化氮通过氧亚硝酸盐等中间体通过细胞毒性反应抑制病毒复制[16]。红细胞表面和血红蛋白四聚体 β 链上反应性硫醇的亚硝化作用分别稳定了溶血和氧化损伤[17] [18]，赋予一氧化氮控制新型冠状病毒红细胞相关致病过程的潜力。因为新型冠状病毒会感染内皮细胞，而内皮细胞是一氧化氮合成的主要来源，所以这种分子还能很好地应对病毒攻击。大流行

中的脆弱人群可能具有较低水平的内源性一氧化氮。由一氧化氮合酶产生的一氧化氮随着年龄的增长而下降，患有慢性血管炎症的患者，如 2 型糖尿病、慢性阻塞性肺病的患者，可能产生较少的一氧化氮合酶[19] [20] [21]。此外，血管紧张素转换酶活性相对于血管紧张素转换酶 2 活性可能在慢性血管炎症患者中升高[22] [23]。患有潜在慢性疾病血管应激源的老年患者可能表现出血管一氧化氮水平不足，增加了他们对缺血/再灌注和缺血/再灌注损伤的脆弱性。因此，针对目标患者群体的外源性一氧化氮可能是一种治疗方法，可以减少肺部的病毒载量，促进 ARDS 的临床恢复。

通过上文的描述不难看出，在新冠肺炎感染的早期，给予适量的、持续的一氧化氮可能会限制向 ARDS 和暴发性全身衰竭的进展，并且可以减少病毒复制，下调血管紧张素转换酶，防止任何基于缺氧-复氧/缺血再灌注的炎症的发作，控制细胞因子级联，允许去除细胞碎片，限制脂质过氧化和伴随的细胞损伤，降低有害的血管通透性并保持适当的血流。

2.2. 吸入性糖皮质激素(Inhaled Corticosteroids, ICS)

ICS 作为经典的雾化吸入用药，常常单独使用或与支气管扩张剂联合使用，被广泛用于哮喘的治疗[24]，与支气管扩张剂联合使用在部分 COPD 患者的管理中发挥作用[25]。在新冠肺炎大流行期间使用 ICS 时，关于其对病毒感染和恶化率的影响存在许多争论。过去的研究已经证实，在哮喘和慢性阻塞性肺疾病中使用 ICS 与上呼吸道感染风险增加相关[26] [27]。在慢性阻塞性肺疾病患者中，使用 ICS 与更高的肺炎患病率和肺部微生物组的变化有关，尽管这并不是呼吸系统病毒检测的变化[28] [29]。但有不同的研究提示 ICS 可以成为新冠肺炎的治疗干预。首先，在有急性呼吸窘迫综合征风险的患者中使用 ICS 已被证明可以改善生理状况并降低炎症标记物水平[30]。在入院前使用 ICS 的高危患者中，甚至在控制年龄、性别和慢性呼吸系统疾病后，ARDS 也减少了 50% [31]。此外，ICS 的使用似乎还可以改善肺生理状况[32]。其次，体外数据表明 ICS 在抑制感染上皮细胞的冠状病毒复制(包括 SARSCoV-2)中起作用[33]。在体外，ICS 已被证明可以减弱导致病毒清除延迟的抗病毒先天免疫反应[34] [35]。在以前的新的冠状病毒爆发(SARS, MERS)中，关于 ICS 的研究没有显示出益处或危害[36]。然而，在被诊断为新冠肺炎的患者中，地塞米松显著降低了 28 天的死亡率，特别是在那些接受补充氧气或机械通气的患者[37]。

目前，没有确凿证据表明在冠状病毒引起的急性呼吸道感染中，疾病前使用或持续服用 ICS 是否是不良或有益结果的一个因素。这迫切需要进一步的数据和研究。临床医生应该意识到，没有证据支持在使用这些药物治疗的患者中停用 ICS，这样做很可能产生不利的影响。使用 ICS 时病情稳定的哮喘和慢阻肺患者应继续治疗。

2.3. 羟氯喹

羟氯喹(Hydroxychloroquine, HCQ)为 4-氨基喹啉衍生物类抗疟药，这是一种已获批准的抗疟疾和抗风湿剂，具有众所周知的安全性[38] [39]。HCQ 在体外显示出了抗 SARS-CoV 的活性[40]，这使得其在新冠肺炎大流行期间被提出将其作为用于治疗冠状病毒疾病的再利用药物之一。但是它作为一种有效的新冠肺炎治疗方法的潜力仍然存在争议[41] [42]。所有已发表的临床试验都涉及口服该药物，尽管该疾病主要是呼吸系统疾病。直接吸入给药可以减少与口服相关的副作用，并确保药物在肺部的高浓度。目前，Albariqi A. H.等人已成功制备出 HCQ-舒乐可吸入结晶粉末，可作为潜在的吸入新冠肺炎疗法用于临床试验[43]。在未来，吸入性的 HCQ 若顺利通过临床试验，可能作为一种潜在的治疗选择，以较少的频率和相对较低的剂量将 HCQ 直接输送到肺部治疗新冠肺炎肺部疾病。

3. 新冠肺炎传播与雾化吸入

越来越多的证据证明，SARS-CoV-2 的大部分传播是通过呼吸道途径，病毒潜伏在飞沫中，或者是

气溶胶中[8]。一些超级传播事件提示着呼吸道途径在 SARS-CoV-2 传播疫情方面起着重要作用[8]。特别是，这些事件主要影响那些在通风不良的室内环境中长时间保持密切接触的人。到目前为止，空气采样在一些研究中发现了病毒 RNA，但在另一些研究中没有[44]。显然，当易感人群吸入了在环境中仍能存活的携带病毒的细小呼吸道飞沫时，就会发生空气传播[45]。该病毒可以通过吸入感染者排出的细小飞沫直接传播，也可以通过在感染者身上产生气溶胶的过程传播。因此，受感染患者产生的生物气溶胶是 SARS CoV-2 和其他感染源的主要潜在传播源[46]。意识到病毒通过空气传播的风险使患者在使用吸入性药物时犹豫不决，因为它们被认为是病毒传播和免疫抑制的潜在来源[47]。尽管新冠肺炎上有很多讨论，但对于在家中治疗的肺部疾病患者却鲜有人关注[47]。无论如何，许多医生和患者认为，避免对在家中治疗的新冠肺炎和肺部疾病患者进行不必要的雾化治疗是很重要的[9]。然而，在 2020 年的全球哮喘倡议(GINA)战略中，建议也在新冠肺炎大流行期间，所有哮喘患者按照医生的处方继续使用包括吸入性皮质类固醇在内的所有吸入性药物[48]。控制良好的患者出现哮喘似乎不会增加感染 SARS-CoV-2 的风险，也不会增加新冠肺炎引起的并发症[49]。此外，目前没有任何确凿证据支持冠状病毒感染可能导致哮喘加重的可能性[50]。

总之，为了降低传染他人的风险，患者在使用雾化吸入药物时，应遵循社交距离指导，避免在他人在场的情况下使用。此外，还应实施严格的雾化器卫生等预防措施，雾化应在打开的窗户附近或空气流通增加的区域进行。在适用的情况下，可以考虑使用长效药物进行雾化治疗，这样可以减少给药频率，进一步减少暴露。充分利用好雾化吸入药物的优势，同时避免新冠肺炎传播。

4. 结语

新冠肺炎大流行的出现正对患者身体与医疗基础设施施加着巨大压力，患者迫切需要有效的药物来减缓疾病。疫苗和靶向药物的研究仍在继续，许多医学研究也正在积极探索其感染的病理生理学，寻找合理的干预点。夸张的免疫反应和不受控制的炎症可能是严重疾病的根源[51]。雾化吸入用药在类似的呼吸系统疾病模型中显示出不错的前景，早期报道的概念证明迫切需要治疗新冠肺炎的随机对照试验。如果雾化吸入用药能在为新冠肺炎寻找其适应症时证明它的功效，那么在不久的将来雾化吸入用药定会在全世界抗击新冠肺炎疫情的斗争中发挥重要作用。

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