Essential Takeaways from China's Response to COVID-19

This memo has been written by three top-level Norwegian scientists with links to China and the pharmaceutical industry:

- **Yun Zhou PhD,** Biomedical Researcher from Wuhan, living in Norway. Dr. Zhou reads and speaks Chinese (Mandarin) fluently and has been communicating with some physicians and family members in China and Wuhan about the COVID-19 epidemic, and read Chinese newspapers and searched Chinese web sites on a daily basis since the first cases were reported.
- **Niels Chr. Danbolt MD, PhD, Professor,** Institute of Basic Medical Sciences, University of Oslo, has worked with Dr. Zhou to acquire insight about effective treatments and containment strategies for COVID-19.
- **Stefan Krauss MD, PhD, Professor**, Centre Director HTH Center of Excellence, University of Oslo, has a background in drug development.

The authors believe The CDC and WHO may be missing crucial information about treating and containing COVID-19. They believe the information is missed because it is only available in Chinese.

The authors believe that the information could be important for treating and limiting the spread of the COVID-19.

This memo is primarily based on open-source intelligence which is available to anyone with a medical background who is fluent in Chinese. Some information is also supplemented by statements from personal contacts (physicians and family members) in China.

Key sources:

- Official Chinese websites containing guidelines for treatment (e.g. http://www.gov.cn/)[1,2]
- Chinese medical journals with links to PubMed. Those without such links have been unavailable to us in Norway.
- State controlled newspapers.
- Sources inside the Chinese medical establishment, particularly inside Wuhan itself.

Key points:

1. The morbidity and mortality rates are so high that the virus causes the healthcare systems to be overwhelmed. The virus must be contained, and that explains the massive Chinese response with extensive quarantine measures.

2. While an approved drug for COVID-19 treatment does not exist, some drugs appear to be effective in treating the disease. One of these is the malaria drug chloroquine (both the phosphate version, and the hydroxy-variant). Chloroquine appears to be most effective if given early in the disease when symptoms are mild. This was reported in Chinese newspapers and other state-controlled media as early as early February[3, 4]. Chloroquine is the drug most often mentioned in Chinese newspapers. It simple and fast to produce in large quantities and its side effects are well known and controllable.

3. For patients not tolerating or responding to chloroquine, three other drugs have been tried: Remdesivir, Lopinavir/Ritonavir and Umifenovir (Arbidol). All of these have moderate to severe side-effects (https://www.nasdaq.com/articles/early-results-dampen-outlook-for-experimental-covid-19-treatment-2020-03-14; https://www.statnews.com/pharmalot/2020/03/13/gilead-coronavirus-covid19-clinical-trials/), they are less studied, and they are more expensive to produce.

4. Chinese authorities have, according to our open-source intelligence, placed large orders on chloroquine, and we have got the impression that they may be using this drug on a vast scale (e.g. https://www.yicaiglobal.com/news/guangzhou-pharma-taps-old-antimalarial-drug-after-covid-19-use-is-proven; https://www.shine.cn/biz/economy/2002202403/). Guangzhou Baiyunshan Guanghua Pharma has resumed full production capacity and has a daily capacity of 2 million tablets, suggesting that the Chinese authorities believe that chloroquine is effective.

5. A key point is that Western publications have not caught up with the above information as it is only available in Chinese. The authors of this memo are concerned that Western authorities (e.g. CDC and WHO) are unaware of important information that can be used to effectively deal with the COVID-19 pandemic. Information on the potential benefits of chloroquine for treatment of COVID-19 mediated disease is beginning to appear in Western media[5, 6, 7, 8].

6. To what extent chloroquine treatment has been a key factor in the apparent Chinese success in fighting COVID-19 is unknown, but the evidence for a key role of chloroquine in this epidemic is compelling and needs to be investigated.

7. Our sources indicate that chloroquine administered at a sufficiently early stage may lower the number of patients that will require hospitalization. In fact, this is what the Chinese have tried to do. Early treatment of infected people in Wuhan City reduced the percentage of severe conditions from 38% to 18%[9]. In contrast, when the disease has progressed into a serious condition requiring intensive care admission and artificial ventilation, the treatment is less effective and a significant number of patients will die. To summarize:

    a. There is an existing drug, well tested, well documented and with manageable side effects, which is neither exceptionally expensive nor difficult to produce and is fairly effective if administered at the correct time.
    b. In order to maximize the effectiveness of chloroquine it will be necessary to identify infected patients as early as possible through extensive testing with a rapid turn-around time.

8. There are also rumors that chloroquine may prevent the development of the disease if given at smaller doses to asymptomatic individuals. If this is correct, then prophylactic treatment of people at risk (e.g. health personnel and individuals with underlying conditions) may be possible.

9. A high percentage of infected people may be absent from work for months and the Chinese are becoming stricter with respect to declaring an infected patient disease-free. Effective March 6th, 2020, they only release infected patients from quarantine after they have developed COVID-19 neutralizing antibodies[10]. Infected patients with no or minimal antibody response are kept in quarantine as there is increasing evidence that they continue to shed virus and therefore can infect others. We have also been told by friends in Wuhan (undocumented personal information)

that China is considering 4 weeks of quarantine rather than the current recommendation of 2 weeks.

10. There are speculations that some patients die from an uncontrolled immune response (a.k.a. “cytokine storm”) and the immune suppressing drug Tocilizumab is being tested to prevent or stop this serious complication.

11. There are discussions whether ADE (antibody-dependent enhancement) may complicate vaccine development and pose a significant risk if reinfection occurs with a mutated virus.

12. Because the disease originated in animals, it may be worthwhile to check whether domestic animals need protection.

Potential strategy implications based on the above findings:

1. More resources need to be allocated to learn more about what has actually happened in China and what the Chinese have learnt from it. Relevant agencies should search Chinese sources and also interview Chinese doctors and other relevant persons. This latter part may be somewhat challenging, for obvious reasons.

2. The capacity for early diagnosis need to be radically expanded and combined with a decentralized access to relevant drugs (including chloroquine phosphate and/or hydroxychloroquine). The majority of the infected may then be able to treat themselves at home under remote medical guidance. This could have major implications because the number of patients admitted to hospitals would decrease and fewer people would need long sick-leaves. This in turn would also reduce the infection rate among healthcare workers.

3. The production of chloroquine in sufficient amounts to cover the entire US population, and hopefully also those of US allies, should be contemplated. At present, we are dependent on the Chinese for production both of chloroquine and the central materials needed to make it.

4. The West should increase own production of a panel of anti-viral drugs and antibiotics. Anti-viral drugs reported by the Chinese and others to be effective, are not available in sufficient quantities (e.g. https://theprint.in/theprint-essential/what-are-apis-and-how-they-threaten-indias-status-of-a-pharmacy-to-the-world/370941/).

An additional point:
It is currently speculated whether chloroquine is able, not only to cure, but also prevent the onset of a Corvid-19 infection. How can we get an indication if it can work prophylactically? Patients suffering from rheumatoid arthritis and patients with systemic lupus erythematosus are often receiving hydroxy-chloroquine to keep the disease in check. If these patients do not get infected (or have a reduced risk to get infected) with coronavirus, then a likely interpretation is that chloroquine may have a protective effect. We got the following information from a hospital in Wuhan: "In the early stage of the study group, through the clinical analysis of 178 patients with new coronavirus received by the hospital from December 2019, it was found that none of them has systemic lupus erythematosus. After that, in the consultation of 80 patients with systemic lupus erythematosus treated by dermatology department of the hospital, it was found that they were not infected with new coronavirus pneumonia.

(https://www.jqknews.com/news/388543). This is at current only an indication. We therefore propose that the US authorities explores health registries to identify a potential connection between hydroxychloroquine treatment and Covid-19 prevalence. Information could be gained within days. Particular good sources may be European countries and South Korea, but also China. If hydroxychloroquine has a protective function, we may - in combination with traditional measures (quarantine etc.) – be able to bring the transmission rate below 1 (each infected will infect on average less than 1 other person) and the epidemic may be contained in short time.

Attachments

[1] 2020-02-18 Chinese Guideline VI The Prevention, Diagnosis and Treatment of Pneumonia caused by COVID 19
[2] 2020-03-03 Chinese Guideline VII The Prevention, Diagnosis and Treatment of Pneumonia caused by COVID 19
[3] 2020-02-20 Chinese social media-The potentials of chloroquine in the treatment of Covid 19
[4] 2020-03-12 Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia
[5] Colson et al 2020
[6] Gao et al 2020
[7] Touret and de Lamballerie 2020
[8] Wang et al 2020
[9] 2020-02-17 Early Diagnosis and Treatment
[10] 2020-03-06 Recovered patients must have developed antibodies to be released

Attachments

新型冠状病毒肺炎诊疗方案

（试行第六版）

2019 年 12 月以来，湖北省武汉市陆续发现了多例新型冠状病毒肺炎患者，随着疫情的蔓延，我国其他地区及境外也相继发现了此类病例。该病作为急性呼吸道传染病已纳入《中华人民共和国传染病防治法》规定的乙类传染病，按甲类传染病管理。随着疾病认识的深入和诊疗经验的积累，我们对《新型冠状病毒肺炎诊疗方案（试行第五版 修正版）》进行修正，形成了《新型冠状病毒肺炎诊疗方案（试行第六版）》。

一、病原学特点

新型冠状病毒属于β属的冠状病毒，有包膜，颗粒呈圆形或椭圆形，常为多形性，直径 60-140nm。其基因特征与 SARSr-CoV 和 MERSr-CoV 有明显区别。目前研究显示与蝙蝠 SARS 样冠状病毒（bat-SL-CoVZC45）同源性达 85%以上。体外分离培养时，2019-nCoV 96 个小时左右即可在人呼吸道上皮细胞内发现，而在 Vero E6 和 Huh-7 细胞系中分离培养需约 6 天。

对冠状病毒理化特性的认识多来自对 SARSr-CoV 和 MERSr-CoV 的研究。病毒对紫外线和热敏感，56℃ 30 分钟、乙醚、75%乙醇、含氯消毒剂、过氧乙酸和氯仿等脂溶剂均可有效灭活病毒，氯已定不能有效灭活病毒。

二、流行病学特点

（一）传染源。

目前所见传染源主要是新型冠状病毒感染的患者。无症状感染者也可能成为传染源。

（二）传播途径。

经呼吸道飞沫和密切接触传播是主要的传播途径。在相对封闭的环境中长时间暴露于高浓度气溶胶情况下存在经气溶胶传播的可能。

（三）易感人群。

人群普遍易感。

三、临床特点

（一）临床表现。

基于目前的流行病学调查，潜伏期 1-14 天，多为 3-7 天。

以发热、干咳、乏力为主要表现。少数患者伴有鼻塞、流涕、咽痛、肌痛和腹泻等症状。重症患者多在发病一周后出现呼吸困难和/或低氧血症，严重者可快速进展为急性呼吸窘迫综合征、脓毒症休克、难以纠正的代谢性酸中毒和出凝血功能障碍及多器官功能衰竭等。值得注意的是重型、危重型患者病程中可为中低热，甚至无明显发热。

轻型患者仅表现为低热、轻微乏力等，无肺炎表现。

从目前收治的病例情况看，多数患者预后良好，少数患者病情危重。老年人和有慢性基础疾病者预后较差。儿童病例症状相对较轻。

（二）实验室检查。

发病早期外周血白细胞总数正常或减少，淋巴细胞计数减少，部分患者可出现肝酶、乳酸脱氢酶（LDH）、肌酶和肌红蛋白增高；部分危重者可见肌钙蛋白增高。多数患者C反应蛋白（CRP）和血沉升高，降钙素原正常。严重者D-二聚体升高、外周血淋巴细胞进行性减少。重型、危重型患者常有炎症因子升高。

在鼻咽拭子、痰和其他下呼吸道分泌物、血液、粪便等标本中可检测出新型冠状病毒核酸。

为提高核酸检测阳性率，建议尽可能留取痰液，实施气管插管患者采集下呼吸道分泌物，标本采集后尽快送检。

（三）胸部影像学。

早期呈现多发小斑片影及间质改变，以肺外带明显。进而发展为双肺多发磨玻璃影、浸润影，严重者可出现肺实变，胸腔积液少见。

四、诊断标准

（一）疑似病例。

结合下述流行病学史和临床表现综合分析：

1.流行病学史

（1）发病前14天内有武汉市及周边地区，或其他有病例报告社区的旅行史或居住史；

（2）发病前14天内与新型冠状病毒感染者（核酸检测阳性者）有接触史；

（3）发病前14天内曾接触过来自武汉市及周边地区，或来自有病例报告社区的发热或有呼吸道症状的患者；

（4）聚集性发病。

2.临床表现

（1）发热和/或呼吸道症状；

（2）具有上述新型冠状病毒肺炎影像学特征；

（3）发病早期白细胞总数正常或降低，淋巴细胞计数减少。

有流行病学史中的任何一条，且符合临床表现中任意2条。无明确流行病学史的，符合临床表现中的3条。

（二）确诊病例。

疑似病例，具备以下病原学证据之一者：

1.实时荧光RT-PCR检测新型冠状病毒核酸阳性；

2.病毒基因测序，与已知的新型冠状病毒高度同源。

五、临床分型

（一）轻型。

临床症状轻微，影像学未见肺炎表现。

（二）普通型。

具有发热、呼吸道等症状，影像学可见肺炎表现。

（三）重型。

符合下列任何一条：

1.出现气促，RR≥30次/分；

2.静息状态下，指氧饱和度≤93%；

3.动脉血氧分压（PaO_2）/吸氧浓度（FiO_2）≤300mmHg

（1mmHg=0.133kPa）。

高海拔（海拔超过1000米）地区应根据以下公式对PaO_2/FiO_2进行校正：PaO_2/FiO_2 x [大气压(mmHg)/760]

肺部影像学显示24-48小时内病灶明显进展>50%者按重型管理。

（四）危重型。

符合以下情况之一者：

1.出现呼吸衰竭，且需要机械通气；

2.出现休克；

3.合并其他器官功能衰竭需ICU监护治疗。

六、鉴别诊断

（一）新型冠状病毒感染轻型表现需与其它病毒引起的上呼吸道感染相鉴别。

（二）新型冠状病毒肺炎主要与流感病毒、腺病毒、呼吸道合胞病毒等其他已知病毒性肺炎及肺炎支原体感染鉴别，尤其是对疑似病例要尽可能采取包括快速抗原检测和多重PCR核酸检测等方法，对常见呼吸道病原体进行检测。

（三）还要与非感染性疾病，如血管炎、皮肌炎和机化性肺炎等鉴别。

七、病例的发现与报告

各级各类医疗机构的医务人员发现符合病例定义的疑似病例后，应当立即进行单人间隔离治疗，院内专家会诊或主诊医师会诊，仍考虑疑似病例，在2小时内进行网络直报，并采集

标本进行新型冠状病毒核酸检测，同时在确保转运安全前提下立即将疑似病例转运至定点医院。与新型冠状病毒感染者有密切接触的患者，即便常见呼吸道病原检测阳性，也建议及时进行新型冠状病毒病原学检测。

八、治疗

（一）根据病情确定治疗场所。

1.疑似及确诊病例应在具备有效隔离条件和防护条件的定点医院隔离治疗，疑似病例应单人单间隔离治疗，确诊病例可多人收治在同一病室。

2.危重型病例应当尽早收入 ICU 治疗。

（二）一般治疗。

1.卧床休息，加强支持治疗，保证充分热量；注意水、电解质平衡，维持内环境稳定；密切监测生命体征、指氧饱和度等。

2.根据病情监测血常规、尿常规、CRP、生化指标（肝酶、心肌酶、肾功能等）、凝血功能、动脉血气分析、胸部影像学等。有条件者可行细胞因子检测。

3.及时给予有效氧疗措施，包括鼻导管、面罩给氧和经鼻高流量氧疗。

4.抗病毒治疗：可试用α-干扰素（成人每次 500 万 U 或相当剂量，加入灭菌注射用水 2ml，每日 2 次雾化吸入）、洛匹那韦/利托那韦（成人 200mg/50mg/粒，每次 2 粒，每日 2 次，疗程不超过 10 天）、利巴韦林（建议与干扰素或洛匹那韦/利托那

韦联合应用，成人500mg/次，每日2至3次静脉输注，疗程不超过10天）、磷酸氯喹（成人500mg，每日2次，疗程不超过10天）、阿比多尔（成人200mg，每日3次，疗程不超过10天）。要注意洛匹那韦/利托那韦相关腹泻、恶心、呕吐、肝功能损害等不良反应，同时要注意和其他药物的相互作用。在临床应用中进一步评价目前所试用药物的疗效。不建议同时应用3种及以上抗病毒药物，出现不可耐受的毒副作用时应停止使用相关药物。

5. 抗菌药物治疗：避免盲目或不恰当使用抗菌药物，尤其是联合使用广谱抗菌药物。

（三）重型、危重型病例的治疗。

1. 治疗原则：在对症治疗的基础上，积极防治并发症，治疗基础疾病，预防继发感染，及时进行器官功能支持。

2. 呼吸支持：

(1) 氧疗：重型患者应当接受鼻导管或面罩吸氧，并及时评估呼吸窘迫和（或）低氧血症是否缓解。

(2) 高流量鼻导管氧疗或无创机械通气：当患者接受标准氧疗后呼吸窘迫和（或）低氧血症无法缓解时，可考虑使用高流量鼻导管氧疗或无创通气。若短时间（1-2小时）内病情无改善甚至恶化，应当及时进行气管插管和有创机械通气。

(3) 有创机械通气：采用肺保护性通气策略，即小潮气量（4-8ml/kg理想体重）和低吸气压力（平台压<30cmH2O）进行机械通气，以减少呼吸机相关肺损伤。较多患者存在人机不同

步，应当及时使用镇静以及肌松剂。

(4) 挽救治疗：对于严重 ARDS 患者，建议进行肺复张。在人力资源充足的情况下，每天应当进行 12 小时以上的俯卧位通气。俯卧位通气效果不佳者，如条件允许，应当尽快考虑体外膜肺氧合（ECMO）。

3. 循环支持：充分液体复苏的基础上，改善微循环，使用血管活性药物，必要时进行血流动力学监测。

4. 康复者血浆治疗：适用于病情进展较快、重型和危重型患者。用法用量参考《新冠肺炎康复者恢复期血浆临床治疗方案（试行第一版）》。

5. 其他治疗措施

对于氧合指标进行性恶化、影像学进展迅速、机体炎症反应过度激活状态的患者，酌情短期内（3～5 日）使用糖皮质激素，建议剂量不超过相当于甲泼尼龙 1～2mg/kg/日，应当注意较大剂量糖皮质激素由于免疫抑制作用，会延缓对冠状病毒的清除；可静脉给予血必净 100ml/次，每日 2 次治疗；可使用肠道微生态调节剂，维持肠道微生态平衡，预防继发细菌感染；对有高炎症反应的重危患者，有条件的可考虑使用血浆置换、吸附、灌流、血液/血浆滤过等体外血液净化技术。

患者常存在焦虑恐惧情绪，应当加强心理疏导。

（四）中医治疗。

本病属于中医“疫”病范畴，病因为感受“疫戾”之气，各地可根据病情、当地气候特点以及不同体质等情况，参照下

列方案进行辨证论治。涉及到超药典剂量，应当在医师指导下使用。

1. 医学观察期

临床表现 1：乏力伴胃肠不适

推荐中成药：藿香正气胶囊（丸、水、口服液）

临床表现 2：乏力伴发热

推荐中成药：金花清感颗粒、连花清瘟胶囊（颗粒）、疏风解毒胶囊（颗粒）

2. 临床治疗期（确诊病例）

2.1 清肺排毒汤

适用范围：适用于轻型、普通型、重型患者，在危重型患者救治中可结合患者实际情况合理使用。

基础方剂：麻黄 9g、炙甘草 6g、杏仁 9g、生石膏 15～30g（先煎）、桂枝 9g、泽泻 9g、猪苓 9g、白术 9g、茯苓 15g、柴胡 16g、黄芩 6g、姜半夏 9g、生姜 9g、紫菀 9g、冬花 9g、射干 9g、细辛 6g、山药 12g、枳实 6g、陈皮 6g、藿香 9g。

服法：传统中药饮片，水煎服。每天一付，早晚两次(饭后四十分钟)，温服，三付一个疗程。

如有条件，每次服完药可加服大米汤半碗，舌干津液亏虚者可多服至一碗。(注：如患者不发热则生石膏的用量要小，发热或壮热可加大生石膏用量)。若症状好转而未痊愈则服用第二个疗程，若患者有特殊情况或其他基础病，第二疗程可以根据实际情况修改处方，症状消失则停药。

处方来源：国家卫生健康委办公厅 国家中医药管理局办公室《关于推荐在中西医结合救治新型冠状病毒感染的肺炎中使

用“清肺排毒汤”的通知》（国中医药办医政函〔2020〕22号）。

2.2 轻型

（1）寒湿郁肺证

临床表现：发热，乏力，周身酸痛，咳嗽，咯痰，胸紧憋气，纳呆，恶心，呕吐，大便粘腻不爽。舌质淡胖齿痕或淡红，苔白厚腐腻或白腻，脉濡或滑。

推荐处方：生麻黄6g、生石膏15g、杏仁9g、羌活15g、葶苈子15g、贯众9g、地龙15g、徐长卿15g、藿香15g、佩兰9g、苍术15g、云苓45g、生白术30g、焦三仙各9g、厚朴15g、焦槟榔9g、煨草果9g、生姜15g。

服法：每日1剂，水煎600ml，分3次服用，早中晚各1次，饭前服用。

（2）湿热蕴肺证

临床表现：低热或不发热，微恶寒，乏力，头身困重，肌肉酸痛，干咳痰少，咽痛，口干不欲多饮，或伴有胸闷脘痞，无汗或汗出不畅，或见呕恶纳呆，便溏或大便粘滞不爽。舌淡红，苔白厚腻或薄黄，脉滑数或濡。

推荐处方：槟榔10g、草果10g、厚朴10g、知母10g、黄芩10g、柴胡10g、赤芍10g、连翘15g、青蒿10g（后下）、苍术10g、大青叶10g、生甘草5g。

服法：每日1剂，水煎400ml，分2次服用，早晚各1次。

2.3 普通型

（1）湿毒郁肺证

临床表现：发热，咳嗽痰少，或有黄痰，憋闷气促，腹胀，便秘不畅。舌质暗红，舌体胖，苔黄腻或黄燥，脉滑数或弦滑。

推荐处方：生麻黄6g、苦杏仁15g、生石膏30g、生薏苡仁30g、茅苍术10g、广藿香15g、青蒿草12g、虎杖20g、马鞭草30g、干芦根30g、葶苈子15g、化橘红15g、生甘草10g。

服法：每日1剂，水煎400ml，分2次服用，早晚各1次。

（2）寒湿阻肺证

临床表现：低热，身热不扬，或未热，干咳，少痰，倦怠乏力，胸闷，脘痞，或呕恶，便溏。舌质淡或淡红，苔白或白腻，脉濡。

推荐处方：苍术15g、陈皮10g、厚朴10g、藿香10g、草果6g、生麻黄6g、羌活10g、生姜10g、槟榔10g。

服法：每日1剂，水煎400ml，分2次服用，早晚各1次。

2.4 重型

（1）疫毒闭肺证

临床表现：发热面红，咳嗽，痰黄粘少，或痰中带血，喘憋气促，疲乏倦怠，口干苦粘，恶心不食，大便不畅，小便短赤。舌红，苔黄腻，脉滑数。

推荐处方：生麻黄6g、杏仁9g、生石膏15g、甘草3g、藿香10g（后下）、厚朴10g、苍术15g、草果10g、法半夏9g、茯苓15g、生大黄5g（后下）、生黄芪10g、葶苈子10g、赤芍10g。

服法：每日1～2剂，水煎服，每次100ml～200ml，一日2～4次，口服或鼻饲。

（2）气营两燔证

临床表现：大热烦渴，喘憋气促，谵语神昏，视物错瞥，或发斑疹，或吐血、衄血，或四肢抽搐。舌绛少苔或无苔，脉沉细数，或浮大而数。

推荐处方：生石膏 30～60g（先煎）、知母 30g、生地 30～60g、水牛角 30g（先煎）、赤芍 30g、玄参 30g、连翘 15g、丹皮 15g、黄连 6g、竹叶 12g、葶苈子 15g、生甘草 6g。

服法：每日 1 剂，水煎服，先煎石膏、水牛角后下诸药，每次 100ml～200ml，每日 2～4 次，口服或鼻饲。

推荐中成药：喜炎平注射液、血必净注射液、热毒宁注射液、痰热清注射液、醒脑静注射液。功效相近的药物根据个体情况可选择一种，也可根据临床症状联合使用两种。中药注射剂可与中药汤剂联合使用。

2.5 危重型（内闭外脱证）

临床表现：呼吸困难、动辄气喘或需要机械通气，伴神昏，烦躁，汗出肢冷，舌质紫暗，苔厚腻或燥，脉浮大无根。

推荐处方：人参 15g、黑顺片 10g（先煎）、山茱萸 15g，送服苏合香丸或安宫牛黄丸。

推荐中成药：血必净注射液、热毒宁注射液、痰热清注射液、醒脑静注射液、参附注射液、生脉注射液、参麦注射液。功效相近的药物根据个体情况可选择一种，也可根据临床症状联合使用两种。中药注射剂可与中药汤剂联合使用。

注：重型和危重型中药注射剂推荐用法

中药注射剂的使用遵照药品说明书从小剂量开始、逐步辨证调整的原则，推荐用法如下：

病毒感染或合并轻度细菌感染：0.9%氯化钠注射液 250ml 加喜炎平注射液 100mg bid，或 0.9% 氯化钠注射液 250 ml 加热毒宁注射液 20 ml，或 0.9%氯化钠注射液 250ml 加痰热清注

射液 40ml bid。

高热伴意识障碍：0.9%氯化钠注射液 250ml 加醒脑静注射液 20ml bid。

全身炎症反应综合征或/和多脏器功能衰竭：0.9%氯化钠注射液 250ml 加血必净注射液 100ml bid。

免疫抑制：0.9%氯化钠注射液 250ml 加参麦注射液 100ml bid。

休克：0.9%氯化钠注射液 250ml 加参附注射液 100ml bid。

2.6 恢复期

（1） 肺脾气虚证

临床表现：气短，倦怠乏力，纳差呕恶，痞满，大便无力，便溏不爽。舌淡胖，苔白腻。

推荐处方：法半夏 9g、陈皮 10g、党参 15g、炙黄芪 30g、炒白术 10g、茯苓 15g、藿香 10g、砂仁 6g（后下）、甘草 6g。

服法：每日 1 剂，水煎 400ml，分 2 次服用，早晚各 1 次。

（2）气阴两虚证

临床表现：乏力，气短，口干，口渴，心悸，汗多，纳差，低热或不热，干咳少痰。舌干少津，脉细或虚无力。

推荐处方：南北沙参各 10g、麦冬 15g、西洋参 6g，五味子 6g、生石膏 15g、淡竹叶 10g、桑叶 10g、芦根 15g、丹参 15g、生甘草 6g。

服法：每日 1 剂，水煎 400ml，分 2 次服用，早晚各 1 次。

九、解除隔离和出院后注意事项

（一）解除隔离和出院标准。

1.体温恢复正常3天以上;

2.呼吸道症状明显好转;

3.肺部影像学显示急性渗出性病变明显改善;

4.连续两次呼吸道标本核酸检测阴性(采样时间至少间隔1天)。

满足以上条件者,可解除隔离出院。

(二)出院后注意事项。

1.定点医院要做好与患者居住地基层医疗机构间的联系,共享病历资料,及时将出院患者信息推送至患者辖区或居住地居委会和基层医疗卫生机构。

2.患者出院后,因恢复期机体免疫功能低下,有感染其它病原体风险,建议应继续进行14天自我健康状况监测,佩戴口罩,有条件的居住在通风良好的单人房间,减少与家人的近距离密切接触,分餐饮食,做好手卫生,避免外出活动。

3.建议在出院后第2周、第4周到医院随访、复诊。

十、转运原则

按照我委印发的《新型冠状病毒感染的肺炎病例转运工作方案(试行)》执行。

十一、医疗机构内感染预防与控制

严格按照我委《医疗机构内新型冠状病毒感染预防与控制技术指南(第一版)》、《新型冠状病毒感染的肺炎防护中常见医用防护用品使用范围指引(试行)》的要求执行。

抄送：各省、自治区、直辖市及新疆生产建设兵团应对新型冠状病毒肺炎疫情联防联控机制（领导小组、指挥部）。

国家卫生健康委办公厅　　2020年2月18日印发

校对：杜青阳

新型冠状病毒肺炎诊疗方案
（试行第七版）

2019 年 12 月以来，湖北省武汉市出现了新型冠状病毒肺炎疫情，随着疫情的蔓延，我国其他地区及境外多个国家也相继发现了此类病例。该病作为急性呼吸道传染病已纳入《中华人民共和国传染病防治法》规定的乙类传染病，按甲类传染病管理。通过采取一系列预防控制和医疗救治措施，我国境内疫情上升的势头得到一定程度的遏制，大多数省份疫情缓解，但境外的发病人数呈上升态势。随着对疾病临床表现、病理认识的深入和诊疗经验的积累，为进一步加强对该病的早诊早治，提高治愈率，降低病亡率，最大可能避免医院感染，同时提醒注意境外输入性病例导致的传播和扩散，我们对《新型冠状病毒肺炎诊疗方案（试行第六版）》进行修订，形成了《新型冠状病毒肺炎诊疗方案（试行第七版）》。

一、病原学特点

新型冠状病毒属于β属的冠状病毒，有包膜，颗粒呈圆形或椭圆形，常为多形性，直径 60-140nm。其基因特征与 SARS-CoV 和 MERS-CoV 有明显区别。目前研究显示与蝙蝠 SARS 样冠状病毒（bat-SL-CoVZC45）同源性达 85%以上。体外分离培养时，新型冠状病毒 96 个小时左右即可在人呼吸道上皮细胞内发现，而在 Vero E6 和 Huh-7 细胞系中分离培养需约 6 天。

对冠状病毒理化特性的认识多来自对SARS-CoV和MERS-CoV的研究。病毒对紫外线和热敏感，56℃ 30分钟、乙醚、75%乙醇、含氯消毒剂、过氧乙酸和氯仿等脂溶剂均可有效灭活病毒，氯已定不能有效灭活病毒。

二、流行病学特点

（一）传染源。

目前所见传染源主要是新型冠状病毒感染的患者。无症状感染者也可能成为传染源。

（二）传播途径。

经呼吸道飞沫和密切接触传播是主要的传播途径。在相对封闭的环境中长时间暴露于高浓度气溶胶情况下存在经气溶胶传播的可能。由于在粪便及尿中可分离到新型冠状病毒，应注意粪便及尿对环境污染造成气溶胶或接触传播。

（三）易感人群。

人群普遍易感。

三、病理改变

根据目前有限的尸检和穿刺组织病理观察结果总结如下。

（一）肺脏。

肺脏呈不同程度的实变。

肺泡腔内见浆液、纤维蛋白性渗出物及透明膜形成；渗出细胞主要为单核和巨噬细胞，易见多核巨细胞。II型肺泡上皮细胞显著增生，部分细胞脱落。II型肺泡上皮细胞和巨噬细胞

内可见包涵体。肺泡隔血管充血、水肿，可见单核和淋巴细胞浸润及血管内透明血栓形成。肺组织灶性出血、坏死，可出现出血性梗死。部分肺泡腔渗出物机化和肺间质纤维化。

肺内支气管黏膜部分上皮脱落，腔内可见黏液及黏液栓形成。少数肺泡过度充气、肺泡隔断裂或囊腔形成。

电镜下支气管黏膜上皮和II型肺泡上皮细胞胞质内可见冠状病毒颗粒。免疫组化染色显示部分肺泡上皮和巨噬细胞呈新型冠状病毒抗原阳性，RT-PCR检测新型冠状病毒核酸阳性。

（二）脾脏、肺门淋巴结和骨髓。

脾脏明显缩小。淋巴细胞数量明显减少，灶性出血和坏死，脾脏内巨噬细胞增生并可见吞噬现象；淋巴结淋巴细胞数量较少，可见坏死。免疫组化染色显示脾脏和淋巴结内CD4+T和CD8+T细胞均减少。骨髓三系细胞数量减少。

（三）心脏和血管。

心肌细胞可见变性、坏死，间质内可见少数单核细胞、淋巴细胞和（或）中性粒细胞浸润。部分血管内皮脱落、内膜炎症及血栓形成。

（四）肝脏和胆囊。

体积增大，暗红色。肝细胞变性、灶性坏死伴中性粒细胞浸润；肝血窦充血，汇管区见淋巴细胞和单核细胞细胞浸润，微血栓形成。胆囊高度充盈。

（五）肾脏。

肾小球球囊腔内见蛋白性渗出物，肾小管上皮变性、脱落，可见透明管型。间质充血，可见微血栓和灶性纤维化。

（六）其他器官。

脑组织充血、水肿，部分神经元变性。肾上腺见灶性坏死。食管、胃和肠管黏膜上皮不同程度变性、坏死、脱落。

四、临床特点

（一）临床表现。

基于目前的流行病学调查，潜伏期1-14天，多为3-7天。

以发热、干咳、乏力为主要表现。少数患者伴有鼻塞、流涕、咽痛、肌痛和腹泻等症状。重症患者多在发病一周后出现呼吸困难和/或低氧血症，严重者可快速进展为急性呼吸窘迫综合征、脓毒症休克、难以纠正的代谢性酸中毒和出凝血功能障碍及多器官功能衰竭等。值得注意的是重型、危重型患者病程中可为中低热，甚至无明显发热。

部分儿童及新生儿病例症状可不典型，表现为呕吐、腹泻等消化道症状或仅表现为精神弱、呼吸急促。

轻型患者仅表现为低热、轻微乏力等，无肺炎表现。

从目前收治的病例情况看，多数患者预后良好，少数患者病情危重。老年人和有慢性基础疾病者预后较差。患有新型冠状病毒肺炎的孕产妇临床过程与同龄患者相近。儿童病例症状

相对较轻。

（二）实验室检查。

1．一般检查

发病早期外周血白细胞总数正常或减少，可见淋巴细胞计数减少，部分患者可出现肝酶、乳酸脱氢酶（LDH）、肌酶和肌红蛋白增高；部分危重者可见肌钙蛋白增高。多数患者C反应蛋白（CRP）和血沉升高，降钙素原正常。严重者D-二聚体升高、外周血淋巴细胞进行性减少。重型、危重型患者常有炎症因子升高。

2．病原学及血清学检查

（1）病原学检查：采用RT-PCR或/和NGS方法在鼻咽拭子、痰和其他下呼吸道分泌物、血液、粪便等标本中可检测出新型冠状病毒核酸。检测下呼吸道标本（痰或气道抽取物）更加准确。标本采集后尽快送检。

（2）血清学检查：新型冠状病毒特异性IgM抗体多在发病3-5天后开始出现阳性，IgG抗体滴度恢复期较急性期有4倍及以上增高。

（三）胸部影像学。

早期呈现多发小斑片影及间质改变，以肺外带明显。进而发展为双肺多发磨玻璃影、浸润影，严重者可出现肺实变，胸腔积液少见。

五、诊断标准

（一）疑似病例。

结合下述流行病学史和临床表现综合分析：

1.流行病学史

（1）发病前14天内有武汉市及周边地区，或其他有病例报告社区的旅行史或居住史；

（2）发病前14天内与新型冠状病毒感染者（核酸检测阳性者）有接触史；

（3）发病前14天内曾接触过来自武汉市及周边地区，或来自有病例报告社区的发热或有呼吸道症状的患者；

（4）聚集性发病（2周内在小范围如家庭、办公室、学校班级等场所，出现2例及以上发热和/或呼吸道症状的病例）。

2.临床表现

（1）发热和/或呼吸道症状；

（2）具有上述新型冠状病毒肺炎影像学特征；

（3）发病早期白细胞总数正常或降低，淋巴细胞计数正常或减少。

有流行病学史中的任何一条，且符合临床表现中任意2条。无明确流行病学史的，符合临床表现中的3条。

（二）确诊病例。

疑似病例同时具备以下病原学或血清学证据之一者：

1.实时荧光RT-PCR检测新型冠状病毒核酸阳性；

2.病毒基因测序，与已知的新型冠状病毒高度同源；

3. 血清新型冠状病毒特异性 IgM 抗体和 IgG 抗体阳性；血清新型冠状病毒特异性 IgG 抗体由阴性转为阳性或恢复期较急性期 4 倍及以上升高。

六、临床分型

（一）轻型。

临床症状轻微，影像学未见肺炎表现。

（二）普通型。

具有发热、呼吸道等症状，影像学可见肺炎表现。

（三）重型。

成人符合下列任何一条：

1. 出现气促，RR≥30 次/分；

2. 静息状态下，指氧饱和度≤93%；

3. 动脉血氧分压（PaO_2）/吸氧浓度（FiO_2）≤300mmHg（1mmHg=0.133kPa）。

高海拔(海拔超过 1000 米)地区应根据以下公式对 PaO_2/FiO_2 进行校正：$PaO_2/FiO_2 \times$[大气压(mmHg)/760]。

肺部影像学显示 24-48 小时内病灶明显进展>50%者按重型管理。

儿童符合下列任何一条：

1. 出现气促（<2 月龄，RR≥60 次/分；2～12 月龄，RR≥50 次/分；1～5 岁，RR≥40 次/分；>5 岁，RR≥30 次/分），除外发热和哭闹的影响；

2. 静息状态下，指氧饱和度≤92%；

3. 辅助呼吸（呻吟、鼻翼扇动、三凹征），发绀，间歇性呼吸暂停；

4. 出现嗜睡、惊厥；

5. 拒食或喂养困难，有脱水征。

（四）危重型。

符合以下情况之一者：

1. 出现呼吸衰竭，且需要机械通气；

2. 出现休克；

3. 合并其他器官功能衰竭需 ICU 监护治疗。

七、重型、危重型临床预警指标

（一）成人。

1. 外周血淋巴细胞进行性下降；

2. 外周血炎症因子如 IL-6、C 反应蛋白进行性上升；

3. 乳酸进行性升高；

4. 肺内病变在短期内迅速进展。

（二）儿童。

1. 呼吸频率增快；

2. 精神反应差、嗜睡；

3. 乳酸进行性升高；

4. 影像学显示双侧或多肺叶浸润、胸腔积液或短期内病变

快速进展；

5.3月龄以下的婴儿或有基础疾病（先天性心脏病、支气管肺发育不良、呼吸道畸形、异常血红蛋白、重度营养不良等），有免疫缺陷或低下（长期使用免疫抑制剂）。

八、鉴别诊断

（一）新型冠状病毒感染轻型表现需与其他病毒引起的上呼吸道感染相鉴别。

（二）新型冠状病毒肺炎主要与流感病毒、腺病毒、呼吸道合胞病毒等其他已知病毒性肺炎及肺炎支原体感染鉴别，尤其是对疑似病例要尽可能采取包括快速抗原检测和多重PCR核酸检测等方法，对常见呼吸道病原体进行检测。

（三）还要与非感染性疾病，如血管炎、皮肌炎和机化性肺炎等鉴别。

九、病例的发现与报告

各级各类医疗机构的医务人员发现符合病例定义的疑似病例后，应当立即进行单人间隔离治疗，院内专家会诊或主诊医师会诊，仍考虑疑似病例，在2小时内进行网络直报，并采集标本进行新型冠状病毒核酸检测，同时在确保转运安全前提下立即将疑似病例转运至定点医院。与新型冠状病毒感染者有密切接触的患者，即便常见呼吸道病原检测阳性，也建议及时进行新型冠状病毒病原学检测。

疑似病例连续两次新型冠状病毒核酸检测阴性（采样时间至少间隔 24 小时）且发病 7 天后新型冠状病毒特异性抗体 IgM 和 IgG 仍为阴性可排除疑似病例诊断。

十、治疗

（一）根据病情确定治疗场所。

1. 疑似及确诊病例应在具备有效隔离条件和防护条件的定点医院隔离治疗，疑似病例应单人单间隔离治疗，确诊病例可多人收治在同一病室。

2. 危重型病例应当尽早收入 ICU 治疗。

（二）一般治疗。

1. 卧床休息，加强支持治疗，保证充分热量；注意水、电解质平衡，维持内环境稳定；密切监测生命体征、指氧饱和度等。

2. 根据病情监测血常规、尿常规、CRP、生化指标（肝酶、心肌酶、肾功能等）、凝血功能、动脉血气分析、胸部影像学等。有条件者可行细胞因子检测。

3. 及时给予有效氧疗措施，包括鼻导管、面罩给氧和经鼻高流量氧疗。有条件可采用氢氧混合吸入气（H_2/O_2：66.6%/33.3%）治疗。

4. 抗病毒治疗：可试用 α-干扰素（成人每次 500 万 U 或相当剂量，加入灭菌注射用水 2ml，每日 2 次雾化吸入）、洛匹那韦/利托那韦（成人 200mg/50mg/粒，每次 2 粒，每日 2 次，疗程不超过 10 天）、利巴韦林（建议与干扰素或洛匹那韦/利托那

韦联合应用，成人 500mg/次，每日 2 至 3 次静脉输注，疗程不超过 10 天）、磷酸氯喹（18 岁-65 岁成人。体重大于 50 公斤者，每次 500mg、每日 2 次，疗程 7 天；体重小于 50 公斤者，第一、二天每次 500mg、每日 2 次，第三至第七天每次 500mg、每日 1 次）、阿比多尔（成人 200mg，每日 3 次，疗程不超过 10 天）。要注意上述药物的不良反应、禁忌症（如患有心脏疾病者禁用氯喹）以及与其他药物的相互作用等问题。在临床应用中进一步评价目前所试用药物的疗效。不建议同时应用 3 种及以上抗病毒药物，出现不可耐受的毒副作用时应停止使用相关药物。对孕产妇患者的治疗应考虑妊娠周数，尽可能选择对胎儿影响较小的药物，以及是否终止妊娠后再进行治疗等问题，并知情告知。

5. 抗菌药物治疗：避免盲目或不恰当使用抗菌药物，尤其是联合使用广谱抗菌药物。

（三）重型、危重型病例的治疗。

1. 治疗原则：在对症治疗的基础上，积极防治并发症，治疗基础疾病，预防继发感染，及时进行器官功能支持。

2. 呼吸支持：

（1）氧疗：重型患者应当接受鼻导管或面罩吸氧，并及时评估呼吸窘迫和/或低氧血症是否缓解。

（2）高流量鼻导管氧疗或无创机械通气：当患者接受标准氧疗后呼吸窘迫和/或低氧血症无法缓解时，可考虑使用高流量

鼻导管氧疗或无创通气。若短时间（1-2 小时）内病情无改善甚至恶化，应当及时进行气管插管和有创机械通气。

（3）有创机械通气：采用肺保护性通气策略，即小潮气量（6-8mL/kg 理想体重）和低水平气道平台压力（≤30cmH_2O）进行机械通气，以减少呼吸机相关肺损伤。在保证气道平台压≤35cmH_2O 时，可适当采用高 PEEP，保持气道温化湿化，避免长时间镇静，早期唤醒患者并进行肺康复治疗。较多患者存在人机不同步，应当及时使用镇静以及肌松剂。根据气道分泌物情况，选择密闭式吸痰，必要时行支气管镜检查采取相应治疗。

（4）挽救治疗：对于严重 ARDS 患者，建议进行肺复张。在人力资源充足的情况下，每天应当进行 12 小时以上的俯卧位通气。俯卧位机械通气效果不佳者，如条件允许，应当尽快考虑体外膜肺氧合（ECMO）。其相关指征：①在 FiO_2＞90%时，氧合指数小于 80mmHg，持续 3-4 小时以上；②气道平台压≥35cmH_2O。单纯呼吸衰竭患者，首选 VV-ECMO 模式；若需要循环支持，则选用 VA-ECMO 模式。在基础疾病得以控制，心肺功能有恢复迹象时，可开始撤机试验。

3.循环支持：在充分液体复苏的基础上，改善微循环，使用血管活性药物，密切监测患者血压、心率和尿量的变化，以及动脉血气分析中乳酸和碱剩余，必要时进行无创或有创血流动力学监测，如超声多普勒法、超声心动图、有创血压或持续

心排血量（PiCCO）监测。在救治过程中，注意液体平衡策略，避免过量和不足。

如果发现患者心率突发增加大于基础值的20%或血压下降大约基础值20%以上时，若伴有皮肤灌注不良和尿量减少等表现时，应密切观察患者是否存在脓毒症休克、消化道出血或心功能衰竭等情况。

4.肾功能衰竭和肾替代治疗：危重症患者的肾功能损伤应积极寻找导致肾功能损伤的原因，如低灌注和药物等因素。对于肾功能衰竭患者的治疗应注重体液平衡、酸碱平衡和电解质平衡，在营养支持治疗方面应注意氮平衡、热量和微量元素等补充。重症患者可选择连续性肾替代治疗（continuous renal replacement therapy，CRRT）。其指征包括：①高钾血症；②酸中毒；③肺水肿或水负荷过重；④多器官功能不全时的液体管理。

5.康复者血浆治疗：适用于病情进展较快、重型和危重型患者。用法用量参考《新冠肺炎康复者恢复期血浆临床治疗方案（试行第二版）》。

6.血液净化治疗：血液净化系统包括血浆置换、吸附、灌流、血液/血浆滤过等，能清除炎症因子，阻断“细胞因子风暴”，从而减轻炎症反应对机体的损伤，可用于重型、危重型患者细胞因子风暴早中期的救治。

7.免疫治疗：对于双肺广泛病变者及重型患者，且实验室检测 IL-6 水平升高者，可试用托珠单抗治疗。首次剂量 4-8mg/kg，推荐剂量为 400mg、0.9%生理盐水稀释至 100ml，输注时间大于 1 小时；首次用药疗效不佳者，可在 12 小时后追加应用一次（剂量同前），累计给药次数最多为 2 次，单次最大剂量不超过 800mg。注意过敏反应，有结核等活动性感染者禁用。

8.其他治疗措施

对于氧合指标进行性恶化、影像学进展迅速、机体炎症反应过度激活状态的患者，酌情短期内（3～5 日）使用糖皮质激素，建议剂量不超过相当于甲泼尼龙 1～2mg/kg/日，应当注意较大剂量糖皮质激素由于免疫抑制作用，会延缓对冠状病毒的清除；可静脉给予血必净 100ml/次，每日 2 次治疗；可使用肠道微生态调节剂，维持肠道微生态平衡，预防继发细菌感染。

儿童重型、危重型病例可酌情考虑给予静脉滴注丙种球蛋白。

患有重型或危重型新型冠状病毒肺炎的孕妇应积极终止妊娠，剖腹产为首选。

患者常存在焦虑恐惧情绪，应当加强心理疏导。

（四）中医治疗。

本病属于中医“疫”病范畴，病因为感受“疫戾”之气，各地可根据病情、当地气候特点以及不同体质等情况，参照下列方案进行辨证论治。涉及到超药典剂量，应当在医师指导下

使用。

1. 医学观察期

临床表现 1：乏力伴胃肠不适

推荐中成药：藿香正气胶囊（丸、水、口服液）

临床表现 2：乏力伴发热

推荐中成药：金花清感颗粒、连花清瘟胶囊（颗粒）、疏风解毒胶囊（颗粒）

2. 临床治疗期（确诊病例）

2.1 清肺排毒汤

适用范围：结合多地医生临床观察，**适用于轻型、普通型、重型患者，在危重型患者救治中可结合患者实际情况合理使用。**

基础方剂：麻黄 9g、炙甘草 6g、杏仁 9g、生石膏 15～30g（先煎）、桂枝 9g、泽泻 9g、猪苓 9g、白术 9g、茯苓 15g、柴胡 16g、黄芩 6g、姜半夏 9g、生姜 9g、紫菀 9g、冬花 9g、射干 9g、细辛 6g、山药 12g、枳实 6g、陈皮 6g、藿香 9g。

服法：传统中药饮片，水煎服。每天一付，早晚各一次(饭后四十分钟)，温服，三付一个疗程。

如有条件，每次服完药可加服大米汤半碗，舌干津液亏虚者可多服至一碗。(注：如患者不发热则生石膏的用量要小，发热或壮热可加大生石膏用量)。若症状好转而未痊愈则服用第二个疗程，若患者有特殊情况或其他基础病，第二疗程可以根据

实际情况修改处方，症状消失则停药。

处方来源：国家卫生健康委办公厅 国家中医药管理局办公室《关于推荐在中西医结合救治新型冠状病毒感染的肺炎中使用“清肺排毒汤”的通知》（国中医药办医政函〔2020〕22号）。

2.2 轻型

（1）寒湿郁肺证

临床表现：发热，乏力，周身酸痛，咳嗽，咯痰，胸紧憋气，纳呆，恶心，呕吐，大便粘腻不爽。舌质淡胖齿痕或淡红，苔白厚腐腻或白腻，脉濡或滑。

推荐处方：生麻黄6g、生石膏15g、杏仁9g、羌活15g、葶苈子15g、贯众9g、地龙15g、徐长卿15g、藿香15g、佩兰9g、苍术15g、云苓45g、生白术30g、焦三仙各9g、厚朴15g、焦槟榔9g、煨草果9g、生姜15g。

服法：每日1剂，水煎600ml，分3次服用，早中晚各1次，饭前服用。

（2）湿热蕴肺证

临床表现：低热或不发热，微恶寒，乏力，头身困重，肌肉酸痛，干咳痰少，咽痛，口干不欲多饮，或伴有胸闷脘痞，无汗或汗出不畅，或见呕恶纳呆，便溏或大便粘滞不爽。舌淡红，苔白厚腻或薄黄，脉滑数或濡。

推荐处方：槟榔10g、草果10g、厚朴10g、知母10g、黄

芩 10g、柴胡 10g、赤芍 10g、连翘 15g、青蒿 10g（后下）、苍术 10g、大青叶 10g、生甘草 5g。

服法：每日 1 剂，水煎 400ml，分 2 次服用，早晚各 1 次。

2.3 普通型

（1）湿毒郁肺证

临床表现：发热，咳嗽痰少，或有黄痰，憋闷气促，腹胀，便秘不畅。舌质暗红，舌体胖，苔黄腻或黄燥，脉滑数或弦滑。

推荐处方：生麻黄 6g、苦杏仁 15g、生石膏 30g、生薏苡仁 30g、茅苍术 10g、广藿香 15g、青蒿草 12g、虎杖 20g、马鞭草 30g、干芦根 30g、葶苈子 15g、化橘红 15g、生甘草 10g。

服法：每日 1 剂，水煎 400ml，分 2 次服用，早晚各 1 次。

（2）寒湿阻肺证

临床表现：低热，身热不扬，或未热，干咳，少痰，倦怠乏力，胸闷，脘痞，或呕恶，便溏。舌质淡或淡红，苔白或白腻，脉濡。

推荐处方：苍术 15g、陈皮 10g、厚朴 10g、藿香 10g、草果 6g、生麻黄 6g、羌活 10g、生姜 10g、槟榔 10g。

服法：每日 1 剂，水煎 400ml，分 2 次服用，早晚各 1 次。

2.4 重型

（1）疫毒闭肺证

临床表现：发热面红，咳嗽，痰黄粘少，或痰中带血，喘

憋气促，疲乏倦怠，口干苦粘，恶心不食，大便不畅，小便短赤。舌红，苔黄腻，脉滑数。

推荐处方：化湿败毒方

基础方剂：生麻黄6g、杏仁9g、生石膏15g、甘草3g、藿香10g（后下）、厚朴10g、苍术15g、草果10g、法半夏9g、茯苓15g、生大黄5g（后下）、生黄芪10g、葶苈子10g、赤芍10g。

服法：每日1～2剂，水煎服，每次100ml～200ml，一日2～4次，口服或鼻饲。

（2）气营两燔证

临床表现：大热烦渴，喘憋气促，谵语神昏，视物错瞥，或发斑疹，或吐血、衄血，或四肢抽搐。舌绛少苔或无苔，脉沉细数，或浮大而数。

推荐处方：生石膏30～60g（先煎）、知母30g、生地30～60g、水牛角30g（先煎）、赤芍30g、玄参30g、连翘15g、丹皮15g、黄连6g、竹叶12g、葶苈子15g、生甘草6g。

服法：每日1剂，水煎服，先煎石膏、水牛角后下诸药，每次100ml～200ml，每日2～4次，口服或鼻饲。

推荐中成药：喜炎平注射液、血必净注射液、热毒宁注射液、痰热清注射液、醒脑静注射液。功效相近的药物根据个体情况可选择一种，也可根据临床症状联合使用两种。中药注射剂可与中药汤剂联合使用。

2.5 危重型

内闭外脱证

临床表现：呼吸困难、动辄气喘或需要机械通气，伴神昏，烦躁，汗出肢冷，舌质紫暗，苔厚腻或燥，脉浮大无根。

推荐处方：人参 15g、黑顺片 10g（先煎）、山茱萸 15g，送服苏合香丸或安宫牛黄丸。

出现机械通气伴腹胀便秘或大便不畅者，可用生大黄 5～10g。出现人机不同步情况，在镇静和肌松剂使用的情况下，可用生大黄 5～10g 和芒硝 5～10g。

推荐中成药：血必净注射液、热毒宁注射液、痰热清注射液、醒脑静注射液、参附注射液、生脉注射液、参麦注射液。功效相近的药物根据个体情况可选择一种，也可根据临床症状联合使用两种。中药注射剂可与中药汤剂联合使用。

注：重型和危重型中药注射剂推荐用法

中药注射剂的使用遵照药品说明书从小剂量开始、逐步辨证调整的原则，推荐用法如下：

病毒感染或合并轻度细菌感染：0.9%氯化钠注射液 250ml 加喜炎平注射液 100mg bid，或 0.9%氯化钠注射液 250ml 加热毒宁注射液 20ml，或 0.9%氯化钠注射液 250ml 加痰热清注射液 40ml bid。

高热伴意识障碍：0.9%氯化钠注射液 250ml 加醒脑静注射

液 20ml bid。

全身炎症反应综合征或/和多脏器功能衰竭：0.9%氯化钠注射液 250ml 加血必净注射液 100ml bid。

免疫抑制：葡萄糖注射液 250ml 加参麦注射液 100ml 或生脉注射液 20～60ml bid。

2.6 恢复期

（1）肺脾气虚证

临床表现：气短，倦怠乏力，纳差呕恶，痞满，大便无力，便溏不爽。舌淡胖，苔白腻。

推荐处方：法半夏 9g、陈皮 10g、党参 15g、炙黄芪 30g、炒白术 10g、茯苓 15g、藿香 10g、砂仁 6g（后下）、甘草 6g。

服法：每日 1 剂，水煎 400ml，分 2 次服用，早晚各 1 次。

（2）气阴两虚证

临床表现：乏力，气短，口干，口渴，心悸，汗多，纳差，低热或不热，干咳少痰。舌干少津，脉细或虚无力。

推荐处方：南北沙参各 10g、麦冬 15g、西洋参 6g，五味子 6g、生石膏 15g、淡竹叶 10g、桑叶 10g、芦根 15g、丹参 15g、生甘草 6g。

服法：每日 1 剂，水煎 400ml，分 2 次服用，早晚各 1 次。

十一、出院标准和出院后注意事项

（一）出院标准。

1. 体温恢复正常 3 天以上；

2. 呼吸道症状明显好转；

3. 肺部影像学显示急性渗出性病变明显改善；

4. 连续两次痰、鼻咽拭子等呼吸道标本核酸检测阴性（采样时间至少间隔 24 小时）。

满足以上条件者可出院。

（二）出院后注意事项。

1. 定点医院要做好与患者居住地基层医疗机构间的联系，共享病历资料，及时将出院患者信息推送至患者辖区或居住地居委会和基层医疗卫生机构。

2. 患者出院后，建议应继续进行 14 天的隔离管理和健康状况监测，佩戴口罩，有条件的居住在通风良好的单人房间，减少与家人的近距离密切接触，分餐饮食，做好手卫生，避免外出活动。

3. 建议在出院后第 2 周和第 4 周到医院随访、复诊。

十二、转运原则

按照国家卫生健康委印发的《新型冠状病毒感染的肺炎病例转运工作方案（试行）》执行。

十三、医疗机构内感染预防与控制

严格按照国家卫生健康委《医疗机构内新型冠状病毒感染预防与控制技术指南（第一版）》、《新型冠状病毒感染的肺炎防护中常见医用防护用品使用范围指引（试行）》的要求执行。

抄送：各省、自治区、直辖市及新疆生产建设兵团应对新型冠状病毒肺炎疫情联防联控机制（领导小组、指挥部）。

国家卫生健康委办公厅　　2020年3月3日印发

校对：杜青阳

ATTACHMENT 3

Linan +订阅

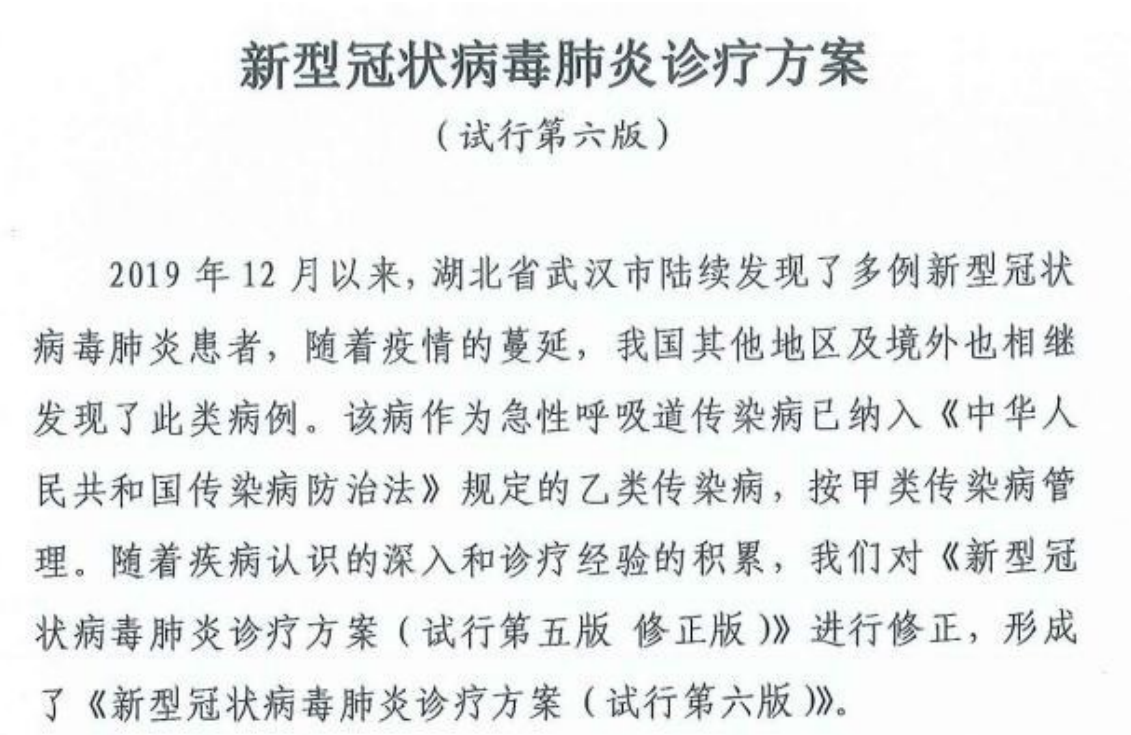
新冠肺炎诊疗方案第六版：磷酸氯喹、阿比多尔转正 这款中成药被踢

来源：新浪医药新闻 2020-02-20

文 | Linan

点击查看：新型冠状病毒肺炎诊疗方案（试行第六版）

2月19日，国家卫健委正式下发《新型冠状病毒肺炎诊疗方案(试行第六版)》，上一版发布时间是2月5日，将近半个月里，最新版本的方案中又有了一些新变化。新版诊疗方案将此前业界多次提到的磷酸氯喹、阿比多尔纳入到抗病毒治疗药物中。在医学观察期中医治疗里，一款中成药被剔除。



新型冠状病毒肺炎诊疗方案

（试行第六版）

2019 年 12 月以来，湖北省武汉市陆续发现了多例新型冠状病毒肺炎患者，随着疫情的蔓延，我国其他地区及境外也相继发现了此类病例。该病作为急性呼吸道传染病已纳入《中华人民共和国传染病防治法》规定的乙类传染病，按甲类传染病管理。随着疾病认识的深入和诊疗经验的积累，我们对《新型冠状病毒肺炎诊疗方案（试行第五版 修正版）》进行修正，形成了《新型冠状病毒肺炎诊疗方案（试行第六版）》。

ATTACHMENT 4

磷酸氯喹、阿比多尔被纳入治疗方案

其中，抗病毒治疗方案较上一版又有了进一步的调整。备受关注的磷酸氯喹、阿比多尔被纳入。

第五版抗病毒治疗里提到，目前没有确认有效的抗病毒治疗方法。可试用α-干扰素雾化吸入（成人每次500万U或相当剂量，加入灭菌注射用水2ml，每日2次）、洛匹那韦/利托那韦（200 mg/50 mg，每粒）每次2粒，每日2次。或可加用利巴韦林（成人首剂4 g，次日每8小时一次，每次1.2 g，或8 mg/kg iv. 每8小时一次）。要注意洛匹那韦/利托那韦相关腹泻、恶心、呕吐、肝功能损害等不良反应，同时要注意和其它药物的相互作用。

而第六版这一段里，去掉了“目前没有确认有效的抗病毒治疗方法”。增加了运用洛匹那韦/利托那韦疗程不超过10天，利巴韦林（建议与干扰素或洛匹那韦/利托那韦联合应用，成人500mg/次，每日2至3次静脉输注，疗程也是不超过10天）、磷酸氯喹（成人200mg，每日2次，疗程不超过10天）、阿比多尔（成人200mg，每日3次，疗程不超过10天）。

4. 抗病毒治疗：可试用α-干扰素（成人每次500万U或相当剂量，加入灭菌注射用水2ml，每日2次雾化吸入）、洛匹那韦/利托那韦（成人200mg/50mg/粒，每次2粒，每日2次，疗程不超过10天）、利巴韦林（建议与干扰素或洛匹那韦/利托那韦联合应用，成人500mg/次，每日2至3次静脉输注，疗程不超过10天）、磷酸氯喹（成人500mg，每日2次，疗程不超过10天）、阿比多尔（成人200mg，每日3次，疗程不超过10天）。要注意洛匹那韦/利托那韦相关腹泻、恶心、呕吐、肝功能损害等不良反应，同时要注意和其他药物的相互作用。在临床应用中进一步评价目前所试用药物的疗效。不建议同时应用3种及以上抗病毒药物，出现不可耐受的毒副作用时应停止使用相关药物。

阿比多尔“转正”

此前，阿比多尔被中国工程院院士、国家委高级别专家组成员李兰娟推荐纳入第六版诊疗方案中。

资料显示，阿比多尔是一种广谱抗病毒药物，由前苏联药物化学研究中心研制开发，于1993年在俄罗斯上市，主要治疗A、B型流感病毒等引起的上呼吸道感染。阿比多尔可以通过抑制病毒的脂膜与宿主细胞的融合，从而能够阻断病毒的复制。新型冠状病毒是一种带有外膜的病毒，因此推测阿比多尔在药理上对新型冠状病毒有抑制作用。

而据长江日报报道，李兰娟团队于2月4日公布治疗新冠病毒感染的肺炎最新研究成果。初步测试发现，在体外细胞实验中，阿比朵尔在10-30微摩尔浓度下，与药物未处理的对照组比较，能有效抑制冠状病毒达60倍，并有显著抑制病毒对细胞的病变效应；达芦那韦在300微摩尔浓度下，显著抑制病毒复制，与未用药物处理组对比，限制效率达280倍。

上述消息发出后，与阿比朵尔、达芦那韦相关的概念股受到了市场热捧，其中瑞康医药、东音股份、九洲药业、人福医药等多股强势涨停。

药企也于日前纷纷采取行动。2月5日，瑞康医药表示，公司关注到李兰娟院士发布的研究成果，目前公司有阿比朵尔在售，且库存充足；美诺华与南京先声制药合作，计划共同研发抗病毒领域原料药盐酸阿比多尔及其他多种抗病毒原料药。不过，与阿比多尔一同步入公众眼球的达芦那韦此次并未出现在最新版的抗病毒治疗方案里。

老药“磷酸氯喹”恢复生产

磷酸氯喹于上个世纪40年代起用于治疗疟疾，后用于治疗类风湿性关节炎等。此次磷酸氯喹在新冠肺炎治疗中的应用是氯喹类药物在“老药新用”方面的又一次探索。

2月3日，同方康泰发布自愿性公告，称获工信部、重庆经信委等部门通知，磷酸氯喹被测试及证实对新型冠状病毒感染的肺炎有一定的疗效，同方康泰旗下康乐制药被工信部要求尽快恢复磷酸氯喹原料药的生产，该集团的原料药还被纳入中央医药储备名单中。当天康乐制药即恢复生产。

2月4日的国家卫健委新闻发布会上，孙燕荣表示，在临床试验中已经初步显示出来了磷酸氯喹对这次新型冠状病毒肺炎是具有一定疗效，正在加紧、递次推进动物实验和临床试验。

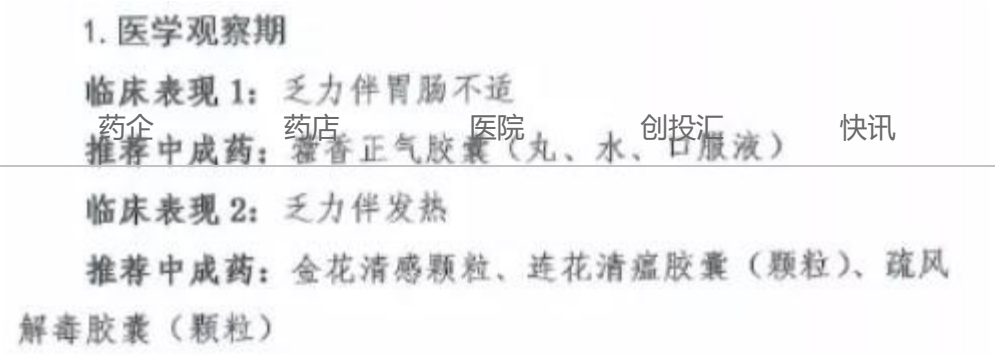
2月17日，国务院联防联控机制召开新闻发布会，介绍医疗救治工作进展情况。科技部生物中心副主任孙燕荣在会上表示，疗效专家组经过认真细致的研讨，最后达成一致意见，一致认为磷酸氯喹是一个上市多年的老药，用于广泛人群治疗的安全性是可控的。基于前期临床机构所开展的临床研究，结果可以明确磷酸氯喹治疗新冠肺炎具有疗效。基于当前临床救治的迫切需求，专家一致推荐，应当尽快将磷酸氯喹纳入到新一版的诊疗指南，扩大临床适用范围。

2月18日，中国工程院院士钟南山也表示，磷酸氯喹对新冠肺炎病情有帮助。日前，众生药业公告称，日前申请公司药品磷酸氯喹片恢复生产，现已获得广东药监局批准签发的《药品补充申请批件》；广药集团下属广州白云山光华制药股份有限公司恢复生产抗疟药物磷酸氯喹片，首批50万片药品已生产完毕将在近日上市并投入临床；另外，上海医药的全资子公司上药中西则已于2月3号复工生产，目前库存原料充足，第一批次的磷酸氯喹片于2月10号正式交付，后续将以每隔3~5天左右一批的速度持续供应。

医学观察期内，不再推荐使用防风通圣丸

国家卫生健康委员会官方网站显示，截至2月18日24时，据31个省（自治区、直辖市）和新疆生产建设兵团报告，现有确诊病例57805例（其中重症病例11977例），累计治愈出院病例14376例，累计死亡病例2004例，累计报告确诊病例74185例，现有疑似病例5248例。累计追踪到密切接触者574418人，尚在医学观察的密切接触者135881人。

对比两版诊疗方案，中医治疗里，医学观察期间内新版诊疗方案去除了防风通圣丸（颗粒），其它中成药藿香正气胶囊、金花清感颗粒、莲花清瘟胶囊（颗粒）、疏风解读胶囊（颗粒）继续推荐使用。


1. 医学观察期

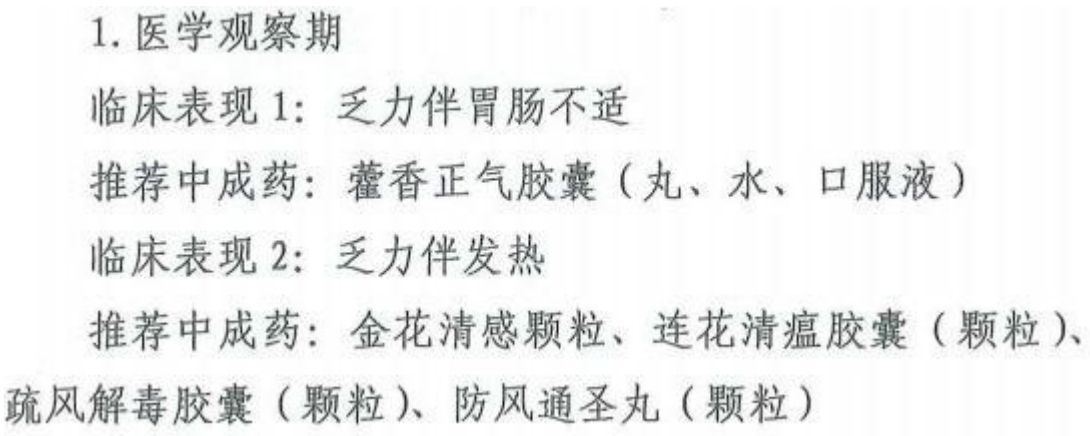
临床表现 1：乏力伴胃肠不适

推荐中成药：藿香正气胶囊（丸、水、口服液）

临床表现 2：乏力伴发热

推荐中成药：金花清感颗粒、连花清瘟胶囊（颗粒）、疏风解毒胶囊（颗粒）

（第六版）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（第五版）

值得一提的是，从国家卫健委、国家中医药管理局发布的《新型冠状病毒感染的肺炎诊疗方案（试行第四版）》开始，藿香正气、连花清瘟、金花清感颗粒就被推荐使用。

2月14日，工信部发布《疫情防控重点保障物资（医疗应急）清单》，藿香正气、金花清感颗粒、连花清瘟等中成药也在清单之列。

另附《新型冠状病毒肺炎诊疗方案（试行第六版）》解读

2020年2月19日，国家卫生健康委员会发布了《新型冠状病毒肺炎诊疗方案（试行第六版）》（以下简称“第六版”），现进行解读如下：

一、传播途径

传播途径将“经呼吸道飞沫和接触传播是主要的传播途径”改为“经呼吸道飞沫和密切接触传播是主要的传播途径。”“接触”前增加“密切”二字。增加“在相对封闭的环境中长时间暴露于高浓度气溶胶情况下中存在经气溶胶传播的可能。”

二、临床表现

重症患者严重者除了“快速进展为急性呼吸窘迫综合征、脓毒症休克、难以纠正的代谢性酸中毒和出凝血功能障碍”外，还可出现“多器官功能衰竭”。实验室检查，强调“为提高核酸检测阳性率，建议尽可能留取痰液，实施气管插管患者采集下呼吸道分泌物，标本采集后尽快送检。”

三、诊断标准

第六版诊断标准取消湖北省和湖北省以外其他省份的区别。统一分为“疑似病例”和“确诊病例”两类。疑似病例判定分两种情形。一是“有流行病学史中的任何一条，且符合临床表现中任意2条（发热和/或呼吸道症状；具有上述肺炎影像学特征；发病早期白细胞总数正常或降低，淋巴细胞计数减少）。二是“无明确流行病学史的，且符合临床表现中的3条（发热和/或呼吸道症状；具有上述肺炎影像学特征；发病早期白细胞总数正常或降低，淋巴细胞计数减少）。确诊病例需有病原学证据阳性结果（实时荧光RT-PCR检测新型冠状病毒核酸阳性；或病毒基因测序，与已知的新型冠状病毒高度同源）。

四、临床分型

仍分为“轻型、普通型、重型和危重型”，对动脉血氧分压（PaO2）/吸氧浓度（FiO2）≤300mmHg（1mmHg=0.133kPa）增加“高海拔（海拔超过1000米）地区应根据以下公式对PaO2/FiO2进行校正：PaO2/FiO2 × [大气压(mmHg)/760]”。将“肺部影像学显示24-48小时内病灶明显进展>50%者”按重型管理。

五、鉴别诊断

按照新型冠状病毒感染轻症和新型冠状病毒肺炎提出相关疾病的鉴别诊断。如新型冠状病毒感染轻型表现需与其它病毒引起的上呼吸道感染相鉴别；

新型冠状病毒肺炎主要与流感病毒、腺病毒、呼吸道合胞病毒等其他已知病毒性肺炎及肺炎支原体感染鉴别。强调“对疑似病例要尽可能采取包括快速抗原检测和多重PCR核酸检测等方法，对常见呼吸道病原体进行检测。”

六、病例的发现与报告

删除“关于湖北省对临床诊断病例的处置要求”。删除“疑似病例”排除标准，疑似病例的解除隔离标准和“解除隔离标准”相一致。

七、治疗

1.根据病情确定治疗场所。删除“疑似及确诊病例”，改为“应在具备有效隔离条件和防护条件的定点医院隔离治疗，确诊病例可多人收治在同一病室。”

2.抗病毒治疗：删除“目前没有确认有效的抗新型冠状病毒治疗方法。”在试用药物中，增加“磷酸氯喹（成人500mg，每日２次）和阿比多尔（成人200mg，每日３次）”两个药物。利巴韦林建议与干扰素或洛匹那韦/利托那韦联合应用。试用药物的疗程均不超过10天。建议在临床应用中进一步评价目前所试用药物的疗效。不建议同时应用3种及以上抗病毒药物，出现不可耐受的毒副作用时应停止使用相关药物。

3.重型、危重型病例的治疗。增加“康复者血浆治疗”，建议适用于病情进展较快、重型和危重型患者。用法用量参考《新冠肺炎康复者恢复期血浆临床治疗方案（试行第一版）》。

4.其他治疗措施：将对有高炎症反应的危重患者，“有条件可以考虑使用体外血液净化技术。”修改为“有条件的可考虑使用血浆置换、吸附、灌流、血液/血浆滤过等体外血液净化技术。”

5.关于中医治疗。通过对病人观察治疗的深入，在总结分析全国各地中医诊疗方案、梳理筛选各地中医治疗经验和有效方药基础上，结合已印发的《关于推荐在中西医结合救治新型冠状病毒感染的肺炎中使用“清肺排毒汤”的通知》、《新型冠状病毒肺炎重型、危重型病例诊疗方案（试行第二版）》和《新型冠状病毒肺炎轻型、普通型病例管理规范》等，对《新型冠状病毒感染

的肺炎诊疗方案（试行第五版 修正版）》进行了调整和补充。延续上一版对疾病全过程的分期，将中医治疗分为医学观察期和临床治疗期（确诊病例），将临床治疗期分为轻型、普通型、重型、危重型、恢复期。医学观察期推荐使用中成药。临床治疗期推荐了通用方剂“清肺排毒汤”，并分别对轻型、普通型、重型、危重型和恢复期从临床表现、推荐处方及剂量、服用方法三个方面予以说明。同时，在方案中增加了适用于重型、危重型的中成药（包括中药注射剂）的具体用法。各地可根据病情、当地气候特点以及不同体质等情况，参照推荐的方案进行辨证论治。

八、解除隔离和出院后注意事项

解除隔离标准需满足以下4个条件：

1.体温恢复正常3天以上；

2.呼吸道症状明显好转；

3.肺部影像学显示急性渗出性病变明显吸收好转；

4.连续两次呼吸道标本核酸检测阴性（采样时间至少间隔1天）。

增加“出院后注意事项”：

1.定点医院要做好与患者居住地基层医疗机构间的联系，共享病历资料，及时将出院患者信息推送至患者辖区或居住地居委会和基层医疗卫生机构。

2.患者出院后，因恢复期机体免疫功能低下，有感染其它病原体风险，建议应继续进行14天自我健康状况监测，佩戴口罩，有条件的居住在通风良好的单人房间，减少与家人的近距离密切接触，分餐饮食，做好手卫生，避免外出活动。

3.建议在出院后第2周、第4周到医院随访、复诊。

文章评论

登录后评论

ATTACHMENT 4

• 新型冠状病毒肺炎专栏 •

2019新型冠状病毒抗病毒治疗有药可期

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摘要

2019新型冠状病毒（2019-nCoV）是武汉不明原因肺炎的致病原。2019-nCoV在遗传学上与一种蝙蝠来源的新型冠状病毒比较接近，与SARS-CoV、MERS-CoV同为β属冠状病毒。目前临床上常用的抗病毒药物，包括神经氨酸酶抑制剂（奥司他韦、帕拉米韦、扎那米韦等）、更昔洛韦、阿昔洛韦、利巴韦林等药物对2019-nCoV均无效，不建议临床应用。目前研究证实可能有效的药物包括：瑞德西韦、洛匹那韦/利托那韦、洛匹那韦/利托那韦联合干扰素-β、恢复期血浆、单克隆抗体。但这些药物在2019-nCoV肺炎患者中的疗效和安全性有待进一步临床实验证实。

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冠状病毒（coronavirus）是有包膜的、正链RNA病毒。在电子显微镜下，冠状病毒边缘具有形态近似日冕的突起，看上去像王冠一样，因此被称作冠状病毒。在武汉新型冠状病毒（2019-nCoV）肺炎疫情暴发前，已知可感染人类的冠状病毒只有6种。其中，只有SARS-CoV、MERS-CoV两种可引起致命的肺炎，另外4种冠状病毒（HcoV-229E、HcoV-NL63、HcoV-HKU1、HcoV-OC43）仅能引起轻症呼吸道感染。

自2003年严重急性呼吸综合征（severe acute respiratory syndrome，SARS）和2012年中东呼吸综合征（Middle East respiratory syndrome coronavirus，MERS）暴发以来，临床医生和病毒学家一直在进行不断探索，积累了一定的经验。SARS和MERS等冠状病毒的研究为我们提供了几种可能有效的药物，包括：瑞德西韦（remdesivir，GS-5734）、洛匹那韦/利托那韦（lopinavir/ritonavir）、干扰素、恢复期血浆等。

因此，可以说，2019-nCoV抗病毒治疗有药可期。

1．洛匹那韦/利托那韦（Lopinavir/Ritonavir）：

洛匹那韦是一种人类免疫缺陷病毒1（HIV-1）蛋白酶抑制剂，通常与利托那韦联合使用，通过抑制细胞色素P450来增加洛匹那韦半衰期。体外实验结果显示，洛匹那韦/利托那韦能够一定程度抑制冠状病毒复制。我国学者利用绒猴动物模型发现，洛匹那韦/利托那韦和干扰素-β联用治疗MERS-CoV感染，比对照组疗效更好[1]。2003年SARS流行期间，我国香港学者发现，与111例利巴韦林单药治疗的SARS患者相比，洛匹那韦/利托那韦和利巴韦林联合治疗的41例SARS患者发生ARDS或死亡的风险更低[2]。2016年沙特阿拉伯王国启动了一项洛匹那韦/利托那韦联合干扰素-β是否能改善MERS-CoV患者临床结局的随机对照试验（MIRACLE试验，NCT02845843），研究正在进行中。该药在2019-nCoV感染患者中的疗效和安全性的临床随机对照研究（ChiCTR2000029308）目前正在进行中。

[1] Chan JF, Yao Y, Yeung ML, et al. **Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset**[J]. J Infect Dis, 2015, 2 DOI: 10.1093/infdis/jiv392.

2．核苷类似物（法匹拉韦及利巴韦林）：

核苷类似物可能具有多种作用机制，体外具有广谱抗病毒作用，包括致死性诱变、专性或非专性链终止以及通过抑制核苷酸的生物合成。法匹拉韦和利巴韦林是核苷类似物的代表，法匹拉韦在日本批准用于流感的替代治疗。中国肺炎研究网牵头的研究结果证明，法匹拉韦联合奥司他韦治疗重症流感效果优于奥司他韦单药[3]。

虽然冠状病毒是RNA病毒，理论上法匹拉韦和利巴韦林具有一定的抗冠状病毒活性。但是，冠状病毒在非结构蛋白14中表达外切核糖核酸酶（nsp14-ExoN），并且在整个冠状病毒家族中具有保守性。目前研究结果显示，nsp14-ExoN具有RNA校对功能[4]，因此推测冠状病毒具有核苷类似物抗性。体外实验结果已经证明利巴韦林对冠状病毒抗病毒作用甚微[5]，同样，理论上法匹拉韦对冠状病毒作用也有限。

3．瑞德西韦（Remdesivir，GS-5734）：

瑞德西韦是一种新的核苷类似物，也是一种广谱抗病毒药物。但与法匹拉韦和利巴韦林不同的是，体外细胞实验及动物实验结果证实，对人感染冠状病毒和各种蝙蝠来源的冠状病毒均具有极强的体外抗病毒活性。另外，随着药物浓度升高，明显抑制病毒在人原代细胞培养中的复制[6]。推测可能的原因为瑞德西韦三磷酸酯不能被nsp14-ExoN切除[7]。

理论上，瑞德西韦是目前治疗2019-nCoV最有潜力的药物。动物实验结果表明，与对照组相比，瑞德西韦可有效降低MERS-CoV感染小鼠肺组织病毒滴度，改善肺组织损伤，且其疗效优于洛匹那韦/利托那韦联合干扰素-β治疗组[8]。该药物已经完成治疗埃博拉病毒感染的III期临床试验，且人体药代动力学和安全性方面均有较完整的数据[9]。《新英格兰医学杂志》近期发表了美国一例2019-nCoV感染患者应用瑞德西韦治愈报道[10]。

但是，瑞德西韦在2019-nCoV感染患者中的疗效和安全性仍需要临床研究进一步证实。其次，瑞德西韦治疗过程中是否会诱导冠状病毒nsp14-ExoN发生耐药性突变有待进一步研究。目前我们已经制定了瑞德西韦在2019-nCoV感染患者中疗效评价的临床随机对照研究方案，并进行了研究注册（轻中度2019-nCoV：NCT04252664；重度2019-nCoV：NCT04257656）。

4．恢复期血浆：

早在100多年前，康复患者血浆制品就已经被用来治疗多种感染性疾病。既往研究结果表明，恢复期血浆治疗能够降低重症甲型流感及SARS-CoV感染患者病死率[11]。然而，2016年在《新英格兰医学杂志》发表的关于Ebola病毒感染的非随机比较性研究结果显示，与常规治疗组患者相比，输注多达500 ml恢复血浆组，生存率并无明显改善[12]。其原因可能是埃博拉病毒感染者输注的恢复期血浆中和抗体滴度不高。因此，恢复期血浆的采集必须在合适的时机，保证其具有较高的中和抗体滴度。恢复期血浆获取的困难也在一定程度上限制了其临床应用。应在精心设计的临床试验中进一步评估恢复期血浆治疗2019-nCoV感染患者疗效和安全性。

5．保护性单克隆抗体：

随着基因工程抗体技术的快速发展，单克隆抗体药物取得长足进步。越来越多的研究结果证实，对于病毒感染，保护性单克隆抗体具有较好的治疗价值。2019年《新英格兰医学杂志》发表了一项前瞻随机对照研究，单克隆抗体REGN-EB3和单克隆抗体114（mAb114）能够显著降低埃博拉患者的病死率[9]。然而，病毒、细菌等病原体感染机体的机制复杂，由于单克隆抗体只能识别单一抗原表位，限制了单克隆抗体药物的抗感染效果。其次，单克隆抗体的研发需要一定的时间周期，对于新发病原体，单克隆抗体短时间内也难以实现其临床应用。

6．其他可能有效药物：

目前也有一些其他类型药物体外试验发现对冠状病毒感染有一定的疗效，如阿比多尔、融合肽（EK1）[13]、Abelson（Abl）激酶抑制剂（包括伊马替尼）[14]等。此外，我国中医药在甲型H1N1流感等新发突发呼吸道传染病的防治中也发挥了一定作用。但其对2019-nCoV疗效有待进一步评价。

总之，目前研究结果已经证实，2019-nCoV是武汉不明原因肺炎的致病原。2019-nCoV在遗传学上与一种蝙蝠来源的新型冠状病毒比较接近，与SARS-CoV、MERS-CoV同为β属冠状病毒。目前临床上常用的抗病毒药物，包括神经氨酸酶抑制剂（奥司他韦、帕拉米韦、扎那米韦等）对2019-nCoV均无效（因为冠状病毒不产生神经氨酸酶），更昔洛韦、阿昔洛韦、利巴韦林等药物作用甚微，均不建议临床应用。目前研究证实可能有效的药物包括：瑞德西韦、洛匹那韦/利托那韦、洛匹那韦/利托那韦联合干扰素-β、恢复期血浆、单克隆抗体。但这些药物在2019-nCoV武汉肺炎中的疗效和安全性有待进一步临床实验证实。

利益冲突　所有作者均声明不存在利益冲突

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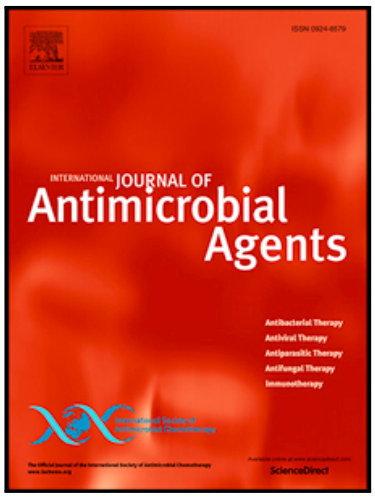
ATTACHMENT 5

Journal Pre-proof



Chloroquine and hydroxychloroquine as available weapons to fight COVID-19

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Hot Topic

Chloroquine and hydroxychloroquine as available weapons to fight COVID-19

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Repositioning of drugs for use as antiviral treatments is a critical need [1]. It is commonly very badly perceived by virologists, as we experienced when reporting the effectiveness of azithromycin for Zika virus [2]. A response has come from China to the respiratory disease caused by the new coronavirus (SARS-CoV-2) that emerged in December 2019 in this country. Indeed, following the very recent publication of results showing the in vitro activity of chloroquine against SARS-CoV-2 [3], data have been reported on the efficacy of this drug in patients with SARS-CoV-2-related pneumonia (named COVID-19) at different levels of severity [4,5]. Indeed, following the in vitro results, 20 clinical studies were launched in several Chinese hospitals. The first results obtained from more than 100 patients showed the superiority of chloroquine compared with treatment of the control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects [4,5]. This has led in China to include chloroquine in the recommendations regarding the prevention and treatment of COVID-19 pneumonia [4,6].

There is a strong rationality for the use of chloroquine to treat infections with intracellular micro-organisms. Thus, malaria has been treated for several decades with this molecule [7]. In addition, our team has used hydroxychloroquine for the first time for intracellular bacterial infections since 30 years to treat the intracellular bacterium *Coxiella burnetii*, the agent of Q fever, for which we have shown both in vitro and then in patients that this compound is the only one efficient for killing these intracellular pathogens [8,9]. Since then, we have also shown the activity of hydroxychloroquine on *Tropheryma whipplei*, the agent of Whipple's disease, which is another intracellular bacterium for which hydroxychloroquine has become a

reference drug [10,11]. Altogether, one of us (DR) has treated ~4000 cases of *C. burnetii* or *T. whipplei* infections over 30 years (personal data).

Regarding viruses, for reasons probably partly identical involving alkalinisation by chloroquine of the phagolysosome, several studies have shown the effectiveness of this molecule, including against coronaviruses among which is the severe acute respiratory syndrome (SARS)-associated coronavirus [1,12,13] (Table 1). We previously emphasised interest in chloroquine for the treatment of viral infections in this journal [1], predicting its use in viral infections lacking drugs. Following the discovery in China of the in vitro activity of chloroquine against SARS-CoV-2, discovered during culture tests on Vero E6 cells with 50% and 90% effective concentrations (EC_{50} and EC_{90} values) of 1.13 μM and 6.90 μM, respectively (antiviral activity being observed when addition of this drug was carried out before or after viral infection of the cells) [3], we awaited with great interest the clinical data [14]. The subsequent in vivo data were communicated following the first results of clinical trials by Chinese teams [4] and also aroused great enthusiasm among us. They showed that chloroquine could reduce the length of hospital stay and improve the evolution of COVID-19 pneumonia [4,6], leading to recommend the administration of 500 mg of chloroquine twice a day in patients with mild, moderate and severe forms of COVID-19 pneumonia. At such a dosage, a therapeutic concentration of chloroquine might be reached. With our experience on 2000 dosages of hydroxychloroquine during the past 5 years in patients with long-term treatment (>1 year), we know that with a dosage of 600 mg/day we reach a concentration of 1 μg/mL [15]. The optimal dosage for SARS-CoV-2 is an issue that will need to be assessed in the coming days. For us, the activity of

hydroxychloroquine on viruses is probably the same as that of chloroquine since the mechanism of action of these two molecules is identical, and we are used to prescribe for long periods hydroxychloroquine, which would be therefore our first choice in the treatment of SARS-CoV-2. For optimal treatment, it may be necessary to administer a loading dose followed by a maintenance dose.

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Competing interests: None declared.

Ethical approval: Not required.

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Table 1

Main results of studies on the activity of chloroquine or hydroxychloroquine on coronaviruses [a]

Reference	Compound(s)	Targeted virus	System used for antiviral activity screening	Antiviral effect
[12]	Chloroquine	SARS-CoV	Vero (African green monkey kidney) E6 cells	EC_{50} = 8.8 ± 1.2 μM
[16]	Chloroquine		Vero E6 cells	EC_{50} = 4.4 ± 1.0 μM
[17]	Chloroquine, chloroquine monophosphate, chloroquine diphosphate	SARS-CoV (four strains)	Vero 76 cells	Chloroquine: EC_{50} = 1–4 μM Chloroquine monophosphate: EC_{50} = 4–6 μM Chloroquine diphosphate: EC_{50} = 3–4 μM

			BALB/c mice	Intraperitoneal or intranasal chloroquine administration, beginning 4 h prior to virus exposure: 50 mg/kg but not 10 mg/kg or 1 mg/kg reduced for the intranasal route (but not the intraperitoneal route) viral lung titres from mean ± S.D. of 5.4 ± 0.5 to 4.4 ± 1.2 in log_{10} $CCID_{50}$/g at Day 3 (considered as not significant)
[18]	Chloroquine, hydroxychloroquine	SARS-CoV	Vero cells	Chloroquine: EC_{50} = 6.5 ± 3.2 μM Hydroxychloroquine: EC_{50} = 34 ± 5 μM
		Feline coronavirus	Crandell–Reese feline kidney (CRFK) cells	Chloroquine: EC_{50} > 0.8 μM Hydroxychloroquine: EC_{50} = 28 ± 27 μM

[19]	Chloroquine	HCoV-229E	Human epithelial lung cells (L132)	Chloroquine at concentrations of 10 μM and 25 μM inhibited HCoV-229E release into the culture supernatant
[20]	Chloroquine	HCoV-OC43	HRT-18 cells	EC_{50} = 0.306 ± 0.0091 μM
			Newborn C57BL/6 mice; chloroquine administration transplacentally and via maternal milk	100%, 93%, 33% and 0% survival rate of pups when mother mice were treated per day with 15, 5, 1 and 0 mg/kg body weight, respectively
[21]	Chloroquine	Feline infectious peritonitis virus (FIPV)	*Felis catus* whole fetus-4 cells	FIPV replication was inhibited in a chloroquine concentration-dependent manner
[22]	Chloroquine	SARS-CoV	Vero E6 cells	EC_{50} = 4.1 ± 1.0 μM
		MERS-CoV	Huh7 cells (human liver cell line)	EC_{50} = 3.0 ± 1.1 μM

		HCoV-229E-GFP (GFP-expressing recombinant HCoV-229E)	Huh7 cells (human liver cell line)	EC_{50} = 3.3 ± 1.2 μM
[3]	Chloroquine	SARS-CoV-2	Vero E6 cells	EC_{50} = 1.13 μM

$CCID_{50}$, 50% cell culture infectious dose; CoV, coronavirus; EC_{50}, 50% effective concentration (mean ± S.D.); GFP, green fluorescent protein; HCoV, human coronavirus; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; S.D., standard deviation.

[a] See also [1] (Table 1) for additional references.

Letter

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Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies

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SUMMARY The coronavirus disease 2019 (COVID-19) virus is spreading rapidly, and scientists are endeavoring to discover drugs for its efficacious treatment in China. Chloroquine phosphate, an old drug for treatment of malaria, is shown to have apparent efficacy and acceptable safety against COVID-19 associated pneumonia in multicenter clinical trials conducted in China. The drug is recommended to be included in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future.

Keywords COVID-19, SARS-CoV-2, 2019-nCoV, pneumonia, chloroquine

The coronavirus disease 2019 (COVID-19) virus, emerged in December 2019, has spread rapidly, with cases now confirmed in multiple countries. As of February 16, 2020, the virus has caused 70,548 infections and 1,770 deaths in mainland China and 413 infections in Japan (*1*). A great deal of effort has been made to find effective drugs against the virus in China (*2*). On February 17, 2020, the State Council of China held a news briefing indicating that chloroquine phosphate, an old drug for treatment of malaria, had demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China (*3*).

In the early *in vitro* studies, chloroquine was found to block COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC_{50}) of 1.13 μM and a half-cytotoxic concentration (CC_{50}) greater than 100 μM (*4*). A number of subsequent clinical trials (ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029837, ChiCTR2000029826, ChiCTR2000029803, ChiCTR2000029762, ChiCTR2000029761, ChiCTR2000029760, ChiCTR2000029740, ChiCTR2000029609, ChiCTR2000029559, and ChiCTR2000029542) have been quickly conducted in China to test the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of COVID-19 associated pneumonia in more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo (*5*). Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course according to the news briefing. Severe adverse reactions to chloroquine phosphate were not noted in the aforementioned patients. Given these findings, a conference was held on February 15, 2020; participants including experts from government and regulatory authorities and organizers of clinical trials reached an agreement that chloroquine phosphate has potent activity against COVID-19. The drug is recommended for inclusion in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China.

Chloroquine is used to prevent and treat malaria and is efficacious as an anti-inflammatory agent for the treatment of rheumatoid arthritis and lupus erythematosus. Studies revealed that it also has potential broad-spectrum antiviral activities by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV (*6,7*). The anti-viral and anti-inflammatory activities of chloroquine may account for its potent efficacy in treating patients with COVID-19 pneumonia.

Chloroquine is a cheap and safe drug that has been used for more than 70 years. In light of the urgent clinical demand, chloroquine phosphate is recommended to treat COVID-19 associated pneumonia in larger populations in the future.

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Commentary

Of chloroquine and COVID-19

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ABSTRACT

Recent publications have brought attention to the possible benefit of chloroquine, a broadly used antimalarial drug, in the treatment of patients infected by the novel emerged coronavirus (SARS-CoV-2). The scientific community should consider this information in light of previous experiments with chloroquine in the field of antiviral research.

Recent publications have brought attention to the possible benefit of chloroquine, a broadly used antimalarial drug, in the treatment of patients infected by the novel emerged coronavirus (SARS-CoV-2) (Colson et al., 2020; Gao et al., 2020). The scientific community should consider this information in light of previous experiments with chloroquine in the field of antiviral research.

The sulfate and phosphate salts of chloroquine have both been commercialised as antimalarial drugs. Hydroxychloroquine has also been used as an antimalarial, but in addition is now broadly used in autoimmune diseases such as lupus and rheumatoid arthritis. Of note, chloroquine and hydroxychloroquine are considered to be safe and side-effects are generally mild and transitory. However, the margin between the therapeutic and toxic dose is narrow and chloroquine poisoning has been associated with cardiovascular disorders that can be life-threatening (Frisk-Holmberg et al., 1983). Chloroquine and hydroxychloroquine use should therefore be subject to strict rules, and self-treatment is not recommended.

The *in vitro* antiviral activity of chloroquine has been identified since the late 1960's (Inglot, 1969; Miller and Lenard, 1981; Shimizu et al., 1972) and the growth of many different viruses can be inhibited in cell culture by both chloroquine and hydroxychloroquine, including the SARS coronavirus (Keyaerts et al., 2004). Some evidence for activity in mice has been found for a variety of viruses, including human coronavirus OC43 (Keyaerts et al., 2009), enterovirus EV-A71 (Tan et al., 2018), Zika virus (Li et al., 2017) and influenza A H5N1 (Yan et al., 2013). However, chloroquine did not prevent influenza infection in a randomized, double-blind, placebo-controlled clinical trial (Paton et al., 2011), and had no effect on dengue-infecteds patient in a randomized controlled trial in Vietnam (Tricou et al., 2010). Chloroquine was also active *ex vivo* but not *in vivo* in the case of ebolavirus in mice (Dowall et al., 2015; Falzarano et al., 2015), Nipah (Pallister et al., 2009) and influenza virus (Vigerust and McCullers, 2007) in ferrets.

The case of chikungunya virus (CHIKV) is of specific interest: chloroquine showed promising antiviral activity *in vitro* (Coombs et al., 1981; Delogu and de Lamballerie, 2011), but was shown to enhance alphavirus replication in various animal models (Maheshwari et al., 1991; Roques et al., 2018; Seth et al., 1999), most probably because of the immune modulation and anti-inflammatory properties of chloroquine *in vivo* (Connolly et al., 1988; Katz and Russell, 2011; Savarino et al., 2003). In a nonhuman primate model of CHIKV infection, chloroquine treatment was shown to exacerbate acute fever and delay the cellular immune response, leading to an incomplete viral clearance (Roques et al., 2018). A clinical trial conducted during the chikungunya outbreak in 2006 in Réunion Island showed that oral chloroquine treatment did not improve the course of the acute disease (De Lamballerie et al., 2008) and that chronic arthralgia on day 300 post-illness was more frequent in treated patients than in the control group (Roques et al., 2018). Altogether, the assessment of previous trials indicates that, to date, no acute virus infection has been successfully treated by chloroquine in humans.

Chloroquine has also been tested in chronic viral diseases. Its use in the treatment of HIV-infected patients has been considered inconclusive (Chauhan and Tikoo, 2015) and the drug has not been included in the panel recommended for HIV treatment. The only modest effect of chloroquine in the therapy of human virus infection was found for chronic hepatitis C: an increase of the early virological response to pegylated interferon plus ribavirin (Helal et al., 2016) and, in a small sample size pilot trial in non-responder HCV patients, a transient viral load reduction (Peymani et al., 2016) were observed. This was not enough to include chloroquine in the standardised therapeutic

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protocols for hepatitis C patients.

Recently, Wang and colleagues (Wang et al., 2020) evaluated *in vitro* five FDA-approved drugs and two broad spectrum antivirals against a clinical isolate of SARS-CoV-2. One of their conclusions was that "chloroquine (is) highly effective in the control of 2019-nCoV infection *in vitro*" and that its "safety track record suggests that it should be assessed in human patients suffering from the novel coronavirus disease". At least 16 different trials for SARS-CoV-2 already registered in the Chinese Clinical Trial Registry (ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029837, ChiCTR2000029826, ChiCTR2000029803, ChiCTR2000029762, ChiCTR2000029761, ChiCTR2000029760, ChiCTR2000029741, ChiCTR2000029740, ChiCTR2000029609, ChiCTR2000029559, ChiCTR2000029542) propose to use chloroquine or hydroxychloroquine in the treatment of COVID-19 ("Chinese Clinical Trial Register" (ChiCTR)). In a recent publication (Gao et al., 2020), Gao and colleagues indicate that, "according to the news briefing", "results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course".

This would represent the first successful use of chloroquine in humans for the treatment of an acute viral disease, and is undoubtedly excellent news, since this drug is cheap and widely available. However, it should be considered carefully before drawing definitive conclusions, since no data has been provided yet to support this announcement. Results were produced in ten different hospitals and possibly from a number of different clinical protocols among those listed above, which include various designs for control groups (none, different antivirals, placebo, etc.) and various outcome primary indicators. The final interpretation is therefore technically demanding, and in the absence of published data, it is difficult to reach any firm conclusion. It will be of the utmost importance to know if the observed efficacy is associated specifically with chloroquine phosphate, or if this includes other salts (e.g., sulfate) of chloroquine, and hydroxychloroquine. It is also necessary to determine if the benefit of chloroquine therapy depends on the age class, the clinical presentation or the stage of the disease.

In conclusion, the option of using chloroquine in the treatment of SARS-CoV-2 should be examined with attention in light of the recent promising announcements, but also of the potential detrimental effect of the drug observed in previous attempts to treat acute viral diseases. We urge Chinese scientists to report the interim trial results currently running in China as soon as they are available. This should be preferentially done in a peer-reviewed publication with detailed information to allow the international scientific community to analyse the results, to confirm in prospective trials the efficacy of the proposed treatment and to guide future clinical practice.

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LETTER TO THE EDITOR OPEN

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

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Dear Editor,

In December 2019, a novel pneumonia caused by a previously unknown pathogen emerged in Wuhan, a city of 11 million people in central China. The initial cases were linked to exposures in a seafood market in Wuhan.[1] As of January 27, 2020, the Chinese authorities reported 2835 confirmed cases in mainland China, including 81 deaths. Additionally, 19 confirmed cases were identified in Hong Kong, Macao and Taiwan, and 39 imported cases were identified in Thailand, Japan, South Korea, United States, Vietnam, Singapore, Nepal, France, Australia and Canada. The pathogen was soon identified as a novel coronavirus (2019-nCoV), which is closely related to sever acute respiratory syndrome CoV (SARS-CoV).[2] Currently, there is no specific treatment against the new virus. Therefore, identifying effective antiviral agents to combat the disease is urgently needed.

An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating related viral infections. The 2019-nCoV belongs to *Betacoronavirus* which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial.[3] In this study, we evaluated the antiviral efficiency of five FAD-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV in vitro.

Standard assays were carried out to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates of 2019-nCoVs. Firstly, the cytotoxicity of the candidate compounds in Vero E6 cells (ATCC-1586) was determined by the CCK8 assay. Then, Vero E6 cells were infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019[2] at a multiplicity of infection (MOI) of 0.05 in the presence of varying concentrations of the test drugs. DMSO was used in the controls. Efficacies were evaluated by quantification of viral copy numbers in the cell supernatant via quantitative real-time RT-PCR (qRT-PCR) and confirmed with visualization of virus nucleoprotein (NP) expression through immunofluorescence microscopy at 48 h post infection (p.i.) (cytopathic effect was not obvious at this time point of infection). Among the seven tested drugs, high concentrations of three nucleoside analogs including ribavirin (half-maximal effective concentration (EC_{50}) = 109.50 μM, half-cytotoxic concentration (CC_{50}) > 400 μM, selectivity index (SI) > 3.65), penciclovir (EC_{50} = 95.96 μM, CC_{50} > 400 μM, SI > 4.17) and favipiravir (EC_{50} = 61.88 μM, CC_{50} > 400 μM, SI > 6.46) were required to reduce the viral infection (Fig. 1a and Supplementary information, Fig. S1). However, favipiravir has been shown to be 100% effective in protecting mice against Ebola virus challenge, although its EC_{50} value in Vero E6 cells was as high as 67 μM,[4] suggesting further in vivo studies are recommended to evaluate this antiviral nucleoside. Nafamostat, a potent inhibitor of MERS-CoV, which prevents membrane fusion, was inhibitive against the 2019-nCoV infection (EC_{50} = 22.50 μM, CC_{50} > 100 μM, SI > 4.44). Nitazoxanide, a commercial antiprotozoal agent with an antiviral potential against a broad range of viruses including human and animal coronaviruses, inhibited the 2019-nCoV at a low-micromolar concentration (EC_{50} = 2.12 μM; CC_{50} > 35.53 μM; SI > 16.76). Further in vivo evaluation of this drug against 2019-nCoV infection is recommended. Notably, two compounds remdesivir (EC_{50} = 0.77 μM; CC_{50} > 100 μM; SI > 129.87) and chloroquine (EC_{50} = 1.13 μM; CC_{50} > 100 μM, SI > 88.50) potently blocked virus infection at low-micromolar concentration and showed high SI (Fig. 1a, b).

Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV[5]) infection in cultured cells, mice and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection.[6] Remdesivir is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination.[7] Our time-of-addition assay showed remdesivir functioned at a stage post virus entry (Fig. 1c, d), which is in agreement with its putative antiviral mechanism as a nucleotide analogue. Warren et al. showed that in NHP model, intravenous administration of 10 mg/kg dose of remdesivir resulted in concomitant persistent levels of its active form in the blood (10 μM) and conferred 100% protection against Ebola virus infection.[7] Our data showed that EC_{90} value of remdesivir against 2019-nCoV in Vero E6 cells was 1.76 μM, suggesting its working concentration is likely to be achieved in NHP. Our preliminary data (Supplementary information, Fig. S2) showed that remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV.[2]

Chloroquine, a widely-used anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug.[8,9] Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[10] Our time-of-addition assay demonstrated that chloroquine functioned at both entry, and at post-entry stages of the 2019-nCoV infection in Vero E6 cells (Fig. 1c, d). Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo. Chloroquine is widely distributed in the whole body, including lung, after oral administration. The EC_{90} value of chloroquine against the 2019-nCoV in Vero

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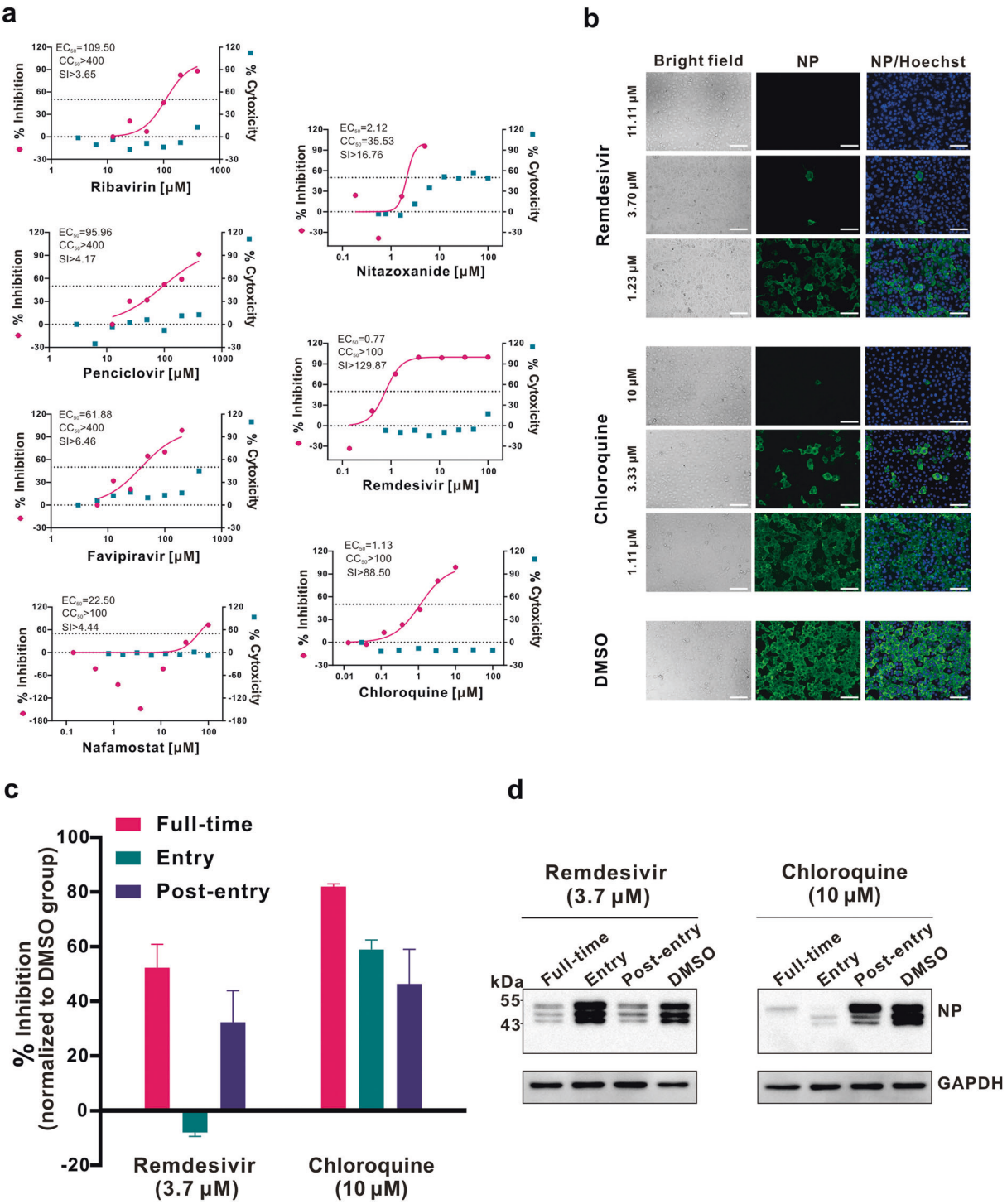

Fig. 1 The antiviral activities of the test drugs against 2019-nCoV in vitro. a Vero E6 cells were infected with 2019-nCoV at an MOI of 0.05 in the treatment of different doses of the indicated antivirals for 48 h. The viral yield in the cell supernatant was then quantified by qRT-PCR. Cytotoxicity of these drugs to Vero E6 cells was measured by CCK-8 assays. The left and right *Y*-axis of the graphs represent mean % inhibition of virus yield and cytotoxicity of the drugs, respectively. The experiments were done in triplicates. **b** Immunofluorescence microscopy of virus infection upon treatment of remdesivir and chloroquine. Virus infection and drug treatment were performed as mentioned above. At 48 h p.i., the infected cells were fixed, and then probed with rabbit sera against the NP of a bat SARS-related CoV[2] as the primary antibody and Alexa 488-labeled goat anti-rabbit IgG (1:500; Abcam) as the secondary antibody, respectively. The nuclei were stained with Hoechst dye. Bars, 100 μm. **c** and **d** Time-of-addition experiment of remdesivir and chloroquine. For "Full-time" treatment, Vero E6 cells were pre-treated with the drugs for 1 h, and virus was then added to allow attachment for 2 h. Afterwards, the virus–drug mixture was removed, and the cells were cultured with drug-containing medium until the end of the experiment. For "Entry" treatment, the drugs were added to the cells for 1 h before viral attachment, and at 2 h p.i., the virus–drug mixture was replaced with fresh culture medium and maintained till the end of the experiment. For "Post-entry" experiment, drugs were added at 2 h p.i., and maintained until the end of the experiment. For all the experimental groups, cells were infected with 2019-nCoV at an MOI of 0.05, and virus yield in the infected cell supernatants was quantified by qRT-PCR **c** and NP expression in infected cells was analyzed by Western blot **d** at 14 h p.i.

E6 cells was 6.90 μM, which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.[11] Chloroquine is a cheap and a safe drug that has been used for more than 70 years and, therefore, it is potentially clinically applicable against the 2019-nCoV.

Our findings reveal that remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro. Since these compounds have been used in human patients with a safety track record and shown to be effective against various ailments, we suggest that they should be assessed in human patients suffering from the novel coronavirus disease.

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AUTHOR CONTRIBUTIONS

G.X., W.Z., Z.H., M.W., R.C., and L.Z. conceived and designed the experiments. X.Y., J.L., M.X., M.W., R.C., and L.Z. participated in multiple experiments; G.X., W.Z., Z.H., Z.S., M.W., R.C., and L.Z. analyzed the data. M.W., L.Z., R.C., and Z.H. wrote the manuscript. G.X., W.Z., and Z.H. provided the final approval of the manuscript.

ADDITIONAL INFORMATION

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ATTACHMENT 9

磷酸氯喹、特异血浆、肺炎一号方……新冠肺炎治疗最新进展！

2020-02-17 19:18 来源： 中国政府网

2月17日下午，国务院联防联控机制召开新闻发布会，介绍了医疗救治工作进展情况，一起来看——

新冠肺炎有没有明确的诊疗方法？治愈后会复发吗？

这个疾病虽然是新发传染性疾病，但是它可防可治。

通过对治愈出院病人的情况分析，应该说对治愈出院的病人形成了一些行之有效的诊疗策略和诊疗方法。这些出院病人中大概90%左右是轻症，10%左右是重症和危重症。

从患者发病到确诊的时间段来看，全国平均是4.95天，说明我们缩短诊断时间，及时诊疗，早诊早治，也是提高治愈率的一个非常有效措施。

90%以上的患者都是采用了抗病毒治疗、对症治疗，包括呼吸支持、循环支持、提高免疫力等综合的一系列的诊疗手段，来加速患者的治愈。

武汉的情况也有很大改变。特别是近期通过早诊早治，通过对轻症病人收治后的连续观察，可以看到重症占比从初期的38%已经下降到目前的18%。所以应该说“四早”“四集中”是提高治愈率、收治率，降低感染率和病死率非常有效的措施。

正在进行临床试验的磷酸氯喹、法匹拉韦和瑞德西韦三种药物，有明确疗效吗？

我们组织北京、广东和湖南几省十余家医院联合开展关于磷酸氯喹对于新冠肺炎治疗的安全性和有效性评价。在临床上，我们非常确定地看到了疗效，无论从重症化率、退热现象还是肺部的影像好转时间、病毒核酸的转阴时间和转阴率，以及缩短病程等一系列指标，进行系统地、综合研判，用药组优于对照组。举一个例子，北京一位病人54岁发病第4天住进医院，服药一周后核酸转阴，所有指标全部向好，达到解除隔离和出院标准。

药物安全性方面也是我们极为关注的。100余例的用药患者中至今没有发现和药物相关的、明显的严重不良反应。专家组经过认真、细致地研讨最后达成一致意见，认为“该药是一个上市多年的老药，用于广泛人群治疗的安全性是可控的。基于前期临床机构所开展的研究结果，可以明确磷酸氯喹治疗新冠肺炎具有一定疗效”。

专家一致推荐“应当尽快将磷酸氯喹纳入到新一版的诊疗指南，扩大临床试用范围”。

特异血浆有效吗？

当前对于重症治疗，临床研究显示恢复期血浆具有安全性和一定疗效，是对重症、危重症非常有效的重要手段。在诊疗方案第五版当中已经将康复者恢复期血浆的治疗方法纳入其中，在即将修订形成的第六版的方案中，我们还将细化相关内容。

现在治疗的患者中有1位已经出院，1位已经可以下地行走，余下的几位患者都在康复期间，我们也会密切关注临床进展。

呼吁能够在全社会开展“千人献浆救千人”的行动，希望能够让更多的康复者伸出手臂，捐献血浆。

对重症、危重症患者如何有效治疗？

首先，强调重症和危重症病人支持对症的治疗，有效氧疗是最重要的一个手段，通过氧疗或者呼吸机的治疗，使患者的血氧改善以后，最重要脏器的维护是至关重要的。

规范和细化了如何进行氧疗，如何上呼吸机，使基层更好的执行氧疗方案。

对重症病人探索了临床预警指标。

指南里也增加了新疗法，包括恢复期血浆治疗。

轻症患者是否可以自愈？

自限性疾病不等于不需要治疗，尤其是新冠肺炎，传染性很强，所有确诊病例都需要在医疗机构或者像武汉地区方舱这样的机构进行观察照护，一方面隔离阻断传播的风险，另一方面观察病情避免病情的恶化，该病病情进展突然，确实有少部分的轻症病例有突然进展，进入重型、危重型，甚至危及生命。所以我们强调，新冠肺炎病毒感染一定要积极到医院进行救治，不要由于它自限性疾病的特点而延误治疗时机。

新冠病毒从病毒学角度不需要强化抗病毒治疗，有一部分患者通过自身比较强的免疫可以把病毒有效地清除，不会变成慢性。

对新型冠状病毒感染，有一部分轻症患者通过一般的支持对症治疗和中药清热解毒的治疗就可以痊愈。

哪些中药方剂比较有效？

在取得214例临床有效数据的情况下，2月6日国家卫健委、国家中医药管理局联合发文向全国推荐使用清肺排毒汤。病例分析统计数据显示清肺排毒汤对治疗新冠肺炎具有良好的临床疗效和救治前景。

各地也推出了一些有效的方剂和方药。比如广州八院推出的“肺炎一号方”也取得了良好的临床疗效。

核酸检测准确吗？

首先核酸检测本身的稳定性是很好的。出现一些所谓检不出的情况或者假阴性的情况，主要原因是任何检测方法都有一个敏感性的问题。从病程方面，可能是病毒量很少，在上呼吸道可能检测不出来，当然还有取样方法问题，比如现在强调咽拭子，当然我们鼓励痰的标本或者下呼吸道的一些肺泡灌洗液，它的诊断阳性率会大幅度递增。目前核酸检测是确诊新冠肺炎的“金标准”，只有通过核酸检测阳性才能确诊。卫健委目前也在联合攻关提高检测的敏感性和特异性。

对于新冠肺炎感染的诊断，结合临床和影像学诊断是非常重要的，我们提出临床诊断的概念，通过临床表现，在没有病原的情况下可以启动对这个病的管理和治疗，通过临床诊断使患者得到隔离和及时救治，提高治愈率，降低病死率，避免进一步传播。现在，临床上我们强化综合诊断能力不断提升。

现在科技部也开展了攻关项目，对临床的病人采用抗原抗体检测，相信这些新方法的使用会进一步提高新冠肺炎诊断的特异性和敏感性，使病人更得到有效、更及时的诊断和救治。

治愈出院后要注意什么？

出院后也要进行居家管理，至少两周时间居家进行相对系统的观察，社区层面还要给予居家指导。同时建议两到四周后回医院进行复查，如果有病情变化及时到医院救治。尽管轻症病例总体病愈后很好，但是极个别的可能有病情变化，我们希望通过系统诊疗照护，能够使病人及时得到治疗并康复。

回应网友关切

采集血浆会不会影响健康？

只要病人达到了出院隔离的标准就可以采集血浆。

血浆采集是单采浆的手段，把血浆取出来，红细胞、白细胞、血小板等回输回去，这种血浆采200到300毫升以后，病人一两周以后血浆就完全恢复到原来的情况，对肌体伤害是很小的，大家不要太多顾虑。

采集血浆和平时献血有什么区别？

对象不同，只有新冠病毒感染后痊愈的恢复期病人才能作为供血者，只有这样的病人血浆里才有综合抗体，可以达到有效治疗新冠病毒感染的作用。

仅采血浆，不采全血。一般献血都是采全血，有红细胞、血小板，然后进行分层以后，临床使用的时候，或者用血浆，或者用血小板，或者用红细胞，是成份输血的方式，这次只要血浆，其他的还给病人回输回去。

除了要做常规检测外还要做新冠病毒核酸检测。常规检测都要做，比如乙肝、丙肝等传染病指标的检测，避免输血的交叉感染。同时有条件的单位要检测新冠病毒的抗体，综合抗体滴度越高，救治效果更好，这是有所区别的。还有一个是做核酸，要检测病毒核酸，必须是阴性的，当然治愈后的病人都是阴性的，但是献血之前还要进行检测，保证没有新冠病毒感染的情况才能献血。

【我要纠错】　　责任编辑：宋岩

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武汉方舱医院“新军规”：查抗体再出院

来源：环球时报
2020-03-06 09:02

本报记者 白云怡

据报道，武汉市江岸方舱医院4日发布《紧急通知》，近期出院患者中复发者较多，导致患者重新入院治疗。为了减少病情复发，确保彻底治愈，达到“零回头”目标，从3月5日起对所有在舱拟出院病人抽血加做病毒抗体Ig-M与Ig-G检查，确保完全康复出院。

武汉江岸方舱医院一名负责人表示，市防疫指挥部通知他们，有患者出舱以后出现核酸检测转阳的情况，所以为了将患者彻底治好，加做病毒抗体Ig-M与Ig-G的检查。

另据武汉市汉阳国博方舱医院负责人透露，该院也已接到武汉市疫情指挥部通知，暂停办理病人出院程序。他表示，“市疫情指挥部下发了通知，暂停执行病人出院，这个通知是针对整个武汉市所有方舱医院的。”但他表示，暂停时间不会太久，因为查血的流程一直都有。

记者注意到，针对部分新冠肺炎出院患者出现核酸检测复检阳性的问题，最新发布的《新型冠状病毒肺炎诊疗方案（试行第七版）》将原来方案中出院患者“应继续进行14天自我健康状况监测”改为“应继续进行14天的隔离管理和健康状况监测”。

相比前一版诊疗方案，第七版的诊疗方案增加了血清学证据，即如果疑似病例的血清学检查新冠病毒特异性Ig-M抗体和Ig-G抗体阳性；血清新冠病毒特异Ig-G抗体由阴性转为阳性或者恢复期比急性期4倍以上升高便可确诊为新冠肺炎。

北京大学公共卫生学院副院长王培玉对《环球时报》记者表示，此前新冠肺炎患者出院主要有两个标准，一是新冠病毒感染的临床症状消失，比如连续至少7天体温正常、CT报告对比有明显的吸收等；二是核酸检测呈阴性，即病毒在人体内消失。此次加做病毒抗体Ig-M与Ig-G检查，意味着要求出院病人不仅体内已不携带病毒，还得产生抗体，不会再次被感染。王培玉表示，一般人体内病毒被消灭和产生抗体之间还会存在几天时间，且核酸检测有呈假阴性的可能，加测病毒抗体Ig-M与Ig-G相当于为出院病人的安全和避免再次传播上了一道“保险”。▲

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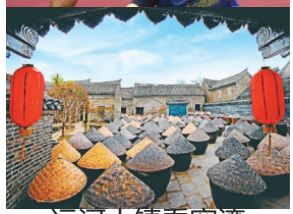

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