新型冠状病毒信息简报

第 42 期（2020 年 4 月 29 日报）

上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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1. 2020 年 4 月 28 日疫情

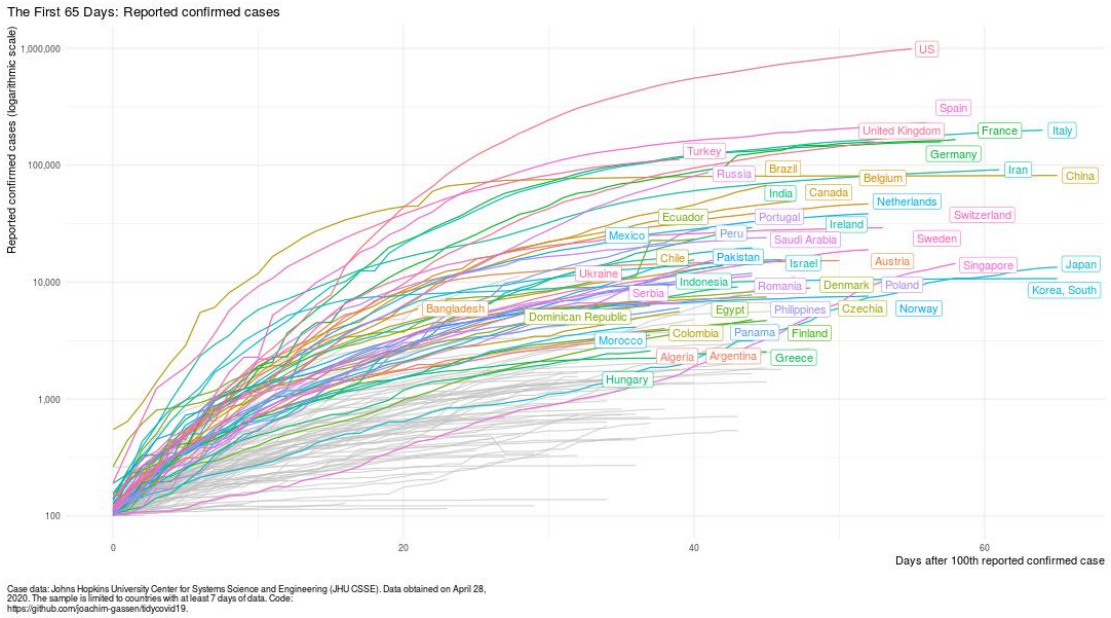
数据来源：WHO

发布时间：2020 年 4 月 28 日北京时间下午 4 点

链接：https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

根据 WHO 提供的数据，2020 年 4 月 28 日全球累计确诊新型冠状病毒病人 2954222 例，当日新增确诊 76026 例，累计死亡 202597 例，当日新增死亡 3932。

中国累计确诊 84347 例，累计死亡 4643 例，当日新增确诊 3 例，新增死亡 0 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 4 月 28 日北京时间下午 4 点）

全国新型冠状病毒肺炎新增确诊病例分布图（4月28日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. COVID-19 在婴幼儿中的非典型表现

Atypical presentation of COVID-19 in young infants

来源：The Lancet
发布时间：2020-04-27
链接：https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30980-6/fulltext

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DOI 或 PUBMED ID：https://doi.org/10.1016/S0140-6736(20)30980-6

编译者：宋张悦

中文摘要：
儿童可能是儿童向成人传播病毒的一个潜在来源，目前在大多数国家，学校已关闭。然而，研究结果似乎表明儿童对 COVID-19 的易感性较低，传染性也较低。在法国实施人口隔离的 7 天内(始于 2020 年 3 月 17 日)，研究人员发现 SARS-CoV-2 感染的幼儿数量增加。在巴黎 Trousseau 医院的儿科，出现发烧或呼吸道症状，或同时出现这两种症状并需要住院的患者被收住到专门的 SARS-CoV-2 感染单元。在隔离的第一周，收住了 14 名小于 3 个月的婴儿，其中 5 名婴儿的鼻咽拭子检测出 SARS-CoV-2 阳性被诊断为 COVID-19。他们的临床表现与文献报道的 COVID-19 患儿的临床表现不同，不过先前也没有来自更小婴儿的数据了。COVID-19 的 5 名婴儿都是男孩，他们在入院前或住院期间均无呼吸道症状(与已公布的数据形成对比)，他们也不需要重症监护。其中 4 名男孩在入院时表现出神经系统症状，如中轴性低张力、嗜睡和呻吟，这促使研究人员对他们进行了腰椎穿刺。研究发现，他们的脑脊液标本都正常，RT-PCR 检测 SARS-CoV-2 均为阴性。除了扑热息痛，这些婴儿没有服用其他药物。他们的临床病程迅速好转，入院后 1-3 天即可出院。虽然婴儿最初可能出现严重感染的迹象，但最小的婴儿对 COVID-19 表现出耐受性，症状迅速改善，这与住院的成人 COVID-19 形成鲜明的对比。目前对婴儿感染 SARS-CoV-2 还知之甚少，因此，至少在确诊后的两周内要做好监测。另外，本研究中所有患儿的父母均表现出轻微的病毒感染症状(如鼻炎、咳嗽或发烧，持续时间均小于 1 周)，可能与 COVID-19 有关。

Abstract:
As of April 27, 2020, more than two million people worldwide have been diagnosed with coronavirus disease 2019 (COVID-19), with Europe being one of the current major clusters of the pandemic. Despite an absence of evidence, children have been targeted as a potential source of children-to-adult virus dissemination, and schools have been closed in most countries. However, findings seem to indicate a lower susceptibility of children to COVID-19 and low contagiousness.2 Within 7 days of imposed population quarantine in France (initiated on March 17, 2020), we observed an increase in number of young infants with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
Here we describe our experience of COVID-19 in five young infants. In the pandemic context, infants younger than 3 months with isolated fever should be tested for SARS-CoV-2. Although infants might initially present signs of severe infection, our experience is that the youngest children tolerate and rapidly improve from COVID-19, in contrast to adults admitted to hospital with COVID-19. However,

because little is known about SARS-CoV-2 infection in infants, close monitoring is required for at least 2 weeks after the diagnosis. All of the infants' parents showed mild signs of viral infection (ie, rhinitis, or cough or fever, or both, for <1 week), which could be related to undiagnosed COVID-19.

3. 一项回顾性研究：关于中国深圳 391 例确诊病例以及他们的 1286 位密切接触者的流行病学和病毒传染模式

Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study

来源：the lancet infectious disease

发布时间：2020-04-28

链接：https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30287-5/fulltext

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中文摘要：

全球大流行的情况下，绝大多数国家和地区没有在第一时间进行防控措施，实施全面的流行病毒调查。本文呈现了深圳疾控中心从 2020 年 1 月 14 到 2 月 12 之间进行的完整流行病学研究。该研究中包括了在此期间所有 391 例 COVID-19 确诊患者以及他们的 1286 位密切接触者。

本文发现确诊病例平均年龄比整个人群要老（平均 45 岁），男女病例平衡（男 187，女 204）。其中 356（91%）个病例在开始接受检查的时候只有轻微到中度症状。到 2020 年 2 月 22，3 例死亡，225 位恢复（恢复的中位时间是 21 天，95%置信度 20-22 天）。平均而言病例在症状发生 4.6 天(95%置信度为 4.1 - 5.0 天)后开始被实施隔离（注：应该是疾控中心对病人开始实施隔离措施），而基于接触的追踪可以将这个时间缩短到 1.9 天(95%置信度为 1.1 - 2.7 天)。家庭传播或者和病人一起旅行相比其他类型近距离接触风险更高(家庭内 OR 是 6.27 [95%置信度为 1.49 - 26.33] and 和病人一起旅行的 OR 为 7.06 [95%置信度为 1.43 - 34.91])。家庭中继发感染概率是 11.2% (95%置信度为 9.1% - 13.8%)，儿童和成年人的感染率相当（10 岁以下儿童 7.4%，普通人群平均 6.6%）。观察到的传染指数（*R*）为 0.4（95%置信度为 0.3-0.5），从一个人传到另一个人的平均间隔时间为 6.3 天（95%置信度为 5.2-7.6）。

该数据显示确诊病例以及他们的未染病的密切接触者为 SARS-CoV-2 的流行病学提供了非常关键的线索。该研究表明隔离以及对密切接触者进行追踪可以缩短有感染性的病例在社区中传播，从而减低传染指数。尽管如此，隔离以及对密切接触者的总体影响仍然有不确定性，和无症状病例的数目有关。儿童和一般人群的感染风险相当，所以在考虑病毒传播和控制时也要考虑他们。

编者注：

我们 4 月 16 日简报第二条“COVID-19 在家庭内部的继发率及相关决定因素”有广州市的类似研究，除了广州研究表明儿童（<20 岁）相比高龄老人（>60 岁）感染率更低（OR 为 0.26）外，其他结果相近基本一致。

Summary:

Background Rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, prompted heightened surveillance in Shenzhen, China. The resulting data provide a rare opportunity to measure key metrics of disease course, transmission, and the impact of control measures.

Methods From Jan 14 to Feb 12, 2020, the Shenzhen Center for Disease Control and Prevention identified 391 SARS-CoV-2 cases and 1286 close contacts. We compared cases identified through symptomatic surveillance and contact tracing, and estimated the time from symptom onset to confirmation, isolation, and admission to hospital. We estimated metrics of disease transmission and analysed factors influencing transmission risk.

Findings Cases were older than the general population (mean age 45 years) and balanced between males (n=187) and females (n=204). 356 (91%) of 391 cases had mild or moderate clinical severity at initial assessment. As of Feb 22, 2020, three cases had died and 225 had recovered (median time to recovery 21 days; 95% CI 20－22). Cases were isolated on average 4.6 days (95% CI 4.1－5.0) after developing symptoms; contact tracing reduced this by 1.9 days (95% CI 1.1－2.7). Household contacts and those travelling with a case were at higher risk of infection (odds ratio 6.27 [95% CI 1.49－26.33] for household contacts and 7.06 [1.43－34.91] for those travelling with a case) than other close contacts. The household secondary attack rate was 11.2% (95% CI 9.1－13.8), and children were as likely to be infected as adults (infection rate 7.4% in children <10 years *vs* population average of 6.6%). The observed reproductive number (R) was 0.4 (95% CI 0.3－0.5), with a mean serial interval of 6.3 days (95% CI 5.2－7.6).

Interpretation Our data on cases as well as their infected and uninfected close contacts provide key insights into the epidemiology of SARS-CoV-2. This analysis shows that isolation and contact tracing reduce the time during which cases are infectious in the community, thereby reducing the R. The overall impact of isolation and contact tracing, however, is uncertain and highly dependent on the number of asymptomatic cases. Moreover, children are at a similar risk of infection to the general population, although less likely to have severe symptoms; hence they should be considered in analyses of transmission and control.

4. **新冠病毒的候选疫苗可能通用于当前所有出现的病毒种类**
   A SARS-CoV-2 vaccine candidate would likely match all currently circulating strains

来源：bioRxiv
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DOI 或 PUBMED ID：https://doi.org/10.1101/2020.04.27.064774
编译者：刘焕珍
中文摘要：
新冠病毒多样化的局面反映了漂移和瓶颈事件，而不是随着病毒的传播逐渐适应人类。新冠肺炎大流行的规模凸显了研发安全有效疫苗的紧迫性。本文作者分析了自 2019 年 12 月以来采样的 5,700 个序列中的新冠病毒序列多样性。作为大多数候选疫苗的目标免疫原的刺突蛋白，包含 93 个享有共同多态性的位点；在目前出现的序列中，发现只有超过 1%的突变。在新冠病毒序列中发现的最小多样性可以用漂移和瓶颈事件来解释，因为该病毒可能由中国武汉扩散来的。重要的是，自 2019 年 12 月以来，几乎没有证据表明该病毒已适应其人类宿主。我们的研究结果表明，单一疫苗应能有效抵抗当前的全球毒株。
Abstract:
The limited diversification of SARS-CoV-2 reflects drift and bottleneck events rather than adaptation to humans as the virus spread.The magnitude of the COVID-19 pandemic underscores the urgency for a safe and effective vaccine. Here we analyzed SARS-CoV-2 sequence diversity across 5,700 sequences sampled since December 2019. The Spike protein, which is the target immunogen of most vaccine candidates, showed 93 sites with shared polymorphisms; only one of these mutations was found in more than 1% of currently circulating sequences. The minimal diversity found among SARS-CoV-2 sequences can be explained by drift and bottleneck events as the virus spread away from its original epicenter in Wuhan, China. Importantly, there is little evidence that the virus has adapted to its human host since December 2019. Our findings suggest that a single vaccine should be efficacious against current global strains.

5. 包括病毒热灭活的弹性 SARS-CoV-2 诊断工作流程

Resilient SARS-CoV-2 diagnostics workflows including viral heat inactivation

来源：medRxiv
发布时间：2020-04-22
链接：https://www.medrxiv.org/content/10.1101/2020.04.22.20074351v1
第一作者：Maria Jose Lista
通讯作者：Rocio Teresa Martinez-Nunez
通讯作者单位：King’s College London Diagnostics Team at Guy’s Campus
DOI 或 PUBMED ID：Preprint
编译者：张鹏伟
中文摘要：
世界范围内缺乏检测 SARS-2 的试剂。许多临床诊断实验室依赖于提供集成的端到端解决方案的商业平台。尽管这提供了已建立的稳定的流水线，但鉴于当前需求量非常大的情况，试剂的供应存在明显的瓶颈。一些实验室采用免试剂盒处理程序，但许多其他小型实验室将无法开发这些程序和/或对其样品进行手动处理。为了提供用于 SARS-CoV-2 核酸检测的多种工作流程，作者比较了几种市售的 RNA 提取方法：QIAamp 病毒 RNA 迷你试剂盒（QIAgen），最近开发的 RNAdvance Blood（Beckman）和 Mag-Bind 病毒 DNA/RNA 96 试剂盒（Omega Bio-tek）。他们还比较了不同的一步 RT-qPCR 主混合品牌：TaqMan™ 快速病毒一步主混合（ThermoFisher Scientific）、qPCRBIO 探针一步 Go Lo-ROX（PCR 生物系统）和 Luna®通用

探针一步 RT-qPCR 试剂盒（NEB）。他们使用疾病控制中心（CDC）推荐的引物检测病毒 N 基因的两个区域，以及根据英国公共卫生（PHE）指南（Charite/WHO/PHE）检测 RdRP 基因区域的引物。他们的数据表明，RNA 提取方法提供了类似的结果。在所测试的 qPCR 试剂中，TaqMan™快速病毒 1 步预混液和 Luna®通用探针一步 RT-qPCR 试剂盒被证明是最敏感的。N1 和 N2 引物探针比 RdRP-SARSr 引物探针组提供更可靠的检测，特别是在病毒滴度低的样品中。重要的是，作者已经实施了一个使用热灭活的方案，并证明它对临床样本中 qPCR 的敏感性影响最小，这可能使 SARS-CoV-2 检测可移植到没有 CL-3 设施的环境中。
总而言之，作者提供了几个测试流程，这些流程可以在其他实验室轻松实现，并在以下位置免费提供了所有规程和 SOPs：https://osf.io/uebvj/.

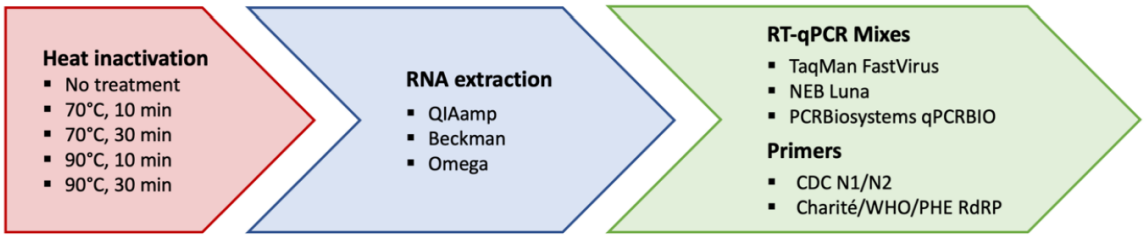

Figure 1. Representation of our workflow. We employed heat inactivation vs non heat inactivation (red); compared three different RNA extraction kits (blue) followed by three RT-qPCR mixes and three sets of primers (green).

Abstract:
There is a worldwide shortage of reagents to perform detection of SARS-2. Many clinical diagnostic laboratories rely on commercial platforms that provide integrated end-to-end solutions. While this provides established robust pipelines, there is a clear bottleneck in the supply of reagents given the current situation of extraordinary high demand. Some laboratories resort to implementing kit-free handling procedures, but many other small laboratories will not have the capacity to develop those and/or will perform manual handling of their samples. In order to provide multiple workflows for SARS-CoV-2 nucleic acid detection we compared several commercially available RNA extraction methods: QIAamp Viral RNA Mini Kit (QIAgen), the recently developed RNAdvance Blood (Beckman) and Mag-Bind Viral DNA/RNA 96 Kit (Omega Bio-tek). We also compared different 1-step RT-qPCR Master Mix brands: TaqMan™ Fast Virus 1-Step Master Mix (ThermoFisher Scientific), qPCRBIO Probe 1-Step Go Lo-ROX (PCR Biosystems) and Luna® Universal Probe One-Step RT-qPCR Kit (NEB). We used the Centre for Disease Control (CDC) recommended primers that detect two regions of the viral N gene as well as those that detect the RdRP gene region as per Public Health England (PHE) guidelines (Charite/WHO/PHE). Our data show that the RNA extraction methods provide similar results. Amongst the qPCR reagents tested, TaqMan™ Fast Virus 1-Step Master Mix and Luna® Universal Probe One-Step RT-qPCR Kit proved most sensitive. The N1 and N2 primer-probes provide a more reliable detection than the RdRP-SARSr primer-probe set, particularly in samples with low viral titres. Importantly, we have implemented a protocol using heat inactivation and demonstrate that it has minimal impact on the sensitivity of the qPCR in clinical samples - potentially making SARS-CoV-2

testing portable to settings that do not have CL-3 facilities.
In summary, we provide several testing pipelines that can be easily implemented in other laboratories and have made all our protocols and SOPs freely available at https://osf.io/uebvj/.

6. SARS-CoV-2 感染患者消化道症状与住院治疗的关系

Association of Digestive Symptoms and Hospitalization in Patients with SARS-CoV-2 Infection

来源： medrxiv
发布时间： 2020-04-28
链接： https://www.medrxiv.org/content/10.1101/2020.04.23.20076935v1
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编译者： 王玮
中文摘要：

背景： COVID-19 患者并发胃肠道症状的发生率很高，但这些消化道症状与是否住院治疗之间的关系尚未确定。
方法： 在我们的伦理审查委员会的快速批准下，我们回顾性分析了从 2020 年 3 月 3 日至 2020 年 4 月 7 日间在我们机构进行的 PCR 检测呈阳性的连续确诊 COVID-19 患者的数据。在急诊室报告收集了基线人口统计数据、临床、实验室和患者报告的症状数据。采用多变量 logistic 回归分析评估住院与胃肠道症状（包括恶心/呕吐、腹泻、腹痛、食欲不振）的相关性。
结果： 在本研究期间，我们发现了 207 名连续确诊的 COVID-19 患者，60 例（29.0%）住院，17 例（8.2%）需要 ICU 护理。34.5%（70 例）的患者同时出现胃肠道症状，其中 90%为轻度。在人口统计学和疾病严重程度控制的多元回归模型中，有胃肠道症状的患者住院的风险增加(adjusted OR 4.84 95% CI: 1.68-13.94, P<0.001)。腹泻患者住院的可能性增加 7 倍(adjusted OR=7.58, 95% CI: 2.49-20.02, P <0.001)，恶心或呕吐患者住院的几率增加 4 倍(adjusted OR 4.39, 95% CI: 1.61-11.4, P = 0.005)。
结论： 我们证明，COVID19 患者中有相当一部分同时出现轻度胃肠道症状，这些消化道症状的出现与住院治疗的需要有关。由于目前的重点是精简分流工作，急救人员应考虑在最初的临床评估和决策中评估消化系统症状。

Abstract:

Background: High rates of concurrent gastrointestinal manifestations have been noted in patients with COVID- 19, however the association between these digestive manifestations and need for hospitalization has not been established.
Methods: Following expedited approval from our Institutional Review Board, we analyzed retrospectively collected data from consecutive patients with confirmed COVID-19 based on a positive polymerase chain reaction testing at our institution from March 03, 2020 to April 7, 2020. Baseline demographic, clinical, laboratory and patient-reported symptom data were collected at presentation in the emergency room. Multivariable logistic regression analyses were performed to evaluate the association between hospitalization and presence of gastrointestinal symptoms.

Results: During this study period, we identified 207 consecutive patients with confirmed COVID-19. 34.5% noted concurrent gastrointestinal symptoms; of which 90% of gastrointestinal symptoms were mild. In a multivariate regression model controlled for demographics and disease severity, an increased risk for hospitalization was noted in patients with any gastrointestinal symptom (adjusted OR 4.84 95% CI: 1.68-13.94]. Diarrhea was associated with a seven-fold higher likelihood for hospitalization (adjusted OR=7.58, 95% CI: 2.49-20.02, P <0.001) and nausea or vomiting had a four times higher odds (adjusted OR 4.39, 95% CI: 1.61-11.4, P = 0.005).

Conclusion: We demonstrate that a significant portion of COVID19 patients have concurrent mild gastrointestinal symptoms and that the presence of these digestive symptoms is associated with a need for hospitalization. With the current focus on streamlining triaging efforts, first responders and frontline providers should consider assessing for digestive symptoms in their initial clinical evaluation and decision-making.

7. 病理学证据表明在一个准备出院的病人的肺部组织中存在残余的 SARS-CoV-2 病毒

Pathological evidence for residual SARS-CoV-2 in pulmonary tissues of a ready-for-discharge patient

来源：Cell research
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中文摘要：

在一些临床治愈出院的 COVID-19 病人中出现了多例在出院后又出现核酸阳性，这些发现让大家开始关注出院的病人。同时，我们仍然非常需要理解 SARS-CoV-2 感染的致病机理。该研究中，作者们对一位准备出院但是突发心脏病去世的 78 岁女性病人进行了尸检。病人的鼻咽拭子核酸检测呈现阴性，心脏，肝、小肠、皮肤也都检测不出病毒核酸或者病毒衣壳蛋白，只有肺部仍然可以检出病毒。病理学检查显示病人的肺部可见病毒引起的病变。这个研究为改善遏制病毒传播以及疾病管理具有临床指导意义。

Abstract:

SARS-CoV-2, a novel coronavirus and causing COVID-19, has given rise to a worldwide pandemic. So far, tens of thousands of COVID-19 patients have been clinically cured and discharged, but multiple COVID-19 cases showed SARS-CoV-2 positive again in discharged patients, which raises an attention for the discharged patients. Also, there is an urgent need to understand the pathogenesis of SARS-CoV-2 infection. Here, we conducted postmortem pathologic study in a ready-for-discharge COVID-19 patient who succumbed to sudden cardiovascular accident. Pathological examination revealed SARS-CoV-2-viruses remaining in pneumocytes and virus-caused pathological changes in the lungs.

Our study provided new insights into SARS-CoV-2 pathogenesis and might facilitate the improvement of clinical guideline for virus containment and disease management.

8. 在人肺细胞和感染表达 SARS-CoV-2 核糖核酸聚合酶嵌合病毒的小鼠动物模型中瑞德西韦能够有效抑制 SARS-CoV-2

Remdesivir potently inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice

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中文摘要：
针对 COVID-19 患者目前由于没有获得批准的治疗方法，这种大流行表明了对安全、广谱的抗 SARS-CoV-2 的迫切需要。作者报道了瑞德西韦 (RDV)，一种腺苷类似物的单磷酸酯前药，能有效地抑制人肺细胞和原代人气道上皮细胞培养物中的 SARS-CoV-2 的复制(EC50=0.01 μM)。在 VeroE6 细胞中观察到较弱的活性(EC50=1.65μM)，可能因为它们代谢 RDV 的能力较低。为了快速评估体内疗效，作者设计了一种嵌合 SARS-CoV 病毒，其编码 RDV 靶标——SARS-CoV-2 核糖核酸依赖性核糖核酸聚合酶（RdRP）。在感染嵌合病毒的小鼠中，与载体治疗的动物相比，治疗性 RDV 给药降低了肺病毒载量并改善了肺功能。这些数据证明了 RDV 在细胞水平和小鼠动物模型中都能有效地对抗 SARS-CoV-2，为其对 COVID-19 治疗的进一步临床试验提供一定的支持。
编者注：
作者之所以采用 SARS-CoV 嵌合病毒是因为小鼠不易感染和复制 SARS-CoV-2，而可以感染和复制 SARS-CoV。
作者中有几位是 GILEAD 公司员工。
Abstract:
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in 2019 as the causative agent of the novel pandemic viral disease COVID-19. With no approved therapies, this pandemic illustrates the urgent need for safe, broad-spectrum antiviral countermeasures against SARS-CoV-2 and future emerging CoVs. We report that remdesivir (RDV), a monophosphoramidate prodrug of an adenosine analog, potently inhibits SARS-CoV-2 replication in human lung cells and primary human airway epithelial cultures (EC50=0.01μM). Weaker activity was observed in Vero E6 cells (EC50=1.65μM) due to their low capacity to metabolize RDV. To rapidly evaluate in vivo efficacy, we engineered a chimeric SARS-CoV encoding the viral target of RDV, the RNA-dependent RNA polymerase, of SARS-CoV-2. In mice infected with chimeric virus, therapeutic RDV administration diminished lung viral load and improved pulmonary function as compared to vehicle treated animals. These

data provide substantial evidence that RDV is potently active against SARS-CoV-2 in vitro and in vivo, supporting its further clinical testing for treatment of COVID-19.

9. 角鲨烯基多药纳米粒促进失控炎症的缓解

Squalene-based multidrug nanoparticles for improved mitigation of uncontrolled inflammation

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DOI 或 PUBMED ID：10.1126/sciadv.aaz5466
编译者：张丽双
中文摘要：
不受控制的炎症过程是许多病理学的根源。最近，对已确诊的 COVID-19 病例的研究表明，死亡可能是由病毒引起的炎症所致。越来越多的证据表明，不受控制的促炎状态通常是由促炎信号和氧化应激之间的持续正反馈回路驱动的。目前还没有有效的方法来有针对性地对抗这种交互作用。文中作者报告了多药纳米粒在缓解失控的炎症方面的进展。纳米粒是通过将内源性脂质角鲨烯与内源性免疫调节剂腺苷偶联，包裹天然抗氧化剂 α-生育酚。这样就得到了高载药量的具有生物相容性的多药纳米颗粒。利用急性炎症部位的血管内皮屏障的功能障碍，这些多药纳米粒能够以靶向的方式递送治疗药物，并在内毒素血症致死模型中为治疗动物提供显著的生存优势。选择性地将腺苷和抗氧化剂结合在一起可以作为一种新的治疗急性炎症的方法，减少副作用，并具有很高的治疗潜力。
Abstract:
Uncontrolled inflammatory processes are at the root of numerous pathologies. Most recently, studies on confirmed COVID-19 cases have suggested that mortality might be due to virally induced hyperinflammation. Growing evidence has indicated that uncontrolled pro-inflammatory states are often driven by continuous positive feedback loops between pro-inflammatory signaling and oxidative stress. There are currently no effective ways to counter this crosstalk in a targeted manner. Here we report on the development of multidrug nanoparticles for the mitigation of uncontrolled inflammation. The nanoparticles are made by conjugating squalene, an endogenous lipid, to adenosine, an endogenous immunomodulator, and then encapsulating α-tocopherol, a natural antioxidant. This resulted in high drug loading, biocompatible, multidrug nanoparticles. By exploiting the vascular endothelial barrier dysfunction at sites of acute inflammation, these multidrug nanoparticles could deliver the therapeutic agents in a targeted manner and conferred a significant survival advantage to treated animals in lethal models of endotoxemia. Selectively delivering adenosine and antioxidants together could serve as a novel approach for the treatment of acute inflammation with reduced-side effects and high therapeutic potential.

10. 处于复制状态的 SARS-CoV-2 聚合酶结构

Structure of replicating SARS-CoV-2 polymerase

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中文摘要：

冠状病毒 SARS-CoV-2 利用依赖 RNA 的 RNA 聚合酶(RdRp)进行基因组的复制和基因的转录。本文中，作者使用冷冻电子显微镜解析了处于复制状态的 SARS-CoV-2 RdRp 结构。该结构包含病毒的 nsp12 蛋白，nsp8 和 nsp7 蛋白，以及超过两轮螺旋的 RNA 模板-产物双螺旋结构。nsp12 蛋白的活性位点裂隙与 RNA 第一轮螺旋结构结合，并通过保守残基介导 RdRp 的活性。两个 nsp8 蛋白结合在 nsp12 活性位点裂隙的对侧，并在 RNA 双螺旋退出时为其定位。nsp8 蛋白中的长螺旋结构沿着 RNA 退出的方向延伸，形成带正电荷的“滑动杆”，可以促进冠状病毒的长基因组进行复制。处于复制状态的 SARS-CoV-2 聚合酶结构的解析，有助于我们对抗病毒药物的抑制机理进行详细的分析。例如目前正处于治疗 COVID-19 临床试验阶段的 remdesivir。

译者注：文中未提供结构文件的 RCSB PDB 或 EMDB 的 ID。

Abstract:

The coronavirus SARS-CoV-2 uses an RNA-dependent RNA polymerase (RdRp) for the replication of its genome and the transcription of its genes. Here we present the cryo-electron microscopic structure of the SARS-CoV-2 RdRp in its replicating form. The structure comprises the viral proteins nsp12, nsp8, and nsp7, and over two turns of RNA template-product duplex. The active site cleft of nsp12 binds the first turn of RNA and mediates RdRp activity with conserved residues. Two copies of nsp8 bind to opposite sides of the cleft and position the RNA duplex as it exits. Long helical extensions in nsp8 protrude along exiting RNA, forming positively charged 'sliding poles' that may enable processive replication of the long coronavirus genome. Our results will allow for a detailed analysis of the inhibitory mechanisms used by antivirals such as remdesivir, which is currently in clinical trials for the treatment of coronavirus disease 2019 (COVID-19).

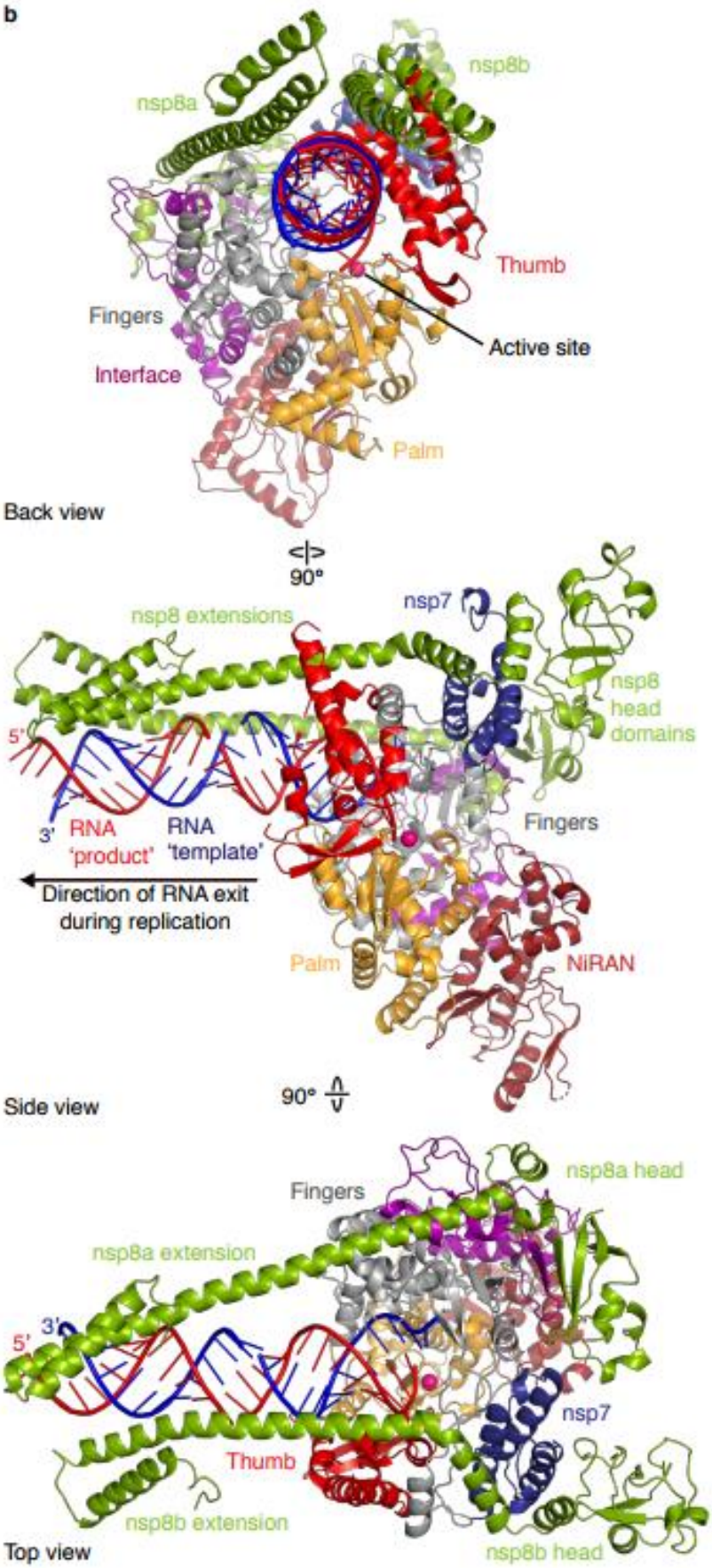

Figure 2 | Structure of SARS-CoV-2 RdRp-RNA complex.

11. Remdesivir 替代物 1’-核糖氰基在 SARS-CoV-2 病毒 RNA 复制中有效抑制核苷酸增加和校正

Role of 1’-Ribose Cyano Substitution for Remdesivir to Effectively Inhibit both Nucleotide Addition and Proofreading in SARS-CoV-2 Viral RNA Replication

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DOI: https://doi.org/10.1101/2020.04.27.063859
编译者：张怡
摘要
COVID-19 最近引起了一场全球健康危机，迫切需要一种有效的介入治疗。SARS-CoV-2 RNA 依赖的 RNA 聚合酶(RdRp)由于其固有的校正核糖核酸外切酶(ExoN)功能，是一个有前景但具有挑战性的药物靶点。核苷三磷酸(NTP)类似物加入到扩增的 RNA 链中，可以终止病毒 RNA 复制，但是 ExoN 可以裂解连接的物质，并阻止它们发挥作用。Remdesivir（瑞德西韦）靶向 SARS-CoV-2 RdRp 具有较高的体内外药效。然而，其潜在的抑制机制仍不明确。文中作者进行了全原子分子动力学(MD)模拟，累计模拟时间为 12.6 微秒，以阐明 remdesivir 在核苷酸增加(RdRp 复合物:nsp12-nsp7-nsp8)和校正((ExoN 复合物:nsp14-nsp10)中抑制作用的分子机制。他们发现 remdesivir 的 1’-cyano 基团具有抑制核苷酸添加和校正的双重作用。对于核苷酸的添加，他们发现加入一个 remdesivir 不足以终止 RNA 的合成。反而在上游位置的 remdesivir 的极性 1’-cyano 基团通过静电与 Asp865 和 Lys593 形成的盐桥的相互作用导致了不稳定，使易位变得不利。这可能最终导致 RNA 延长三个核苷酸的延迟链终止。为了校正，remdesivir 可以通过 1’-cyano 基团和 Asn104 之间的空间冲突抑制裂解。为了进一步研究 1’-cyano 基团在 remdesivir 抑制作用中的作用机制，他们还研究了另外三种 NTP 类似物与其他类型的修饰：法维匹拉韦（favipiravir）、阿糖腺苷（vidarabine）和氟达拉滨（fludarabine）。作者的模拟结果表明这三种物质都有 ExoN 裂解的倾向。他们的计算结果进一步得到了体外实验的支持，在 Vero E6 细胞中使用了有活性的 SARS-CoV-2。剂量-反应曲线表明，在测试的 NTP 类似物中，只有 remdesivir 对病毒复制有明显的抑制作用。作者的工作在分子水平上说明了 remdesivir 如何抑制病毒 RNA 复制的可能机制，他们的发现可能指导针对 COVID-19 病毒复制的新治疗方法的合理设计。

Figures:

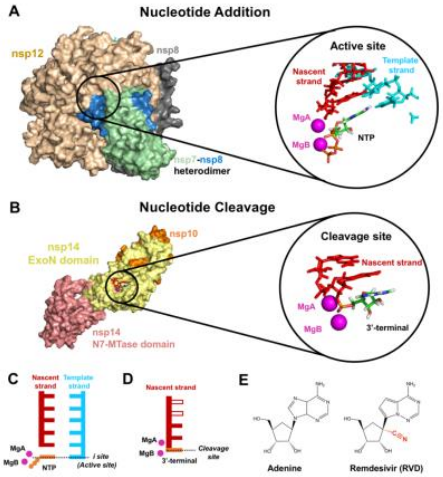

Fig. 1 Structural model of SARS-CoV-2 RdRp and ExoN for investigating the inhibitory mechanism of remdesivir (RDV). (A) Model of nsp12-nsp7-nsp8 complex for nucleotide addition. The active site is circled and amplified on the right panel. The nascent and template strands are colored in red and cyan, respectively. NTP (in orange) is bound at the active site and two Mg^{2+} ions are shown in magenta spheres. (B) Model of nsp14-nsp10 complex, including ExoN domain for nucleotide cleavage. The cleavage site is circled and amplified on the right. Three nucleotides are modelled, including the 3'-terminal site used for modelling RDV or other NTP analogues. Magenta spheres represent two Mg^{2+} ions for cleavage. (C) Cartoon model of the active site in RdRp. (D) Cartoon model of the cleavage site in ExoN. The three terminal nucleotides used in our model are represented by color-filled rectangles. The ones not included in our model are represented by empty rectangles. (E) Chemical structures of adenine and RDV. The 1'-cyano group of RDV is highlighted in red.

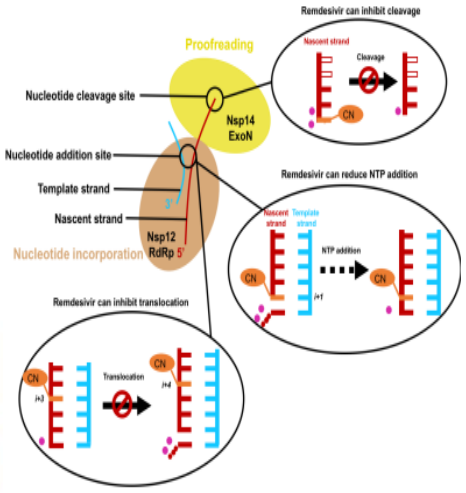

Fig. 7 Cartoon model of remdesivir's inhibition mechanisms in SARS-CoV-2 viral RNA replication.

Abstract

COVID-19 has recently caused a global health crisis and an effective interventional therapy is urgently needed. SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) provides a promising but challenging drug target due to its intrinsic proofreading exoribonuclease (ExoN) function. Nucleoside triphosphate (NTP) analogues added to the growing RNA chain should supposedly terminate viral RNA replication, but ExoN can cleave the incorporated compounds and counteract their efficacy. Remdesivir targeting SARS-CoV-2 RdRp exerts high drug efficacy in vitro and in vivo. However, its underlying inhibitory mechanisms remain elusive. Here, we performed all-atom molecular dynamics (MD) simulations with an accumulated simulation time of 12.6 microseconds to elucidate the molecular mechanisms underlying the inhibitory effects of remdesivir in nucleotide addition (RdRp complex: nsp12-nsp7-nsp8) and proofreading (ExoN complex: nsp14-nsp10). We found that the 1'-cyano group of remdesivir possesses the dual role of inhibiting both nucleotide addition and proofreading. For nucleotide addition, we showed that incorporation of one remdesivir is not sufficient to terminate RNA synthesis. Instead, the presence of the polar 1'-cyano group of remdesivir at an upstream site causes instability via its electrostatic interactions with a salt bridge formed by Asp865 and Lys593, rendering translocation unfavourable. This may eventually lead to a delayed chain termination of RNA extension by three nucleotides. For proofreading, remdesivir can inhibit cleavage via the steric clash between the 1'-cyano group and Asn104. To further examine the role of 1'-cyano group in remdesivir's inhibitory effects, we studied three additional NTP analogues with other types of modifications: favipiravir, vidarabine, and fludarabine. Our

simulations suggest that all three of them are prone to ExoN cleavage. Our computational findings were further supported by an in vitro assay in Vero E6 cells using live SARS-CoV-2. The dose-response curves suggest that among tested NTP analogues, only remdesivir exerts significant inhibitory effects on viral replication. Our work provides plausible mechanisms at molecular level on how remdesivir inhibits viral RNA replication, and our findings may guide rational design for new treatments of COVID-19 targeting viral replication.