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EDITORIAL COMMENTARY

A First Draft of the History of Treating Coronavirus Disease 2019: Use of Repurposed Medications in United States Hospitals

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Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (COVID-19), emerged in China in late 2019 and quickly caused a pandemic [1]. In March and April 2020, patients with COVID-19 overwhelmed hospitals in US hotspots. Lacking specific treatment options, clinicians often turned to existing medications that might inhibit SARS-CoV-2 replication or attenuate deleterious immune responses. Medications repurposed against COVID-19 early in the pandemic included agents with in vitro antiviral activity such as hydroxychloroquine, azithromycin and remdesivir, and immunomodulators such as corticosteroids and interleukin-6 inhibitors (tocilizumab, sarilumab). Clinicians faced competing pressures to "do something" for hospitalized COVID-19 patients, even if that entailed administering medications of unproven utility, and to "learn something" about which treatments were efficacious and safe through clinical trials [2]. As 2020 closes, Kadri et al [3] have analyzed the use of repurposed medications in March through May among patients with COVID-19 in US hospitals. Their paper and other recent studies provide a first draft of the history of treating COVID-19 during the chaotic initial months of the pandemic [4, 5].

Using the Premier Healthcare database, which covers ~20% of US hospitalizations, Kadri et al [3] found that ~60% and ~75% of adults with COVID-19 were treated with hydroxychloroquine and azithromycin in March 2020, respectively (Table 1). Over the next 2 months, the proportion of COVID-19 inpatients receiving the respective agents decreased by ~80% and ~50%. By May, only ~12% of inpatients were treated with hydroxychloroquine [3], and much residual in-hospital azithromycin use in COVID-19 patients was likely as an empiric antibacterial [6]. The COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) reported similar trends in hydroxychloroquine and azithromycin use at participating hospitals in 13 states, and that the proportion of hydroxychloroquine-treated inpatients fell further in June [4]. Other investigators using the IQVIA National Prescription Audit database determined that outpatient hydroxychloroquine prescriptions also decreased by ~80% between March and June [5]. In contrast, estimated percentages of hospitalized COVID-19 patients treated with remdesivir in COVID-NET increased from ~2% and ~4% in March and April, respectively, to ~30% in May and ~34% in June. By Kadri et al's [3] assessment, corticosteroids were administered to 21.5% of inpatients with COVID-19 from March through May, during which time the proportion of inpatients receiving these agents increased by >80%; almost two thirds of mechanically ventilated patients received corticosteroids over this period. Tocilizumab use was documented in only ~5%–6% of SARS-CoV-2-infected inpatients over the 3 months [3]. In June, the percentage of hospitalized patients treated with tocilizumab dropped [4]. Corticosteroids and tocilizumab were administered for a median of 2 hospital days earlier in May versus March [3].

Databases and methodologies used in the studies above had relative strengths, weaknesses, and potential biases that were acknowledged by the authors. Percentages of adult inpatients treated with various agents were higher each month in Kadri et al's [3] analysis, which identified cases by diagnosis codes, than in COVID-NET, which relied upon medical chart reviews of patients with laboratory-confirmed SARS-CoV-2 infections. Both databases are convenience samples from subsets of hospitals, and COVID-19 cases may not be

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fully representative of the US experience. Premier does not provide information on indication for drug use. Completeness of COVID-NET data abstraction varied by site and month, although findings were similar upon sensitivity analyses of the most comprehensive datasets. Despite shortcomings and inconsistencies between studies, the findings convey a coherent narrative of evolving real-world treatment of COVID-19 in US hospitals, and they confirm and challenge popular perceptions about use of repurposed medications (Table 1).

As generally recognized at the time [13, 14], hydroxychloroquine and azithromycin were prescribed liberally by US clinicians in the first months of the pandemic. These practices were likely fueled by poor outcomes among critically ill COVID-19 patients, lack of validated therapeutic options, clinician desperation, pressure from patients and families, poor science and low-quality data, press releases and nonpeer-reviewed preprints of laboratory research and clinical studies, uninformed opinions of public figures, a controversial Emergency Use Authorization of hydroxychloroquine, group thinking, and "what do you have to lose?" mindsets [3, 13, 15]. In retrospect, it may be surprising to realize how quickly and dramatically most clinicians abandoned hydroxychloroquine and azithromycin, as reports emerged of unfavorable data for the drugs and favorable findings for other agents. Uptake of remdesivir increased immediately after a April 29, 2020 press release and White House announcement touting shortened hospital stays of patients with hypoxia not requiring mechanical ventilation in the

Table 1. Use of Medications Repurposed for COVID-19 in United States Hospitals, March–June 2020[a]

Agent	Percentage of Hospitalized Patients Treated With Each Agent, March–May 2020				Potential Explanations for Patterns of Use and Accompanying Comments[b]
	Overall	By Month		Change (May vs March)	
		March	May		
HCQ	46%	60%[c] MV: 80% No MV: 57%	12%[c] MV: 17% No MV: 11%	−80%[c] MV: −79% No MV: −81%	HCQ repurposed in past for use vs other viral infections. February–March: in vitro data vs SARS-CoV-2; nonrandomized COVID-19 studies reported improved clinical status and viral loads; no validated alternative treatment options. March 28, 2020: FDA issued EUA. May: Reports of HCQ clinical ineffectiveness and no impact on viral load. Prominent reports of excess mortality and toxicity with HCQ published May 22, 2020 were retracted June 5, 2020 [7, 8]. June 15, 2020: EUA revoked. Further 65% reduction in use from May to June [4].
Azithromycin	51.5%	75%[c] MV: 83% No MV: 72%	40%[c] MV: 41% No MV: 39%	−47%[c] MV: −51% No MV: −46%	Azithro postulated to decrease viral entry into cells and enhance antiviral immune responses [9]. March: Azithro reported to decrease viral load in combination with HCQ; no alternative validated treatment options. May: Reports of no improvements in mortality or intubation rates with azithro. June: Azithro use still reduced compared to March–April, but not significantly changed compared to May [4]. Residual use was likely to be largely as empiric treatment of bacterial respiratory tract infections [6].
Remdesivir	N/A	2%[d]	30%[d]	+1150%[d]	Remdesivir, an RNA-dependent, RNA polymerase inhibitor with in vitro activity against SARS-CoV-1 and Middle East respiratory syndrome coronavirus, shown to also inhibit SARS-CoV-2 in vitro [10]. April 29, 2020: Press release and White House announcement of ACTT-1 data showing possible shortening of hospitalizations with remdesivir. Dr. Fauci called remdesivir "standard of care" [11]. June: Use increased by 13% compared to May [4].
Corticosteroids	21.5%	16%[c] MV: 50% No MV: 12%	29%[c] MV: 69% No MV: 26%	+82%[c] MV: +37% No MV: +116%	March: Guidelines did not endorse routine corticosteroid treatment. April: IDSA guidelines conditionally suggested corticosteroids for severe COVID-19. June 16, 2020: RECOVERY trial press release reported mortality benefit of dexamethasone in patients requiring respiratory support [12].
Tocilizumab	6%	5%[c] MV: 19% No MV: 1%	6%[c] MV: 21% No MV: 3%	N/S MV: N/S No MV: N/S	March: Patient improvement and increased survival with tocilizumab reported in small, single-arm trial. Phase II/III studies initiated. June: Use of tocilizumab and other IL-6 inhibitors significantly reduced compared to March–May [4].

Abbreviations: ACTT, Adaptive COVID-19 Treatment Trial; Azithro, azithromycin; COVID-19, novel coronavirus disease 2019; FDA, US Food and Drug Administration; EUA, Emergency Use Authorization; HCQ, hydroxychloroquine; IDSA, Infectious Diseases Society of America; IL, interleukin; MV, mechanical ventilation; N/A, not available; N/S, not significant; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Data are taken from [3, 4].

[b]Events and dates are referenced in [3] unless otherwise noted.

[c]Estimated using data from [3].

[d]Estimated using data from [4].

ACTT-1 trial [10]. Although remdesivir was not beneficial in other studies, the agent became standard of care at many hospitals [11].

On June 16, 2020, a press release announced that dexamethasone reduced mortality among patients with COVID-19 requiring respiratory support in the RECOVERY trial [3, 12]. Even before this news, it is striking in Kadri et al's [3] study how widely corticosteroids were administered to mechanically ventilated patients. As such, higher survival among hospitalized COVID-19 patients in summer–fall 2020 likely reflected a combination of factors such as improved critical care management, reduced stress on healthcare systems and workers, and changing patient demographics, rather than being predominantly attributable to greater corticosteroid use [16, 17]. Use of tocilizumab, a more expensive drug than dexamethasone, was low in March–May, and decreased thereafter as RECOVERY results appeared in absence of evidence for benefit of interleukin-6 inhibitors. Taken together, the data paint a mixed picture. Of concern, widespread in-hospital use of hydroxychloroquine, azithromycin, and corticosteroids occurred early in the pandemic despite a lack of rigorous clinical data. However, clinicians adapted practices quickly as data were reported, unlike the often languid pace at which antibiotic prescribing responds to new clinical information [18–20].

What were the consequences of these behaviors? On balance, treated patients were likely neither helped nor harmed by hydroxychloroquine and azithromycin. Widespread corticosteroid use in mechanically ventilated patients may have fortuitously saved some lives early in the pandemic, particularly because clinicians moved to more timely treatment [3]. At the same time, misdirected corticosteroid administration may have had untoward effects. On a societal level, use of unproven medications or refusals to consider hydroxychloroquine due to unvalidated claims of excess toxicity delayed enrollment of clinical trials that might definitively identify beneficial or harmful regimens [14, 15]. Furthermore, demand for hydroxychloroquine may have reduced access for patients taking the drug for rheumatologic diseases [21], and excess azithromycin prescribing ran the risk of promoting bacterial resistance [22, 23]. The net impact of events on COVID-19 clinical outcomes, public health, and global economies requires further study. Ultimately, impact may be mitigated by the likelihood that no COVID-19 treatment is a magic bullet. In the end, we may have gotten lucky that extensive use of repurposed medications did not cause more harm.

Despite challenges posed by prescribing of repurposed medications, scale of the pandemic, and the uncoordinated, inefficient manner in which many studies were launched, COVID-19 treatment, prophylaxis, and vaccine trials were completed with unprecedented speed [24]. Indeed, the success of innovative multicenter studies, including several randomized trials with adaptive platform designs, may prove to be among the most positive scientific legacies of the pandemic [12, 25, 26]. Clinical trials that exploit international collaboration, social media, cloud computing, and electronic health records, simultaneously randomize to several treatment options, quickly discontinue poorly performing therapies, and leverage common enrollment and data management systems can spare clinicians untenable choices between "doing" or "learning," offering instead opportunities to "learn while doing" [2]. Building upon lessons of COVID-19, priority should be given to proactively supporting global networks that can expeditiously design, co-ordinate, and conduct clinical trials during future pandemics.

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