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Coronavirus Disease 2019 (COVID-19) Waves, Treatment Enclaves and Changes in Management

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ABSTRACT

Background: *The coronavirus disease (COVID-19) global pandemic commenced at the end of 2019 and continues into 2022. Throughout the world, countries have seen spikes of an increased number of cases followed by a period of decrease, a phenomenon now referred to as "waves." Recommendations for management of this infection have changed, guided by new experiences, an ever-increasing plethora of medical publications, and rapid developments in vaccines and therapeutics. Some treatments are recommended only in the outpatient setting, while others are indicated for patients admitted to the hospital, creating mutually exclusive "enclaves" for patients to receive recommended therapies. The purpose of this study was to compare and contrast medication use, as well as outcomes between the first two waves of COVID-19 infection.*

Methods: *This is a retrospective cohort study of patients with COVID-19 infection at a community hospital in Massachusetts, USA. Consecutive adult patients admitted to the hospital with consultation by the authors were included. The first wave extended from March 2020 to June 2020, the second wave was from October 2020 to January 2021. Patient demographics, medications used, and outcomes were abstracted from the electronic medical records.*

Results: *Of the 238 patients evaluated, 109 (45.7%) were admitted in the first wave and 129 (54.2%) were admitted in the second wave. A large number of patients received hydroxychloroquine (50%), azithromycin (17%) and tocilizumab (22%) in the first wave, but none of these medications were used during the second wave. Remdesivir was used in 15% patients in the first wave. No patient in the first wave received corticosteroid therapy. In contrast, the majority of patients in the second wave received corticosteroids (70%) and remdesivir (63%). There were marked differences in overall mortality (25% v/s 6%), admission to intensive care unit (48% v/s 8%), and use of mechanical ventilation (31% v/s 5%) between the first and second waves respectively. Monoclonal antibody therapy was not available for use in hospitalized patients.*

Conclusions: *There were remarkable differences in medications used, need for intensive care admission and need for mechanical ventilation for patients with COVID-19 infection between the first two waves of this pandemic. There was an improvement in outcomes in terms of overall mortality, need of intensive care unit admission, and need for mechanical ventilation during the second wave compared to the first. Further research is needed to determine whether the improved outcomes are a reflection exclusively of better therapeutics or a combination of therapeutics and other early interventions and the role of the COVID-19 variant (beta) in second wave compared to the original wild-type virus in both waves.*

Keywords
COVID-19 infection, Waves, Hydroxychloroquine, Tocilizumab, Corticosteroids, Remdesivir.

Introduction

In the middle of December 2019 there were reports of a cluster of patients with respiratory symptoms and fever in Wuhan, China. These patients were diagnosed as "novel" coronavirus - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) -related-pneumonia and since then this virus has caused the pandemic, we now call COVID-19 [1]. This pandemic is now responsible for more than 6.5 million deaths around the globe [2]. "Waves" of infection – where over a few months there is an acute increase in the number of new cases in the community including cases with severe illness requiring hospitalization, followed by a longer period of much lower numbers - is now the experience all over the world. Many explanations for this phenomenon have been proposed. These include host factors: personal protective measures, social gatherings, travel, immunity, therapeutics and vaccination, virus factors: beta, delta and omicron variants, environmental factors: changes in weather etc. Attempts to control this worldwide infection has involved personal and social measures like lock-downs, masking, hand hygiene, social distancing, vaccination, and a large number of therapeutics. However, a definitive cure has been elusive. In the early months of the pandemic, (early 2020) medications like hydroxychloroquine, azithromycin [3], the monoclonal antibody against IL-6 receptor – tocilizumab [4], and convalescent plasma were being used in clinical trials as well as part of various hospital protocols for patients with severe COVID-19 infection. In this early part of the pandemic, the CDC as well as the WHO recommended against use of corticosteroids in the management of patients with COVID-19 infection [5,6]. As the pandemic progressed, new clinical information and research data became available. Treatment strategies moved away from hydroxychloroquine, azithromycin and tocilizumab. Around the same time, the antiviral agent remdesivir [7] as well as corticosteroids [8] were promoted as standard of care for patients with severe COVID-19 infection. All these medications were administered exclusively in the hospital setting. At the same time, extremely limited supplies of monoclonal antibodies (mAb) were being used exclusively in the outpatient setting, thus creating mutually exclusive "enclaves" of therapeutic interventions for patients with COVID-19 infection. Our community hospital in Massachusetts, USA also experienced multiple waves of COVID-19 infections. The first wave was in early 2020 at the beginning of the pandemic, a second wave that started towards the end of 2020 and went into January 2021, a large 3rd wave in November 2021 and a much smaller 4th wave in April 2022.

This report provides information regarding the first two waves of the COVID-19 pandemic seen at our hospital. We document the timelines for the different interventions, and compare and contrast the medications used and outcomes during these two waves.

Methods

Study

The community hospital where the authors practice is located in Worcester, Central Massachusetts which experienced two waves of COVID-19 infections (Figure 1) consistent with what was observed all around the USA at that time. A cohort of 109 consecutive patients admitted to the hospital with COVID-19 infection was evaluated during the first wave – from the beginning of the pandemic to June 2020. A second wave of COVID-19 infections was seen from October 2020 to January 2021 and a cohort of 121 consecutive patients was evaluated for the purpose of this study. COVID-19 infection was diagnosed using reverse transcriptase polymerase chain reaction (PCR). The hospital enclave had access to hydroxychloroquine, azithromycin, tocilizumab, remdesivir and corticosteroids. Monoclonal antibody (mAb) therapy was available in outpatient enclaves and was not available for hospitalized patients. The first wave of COVID-19 infections occurred before the use of corticosteroids as part of standard-of-care. Also, remdesivir became available only at the very end of the first wave. Age, sex, medications used, the number of patients needing care in the intensive care unit (ICU), need for mechanical ventilation (MV) and mortality were extracted from the electronic medical records.

Results

First wave: A total of 109 consecutive patients were evaluated (Table 1). In this cohort, the mean age was 68 years, 44% were female. Fifty-five patients received hydroxychloroquine, 24 patients received tocilizumab and 16 patients received remdesivir therapy. None of the patients in this group received corticosteroids or mAb therapy, though 20 patients received convalescent plasma therapy. The overall mortality was around 25%. Thirty- one percent of patients required MV and mortality in this group was 56%.

Table 1: Demographics of patients in the first wave of COVID-19 infection.

N (%)
Female / Male 48 / 61
Age mean 68
ICU admission 52 (48)
Ventilated 34 (31)
Overall death 27 (25)
Death in ventilated patients 19 (56)
Hydroxychloroquine 55 (50)
Azithromycin 19 (17)
Tocilizumab 24 (22)
Convalescent plasma 20 (20)
Remdesivir 16 (15)
Corticosteroids 0 (0)

Second wave: A total of 129 consecutive patients were evaluated (Table 2). The mean age in this group was 70 years, 49% were female. Ninety patients received corticosteroids (dexamethasone) therapy; 81 patients received remdesivir. None of the patients received tocilizumab, hydroxychloroquine or azithromycin as part of therapy for COVID-19. One patient received hydroxychloroquine as ongoing treatment for arthritis, one patient

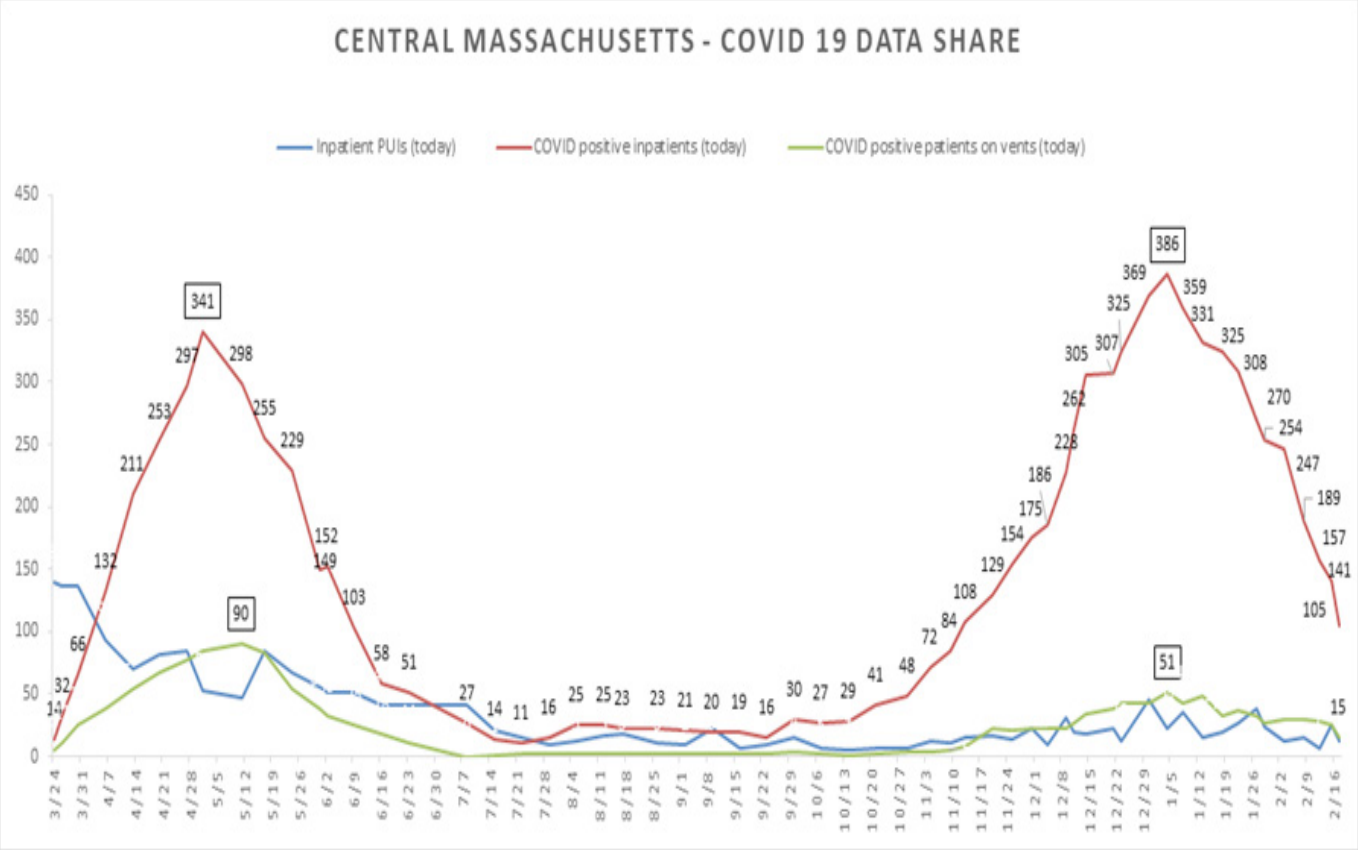

Figure 1: The first two waves of COVID-19 infection in Massachusetts, USA.

received azithromycin for ongoing COPD prophylaxis. None of the patients in this group received mAb therapy, or convalescent plasma therapy. Overall mortality in this cohort was 6%. Fewer patients (only 6) required MV, but mortality in this group was very high (83%).

Table 2: Demographics of patients in the second wave of COVID-19 infection.

N (%)
Female / Male 63 / 66
Age mean 70.5
ICU admission 10 (8)
Ventilated 6 (5)
Overall death 7 (6)
Death in ventilated patients 5 (4)
Hydroxychloroquine 1
Azithromycin 1
Tocilizumab 0
Convalescent plasma 0
Remdesivir 81 (63)
Corticosteroids 90 (70)

Discussion

The devastating effect of a new pandemic was evident in the first wave with severe disease, high mortality and use of multiple different medications. In the earliest period of the pandemic, physicians all over the world were reaching out to interventions that showed early promise based on small studies, only to see subsequent publications indicating either no benefit at best or a potential for severe risk. As the pandemic progressed and scientific information increased exponentially, the patients admitted in the second wave received significantly more evidence-based interventions.

Our study highlights differences in the treatment as well as outcomes between waves 1 and 2 of the pandemic. There were more patients hospitalized with COVID-19 Infection in the second wave compared to the first (129 v/s 109) even though both waves extended over a similar period of roughly 4 months each. The mean patient age was similar during both waves. There were marked differences in the medications used, as well as outcomes when we compared the two waves of COVID-19 infection.

Medications

Our data reflects the use of various medications during different parts of the pandemic based on fast-moving information and availability of new agents.

Very early in the pandemic, Philippe Gautret and colleagues [3] in Marseille, France conducted a small clinical trial (42 patients). They demonstrated the benefit of a combination of hydroxychloroquine and azithromycin in reducing nasopharyngeal carriage of virus in patients infected with COVID-19. By day 6 of the study, all patients treated with this combination had undetected virus by PCR testing. Subsequent larger studies also showed mortality benefit of this combination in hospitalized

patients [9] as well as in the outpatient setting [10]. The role of "cytokine storm" in the pathogenesis of severe pulmonary injury was also quickly appreciated and on March 26, 2020 the US-FDA approved a large multicenter study of tocilizumab [11]. Consistent with the optimism following these early reports, 50% of patients in our hospital received hydroxychloroquine and 17% of patients received azithromycin. Tocilizumab became available in early April 2020 for use in patients with severe COVID-19 infection in the ICU and 22% of patients received this agent in the first wave of COVID-19 infection.

However, subsequent publications questioned the therapeutic benefits and reported increased risk of cardiac side effects of the hydroxychloroquine and azithromycin combination [12], and the use of these medications were discontinued in our hospital by the middle of the first wave. Similarly, the enthusiasm for tocilizumab waned after the release of Phase III COVACTA trial data around the end of July 2020 [13].

These changes in strategies were reflected in our study and none of the patients in the second wave received these medications for treatment of COVID-19 infection.

Meanwhile, a more specific intervention: the antiviral agent – remdesivir – showed great promise in early studies [14,15] and became available for use at our hospital in May 2020 at the flag end of the first wave and 15% patients receive this antiviral agent. The use of remdesivir continued into the second wave of the pandemic and 63% of patients received remdesivir during the second wave of COVID-19 infection.

Subsequently, the "RECOVERY collaborative group" reported results of their study that demonstrated lower 28-day mortality among COVID-19 patients who received dexamethasone therapy [16]. Their preliminary report provided the much-needed hope for patients with severe COVID-19 infection and recommendation for the use of dexamethasone 6 mg once a day for 5-10 days was incorporated in our hospital's COVID-19 management protocol from October 2020 just in time for the second wave of COVID-19 infection. Consequently, 70% of patients received corticosteroids during the second wave of COVID-19 infection.

On November 9th 2020, the FDA issued an Emergency Use Authorization (EUA) for mAb in patients with mild or moderate COVID-19 infection [17]. However, mAb became available to our community only around July 2021 much after the end of the second wave.

Outcomes

In the first wave, the overall mortality was 25%, 48% of patients required ICU admission and 31% of patients required MV. Mortality in patients requiring MV was 56%. In comparison, during the second wave, the overall mortality was 6%, only 8% of patients required ICU admission and only 5% patients required MV. However, during this second wave, the mortality in patients requiring MV was 80% (4 out of 5 patients on MV died).

A number of factors may be responsible for the remarkable differences in the outcomes of patients admitted to the hospital during the two waves of COVID-19 infection. The high mortality and morbidity seen during the first wave could be attributed to a new disease and hence a complete lack of specific cellular and antibody mediated immunity in the individual and in the community, as well as a lack of science to guide optimized therapy. The interventions with hydroxychloroquine, azithromycin, tocilizumab and convalescent plasma tried during the first wave, which were subsequently shown to have no benefit, were not used during the second wave of the pandemic. Instead, the majority of the patients received dexamethasone and remdesivir therapy during the second wave and there were better outcomes. Based on the small number of patients in each of our two cohorts, we were unable to determine the exact role of dexamethasone and / or remdesivir therapy in the dramatic reduction in overall mortality when comparing outcomes between the first two waves of COVID19 infection at our hospital. The differences in mortality, ICU admissions and need for MV may be attributable to the differences in medications used, but could also be a reflection of development of some level of immunity, increased awareness and very early hospitalization and intervention following the diagnosis, or infection with a less pathogenic variant of the virus during the second wave. In the second wave, our study found that in-spite of higher utilization of corticosteroids and remdesivir, there was a very high mortality in those patients admitted to the ICU and requiring MV. Better interventions prior to need for ICU level care, and admission to ICU implying extremely advanced or very severe disease could explain the higher mortality in these patients in the second wave compared to the first.

Our findings however, are in contrast to other published studies that found no difference in inpatient mortality during the first two waves of the COVID-19 infection [18] or mortality specifically in ICU patients when comparing the first two waves of the COVID-19 infection [19,20].

Mutually exclusive treatment enclaves

Monoclonal antibodies (mAb) received emergency use authorization in the United States in November 2020 during the second wave of COVID-19 infection. However, these were not readily available in all communities including Worcester Massachusetts until later the following year. When mAb did become available, they were administered exclusively in the outpatient setting, to patients with mild to moderate COVID-19 infection who had underlying risk factors for progression to severe illness. There was no ability to administer mAb to sicker patients admitted to the hospital or to less sick patients with COVID-19 infection who were admitted to the hospital for non-COVID-19-related problems. Conversely, remdesivir therapy was only available to patients admitted to the hospital and could not be administered to patients not sick enough to be admitted.

Limitations

Our study has the inherent limitations of a retrospective cohort study. In addition, detailed demographic characteristics like race,

social and economic status, and body weight were not extracted. Comorbid conditions like diabetes, hypertension, chronic renal disease, underlying lung disease were also not evaluated in this study. In addition, inflammatory markers C-reactive protein, ferritin, D-dimer, IL-6 data and data on supplemental oxygen use were not consistently available, thus limiting our ability to objectively compare disease severity during the two waves of infection. We also lacked the facilities to test for COVID-19 variants – hence we do not know if the morbidity and mortality differences could be a reflection of the beta variant of the virus.

The primary purpose of this descriptive study was to compare and contrast medications used as well as outcomes between the first two waves of COVID-19 infection at a community hospital in Massachusetts, USA. Our study illustrates the sequential changes in the approach to management of COVID-19 infection during the first two waves of this pandemic, and the marked differences in outcomes. The exact reasons for these differences should be investigated further utilizing data from larger multi-center studies.

Conclusions

There were remarkable differences in medications used, and outcomes in patients hospitalized with COVID-19 infection during the first two waves of this pandemic. There was an improvement in outcomes in terms of overall mortality, need of intensive care unit admission, and need for mechanical ventilation during the second wave compared to the first. Further research is needed to determine whether the improved outcomes are a reflection exclusively of better therapeutics or a combination of therapeutics and other early interventions prior to deterioration, and the role of the COVID-19 variant (beta) in second wave compared to the original wild-type virus in both waves. The authors also suggest that rather than "treatment enclaves," that are presently the norm, an "all-in" approach should be used, where all proven therapeutics like mAb, antiviral agent remdesivir and corticosteroids should be freely accessible and utilized to reduce COVID-19 associated mortality and morbidity during future waves.

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