Treatment options used for management of COVID-19 in Pakistan: Timeline, reality, and challenges

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Abstract

Background: Ever since the first reports of COVID-19 infections across the world, the foremost requirement is to find a treatment regimen that not only fights off or kills the causative agent i.e., the SARS-COV-2 but also controls and treat the associated symptoms and complications of the infection. Due to time consuming process of drug discovery vaccine development, doctors used readily available drugs and therapies to control and treat the infections to minimize the death toll.

Objective: To provide a snap-shot analysis of the major drugs used in a cohort of 1562 Pakistani patients during the May-July period when the first wave peaked in the country.

Methods: A retrospective observational study providing an overview of basic treatments and major drugs used for in-hospital management of 1562 COVID-19 patients admitted to the four major tertiary-care hospitals in the Rawalpindi-Islamabad region of Pakistan was conducted in the period May 2020-July 2020.

Results: Out of all the therapies employed antibiotics were the most common choice and used as the first line of treatment for COVID-19. Azithromycin was the most prescribed drug for the treatment. No trend was seen in the choice of antibiotics monthly and it seemed like a random but favorite choice throughout these months. It was also noted that 2nd and 3rd generation and even antibiotics used for Multidrug-resistant infections (MDR) were prescribed irrespective of the severity or progression of infections. This is alarming as it might lead to antibiotic resistance and liver damage in these patients whose immune system is already compromised because of the COVID-19 infection. A total of 1562 patients (68.1% males and 31.9% females) with a mean (SD) age of 47.35 (17.03) years were included in the study. The highest frequency of patient hospitalizations was in June (52.4%). Of the 19 drugs reportedly used for the treatment of COVID-19 and management of COVID-19-related symptoms, the five most frequently used drugs were antibiotics (Azithromycin (88.6%) and Ceftriaxone (23.6%)), anticoagulants (Heparin (21.6%) and Enoxaparin sodium (19.8%)) and corticosteroids (Hydrocortisone (25.7%).

Conclusions: A targeted treatment regime or an efficient long-lasting vaccine is needed urgently to limit the misuse of antibiotics in the management of Coronavirus. As for the control of symptoms and related complications of the infection clear guidelines are needed for the type and dosage of antibiotics that should be used instead of the hit and trial method that is applied so far.

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Abstract

Background: Ever since the first reports of COVID-19 infections , the foremost requirement is to find a treatment regimen that not only fights the causative agent but also contr ols the associated complications of the infection. Due to time consuming process of drug discovery , doctors used readily available drugs and therapies for treatment of infections to minimize the death toll.
Objectives: To provide a snap-shot analysis of the major drugs used in a cohort of 1562 Pakistani patients during the May-July period when the first wave peaked in the country.
Methods: A retrospective observational study providing an overview of major drugs used in a cohot of 1562 COVID-19 patients admitted to the four major tertiary-care hospitals in the Rawalpindi-Islamabad region of Pakistan during the peak of first wave in Country (May-July 2020).
Results: Antibiotics were the most common choice out of all the therapies employed and were used as first line of treatment for COVID-19. Azithromycin was the most prescribed drug for the treatment. No trend was seen in choice of antibiotics monthly and it appeared like a random but favorite choice throughout these months. It was also noted that even antibiotics used for Multidrug resistant infections (MDR) were prescribed irrespective of the severity or progression of infections. Results of the analysis are aligned as it might lead to antibiotic resistance and complications in immunocompromised COVID-19 patients.. A total of 1562 patients (68.1% males and 31.9% females) with a mean (SD) age of 47.35 (17.03) years were included in the study. The highest frequency of patient hospitalizations was in June (52.4%).
Conclusions: Guidelines for a targeted treatment regime is needed to control related complications and to limit the misuse of antibiotics in the management of Coronavirus.

Keywords: Antibiotic resistance, COVID-19, , Pakistan, Multidrug resistant infections, first

Introduction

The world came to a standstill when a viral outbreak was reported in a city in China during December 2019 [1]. Shortly after the first reports, the virus spread like a wildfire globally and was declared a pandemic by the World Health Organization (WHO) in 2020 [2]. The official name for this pneumonia like disease is COVID-19 (Coronavirus disease 2019), and it is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) [3]. The pathological conditions of COVID-19 infections were classified into five categories starting from asymptomatic to critical according to clinical manifestations [4]. It has already been reported that approximately one fifth of the hospitalized COVID-19 patients get admitted at intensive care unit (ICU) due to difficulty in breathing or acute hypoxemic respiratory failures [5-8].

More than a year has passed, and the virus continues to spread globally, crippling the economy, damaging health, and taking lives each day with the current count reaching to a staggering 112.65 million confirmed infections and 2.49 million death tolls [9, 10]. With the rapid spread of COVID-19 across the world, prompt diagnostic tools, readily available re-purposable drugs, and effective containment measures to control the SARS-CoV-2 infection are of paramount importance. The pandemic has also exposed the inadequate research and health infrastructure globally especially in countries like Pakistan where basic healthcare necessities were scarce when the infections reached its peak in June 2020 [11, 12].

The second wave of COVID-19 infections being reported by various countries including Pakistan is proving to be even more challenging to handle because of the severity of COVID-19 related complications that vary with gender and age [13-15], underlying diseases and disorders and even delay in hospital admissions [16, 17]. Human behavior is also a major factor causing the resurge in infections [18]. The relationship between following precautions and cases of COVID-19 is clear: In areas where fewer people wear masks and more gather indoors to eat, drink, celebrate and socialize, observe religious practices, even if only with family, cases are on the rise [19-21].

With overburdened healthcare system and an increasing number of infections among the medical staff, the ultimate way out of this pandemic remains to be in the discovery of an effective vaccine. While pharmaceutical companies all over the world have introduced several vaccines to date [22, 23], effectively vaccinating a large enough number of people all over the world is a lengthy process [24, 25]. Moreover, with reports of new strains from different regions, the effectiveness of some of these vaccines against multiple mutant strains shows mixed results [26]. As a result, repurposing existing drugs to target SARS CoV-2 and treat COVID-19-associated symptoms still appears as a logical scientific approach for now to contain this pandemic. Identifying and appropriating an effective combination of drugs from the available repertoire is challenge itself. It is a hit and trial method that is dangerous but inevitable in current situation. Small-scale studies were done where a few drugs were reported to be effective, but later proved to bring no significant difference in clinical outcomes [27-29].

Currently, as observed in various reports globally as well as seen in Pakistan, supportive treatment, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) remain the primary choice for medical practitioners. Therapeutic options considered and used include antivirals, antiparasitic, anti-inflammatories, interferon therapy, convalescent plasma therapy, hyperimmunoglobulin, oligonucleotide-based therapies and rarely RNAi, and mesenchymal stem cell therapy [30-32].

In this study, we explored the usage of antibiotics and antivirals that were used for the treatment of patients admitted during the peak of the first wave of COVID-19 in Pakistan (May-July 2020). Directions during the first wave phase were not so clear, many necessities including drugs were out of stock in local markets due to lockdowns, high demand, limited stocks and closure of borders.

Methods

Study Design

Clinical data of 1,812 confirmed COVID-19 patients, admitted to four major tertiary care hospitals in Pakistan, i.e., Pakistan Air Force Hospital (PAFH), Islamabad, Pakistan Institute of Medical Sciences (PIMS) Hospital, Islamabad, Holy Family Hospital (HFH), Rawalpindi and Benazir Bhutto Shaheed Hospital (BBH), Rawalpindi, were retrospectively collected during the period February 2020 - August 2020.

Patient Selection, Timeline and data Collection

Confirmed COVID-19 cases were defined as patients with a positive polymerase chain reaction (PCR) test for COVID-19 from nasal and oropharyngeal swab sample taken at the time of admission to the hospital. Patients with incomplete data were excluded. Descriptive data of 1562 patients admitted during the months of May 2020 to July 2020 was abstracted and analyzed accordingly. The data included information about age, gender, dates of admission and discharge (or death), medical history, presenting signs and symptoms and initial categorization of COVID-19 (mild, moderate, severe and critical) and types of therapeutic agents (including but not limited to use of antibiotics, antimalarials, antivirals, antiparasitics, anticoagulants and corticosteroids) used for treatment and management of COVID-19 during hospital stay.

The statistical analysis was conducted using IBM SPSS version 24 and Stata 16.1. Categorical variables were described using frequencies and percentages [33, 34]. Chi-Square test and Fisher's Exact tests were used to compare percentages wherever appropriate. This retrospective cohort study was approved by the ethics review board of Rawalpindi Medical University (RMU). Data were collected with approval of the National Institute of Health (NIH), Pakistan.

Results

A total of 1562 patients 1064 (68.1%) males and 498 (31.9%) females) with mean (SD) age of 47.35 (17.03) years were included in the study. The basic demographic characteristics of the hospitalized COVID-19 patients and their distribution across hospitals are shown in Table 1. The Frequency of admissions during months of May to July 2020 period were 37.9%, 54.2% and 7.9% respectively.

Table 1 Baseline characteristics

Characteristics	Frequency (n)	Percentage (%)
Total Number of patients during May 2020 to July 2020	**1562**	
Age (years), mean (SD)	47.35 (17.03)	
Gender		
Male	1064	68.1
Females	498	31.9
Admission Frequency of patients across Hospitals		
Benazir Bhutto Shaheed Hospital, Rawalpindi (BBH)	813	52.0
Holy Family Hospital, Rawalpindi (HFH)	470	30.1
Pakistan Institute of Medical Sciences Hospital, Islamabad (PIMS)	135	8.3
Pakistan Air Force Hospital, Islamabad (PAFH)	144	9.2
Admission Frequency of patients across period of the study		
May 2020	592	37.9
June 2020	846	54.2
July 2020	124	7.93

Of all the 19 drugs reportedly used for treatment of COVID-19 and management of COVID-19-related symptoms, the most frequently used antibiotic was Azithromycin (88.6%), followed by

Ceftriaxone (23.6%). Anticoagulants like Heparin (21.6%) and Enoxaparin sodium (19.8%) and steroids like Hydrocortisone (25.7%) were also among the top five most frequently used drugs. The relative distribution of administered drugs across hospitals during first wave of COVID-19 is given in Figure 1. Load of patients on each hospital was different but the trend of regime used was similar. The peak of first wave of COVID-19 in Rawalpindi-Islamabad was observed during June 2020. The trend of drugs utilization during the first wave of COVID-19 is shown in Figure 2. Although the load over hospital varied during the three months but the choices in drugs used against COVID-19 remained same. Frequencies and percentages of these drugs are given in Table 2. Different combinations were used, and these combinations had drugs from various categories of drugs like anticoagulants, corticosteroids and antibiotics etc.

Table 2 Drugs used during first wave of COVID-19 in all four hospitals

Cumulative frequencies of various drugs used during May-July 2020	Frequency (n)	Percentage (%)
Antibiotics		
Azithromycin	1384	88.6
Cefatriazone	369	23.6
Cefixime	8	0.51
Meropenem	56	3.6
Imipenem/Cilastatin	139	8.9
Piperacilin/Tanzobactam	266	17.0
Vancomycin	9	0.6
Clarithromycin	28	1.8
Moxifloxacin	21	1.3
Levofloxacin	18	1.1
Corticosteroids		
Hydrocortisone	409	26.2
Methylprednisolone	197	12.6
Dexamethasone	130	8.3
Anticoagulants		
Enoxaparin sodium	310	19.8
Heparin	337	21.6
Antimalarial		
Hydroxychloroquine	208	13.3
Antiparasitic		
Ivermectin	34	2.2
Antiviral		
Acyclovir	8	0.5
Oseltamivir	12	0.8

Discussion

Our results show that the highest proportion of admissions were in the month of June (54.2%), just after Eid-ul-Fitr, (Muslim festival held on 23rd and 24th of May 2020). It is worth noting that this was the time when the first wave of COVID-19 infections was at its peak in Pakistan but the trend of treatment regimen remained the same during the period of first wave [35-37]. Nevertheless, after this period a dramatic decrease in infections was seen due to effective precautions and regulations imposed by the government including smart lockdown in potential hotspots, implementation of standard operating procedures (SOPs) and closure of academic buildings etc. [38].

Our study reports the use of up to 10 antibiotics of different classes. The use of antibiotics for treatment of COVID-19 is debatable and evidence of their direct inhibitory effect on viral replication or pathogenesis remains to be proved. These antibiotics are generally used to treat infections of upper respiratory tract, pneumonia, and other infections caused by opportunistic bacteria due to low immunity during viral infection. Azithromycin was widely used because it is a broad-spectrum antibiotic and can treat chest infections including pneumonia which is also a manifestation in COVID-19 infection, infections of the nose and throat such as sinus infection (sinusitis), skin infections, Lyme disease, and some sexually transmitted infections [39].

Besides antibiotics, some other frequently used drugs were anticoagulants (Heparin and Enoxaparin Sodium) and corticosteroids (Hydrocortisone and Methylprednisolone). Use of anticoagulants and steroids is indicated for reduction of inflammatory effects of the SARS-CoV-2 which helps control disease progression to a limited extent, but no succinct combination was observed in terms of treating COVID-19 [40].

Challenges / Shortcomings on the therapeutic front

Despite the fact that the antibiotics supported the combined therapies used against Corona virus, there is still no evidence that augments the irrational usage of these antibiotics to treat a viral infection by our healthcare professionals. Other drugs like anticoagulants and steroids were also used as supportive therapy but there is a need of standard guidelines to be followed to treat patients with COVID-19 related complications.. It was experimental hit and trial of various combinations of drugs and the alarming frequency with which antibiotics were used frequently will eventually lead us to antibiotic resistance in human population. One of the major challenge faced by healthcare professionals globally was the reliability on the available therapies against newly introduced virus. Mutations in RNA viruses are more frequent as compared to DNA species and COVID-19 being a RNA virus is a great threat to humanity. Modern research is required to study mutable infectious agents to develop multifaceted therapies to target pathways utilized.

Conclusion

Current study highlights the trend of drugs used in early months of COVID-19 infections across Pakistan. The irrational usage of antibiotics use by healthcare professionals is also questionable. It signifies the lack of specific guidelines that must be followed by all hospitals in terms of treatment regimen and organizations like the National institute of health (NIH), center for disease control (CDC) etc. must not only provide guidelines to tackle the pandemic but also make sure that those guidelines are strictly being followed throughout the country. The study reveals the weaknesses in our healthcare infrastructure and inadequacy of hospitals and staff in Pakistan. With the second wave hitting various countries and a mutant strain causing infections it is important to make sure the SOPs are being strictly followed, a proper treatment guideline is provided, and drugs used for symptomatic treatment are monitored to avoid resistance in future.

Limitations of the study

The study was limited to Rawalpindi / Islamabad region of Pakistan which are big cities with

relatively better healthcare facilities and check and balance on healthcare practitioners. Data from other cities especially small towns and rural region can be helpful in analyzing the misuse of medicines prescribed for treatment of COVID-19 related symptoms and complications. The study was done on patients admitted in the mid months of 2020 during the peak of first wave and a better analysis can be made if more data is taken from months of second wave too. Collecting data during first wave was difficult due to limited access to COVID-19 wards and shortage of personal protection equipment (PPE). Number of subjects included in the study were under 2000 but comprehensive information could be gathered on large population size.

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Conflicts of Interest

The authors declare no conflict of interest.

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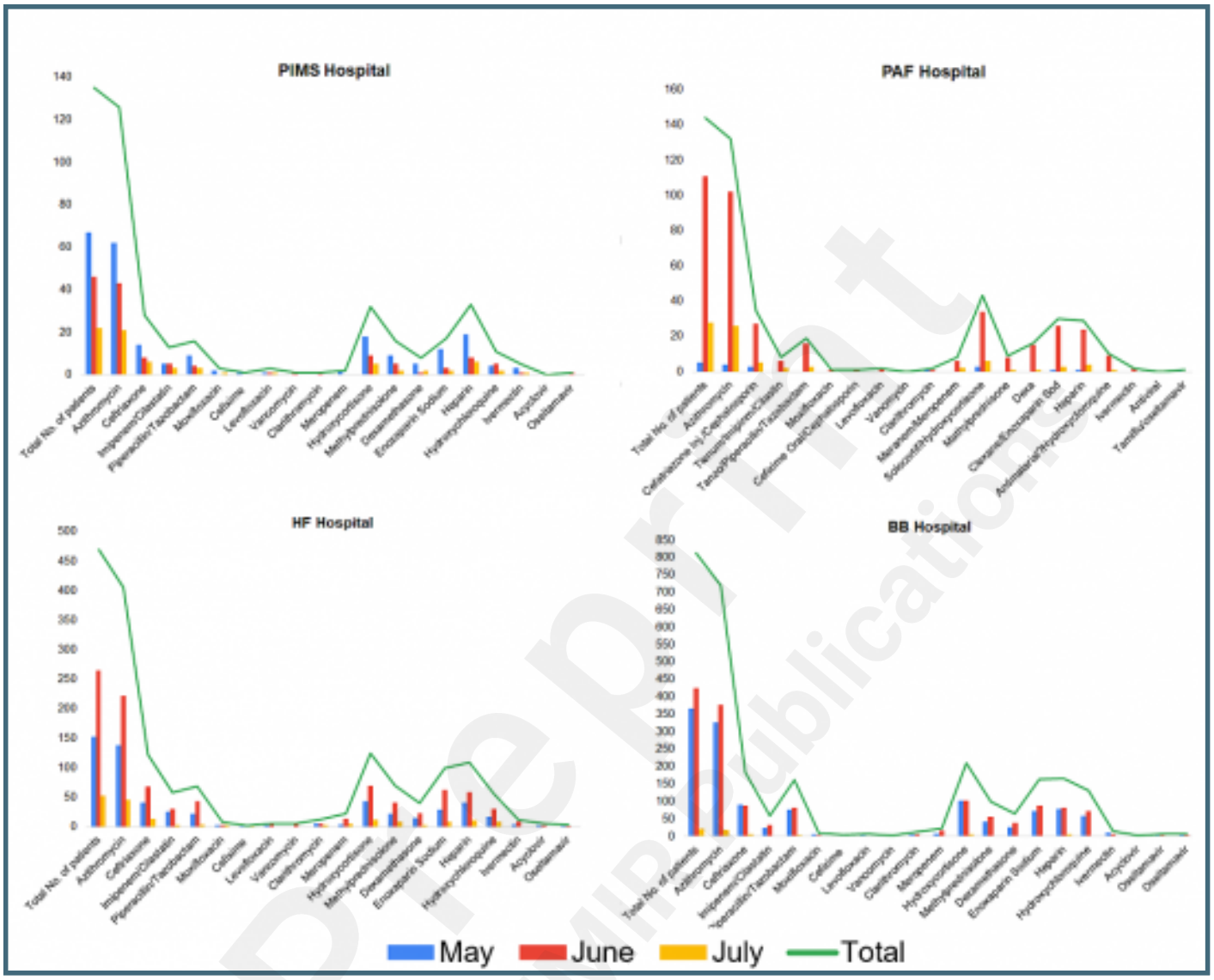
List of Figures

Figure 2 Relative distribution of different drugs administered to COVID-19 patients in each month during the first wave (Mat 2020- July 2020) in Pakistan. Yes [May (blue), Jun (orange), July (yellow)] vs. No (gray)

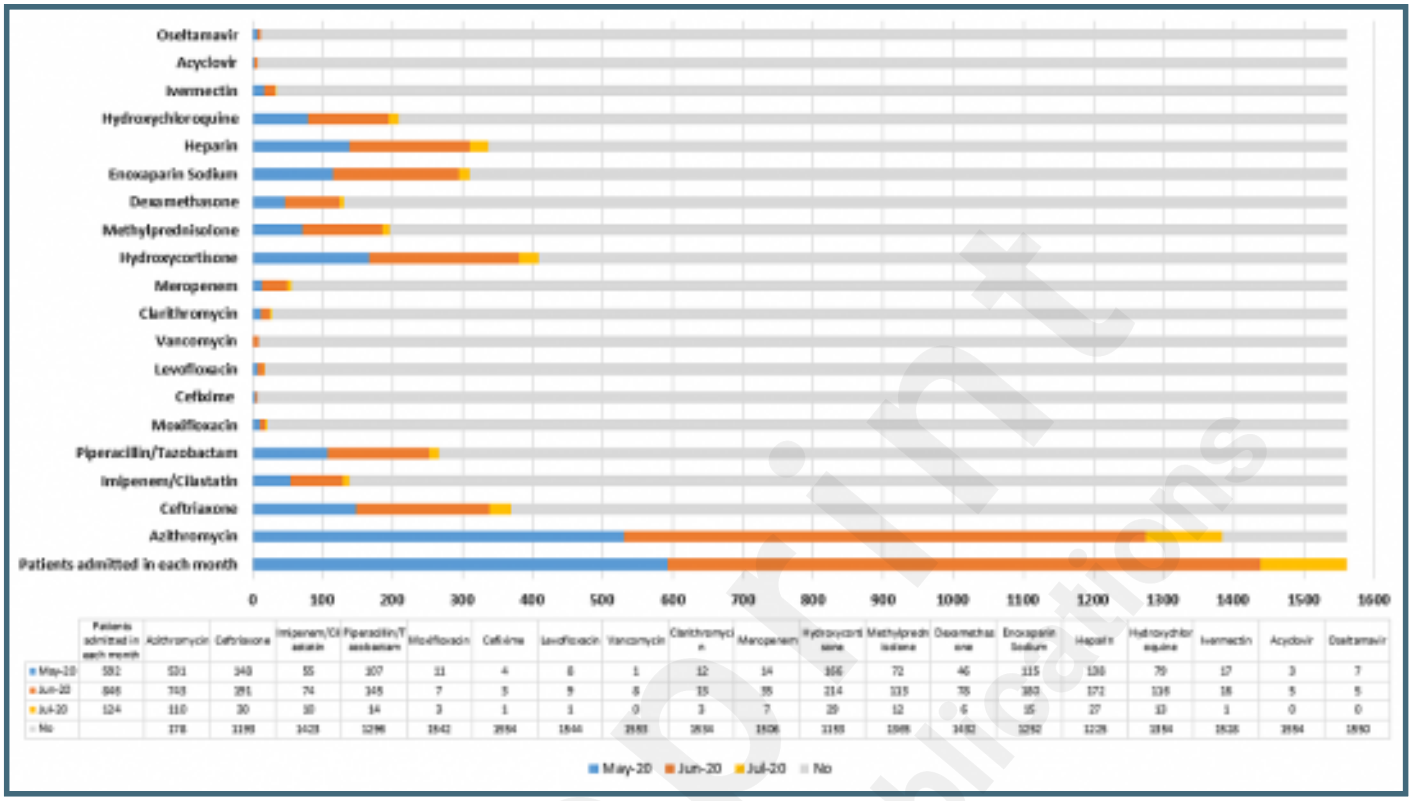
Supplementary Files

Figures

Hospital wise relative distribution of different drugs administered to COVID-19 patients during first wave in Pakistan.



Relative distribution of different drugs administered to COVID-19 patients in each month during the first wave (Mat 2020- July 2020) in Pakistan. Yes [May (blue), Jun (orange), July (yellow)] vs. No (gray).



TOC/Feature image for homepages

A spoon full of Medicines shows failure in drug of choices among COVID-19 patients.