



Original article

Pharmaceutical situation of the pharmacological treatment of hospitalized patients with COVID-19 in Libya

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Abstract: By January 2020, severe acute respiratory syndrome coronavirus-2 has spread internationally to a pandemic that mainly targets the respiratory system. The relevant infectious disease has been identified as coronavirus disease-2019 (COVID-19) by World Health Organization and declared as a global pandemic. In Libya, National Center for Disease Control reported the first case of coronavirus disease-2019 on 24th March, 2020. The authorities decided to close borders and activate designated treatment centers to deal with COVID-19 cases and contain the outbreak of SARS-COV-2. This study aimed to assess and evaluate the pharmaceutical situation of medications used in pharmacological management of hospitalized COVID-19 patients in Tripoli, Libya. Three WHO availability indicators were selected to be studied and reported. A comprehensive list of medicines used in the management of hospitalized COVID-19 patients was constructed after reviewing and comparing seven national and international pharmacological management protocols and guidelines for hospitalized COVID-19 patients. This comparison revealed that nearly 50 medications are intended for use in COVID-19 inpatient pharmacological management. They all agreed about the use of three medications, representing one from each main class. This list was used to cross check their availability at the chosen designated COVID-19 treatment center. This study proved that local treatment center's protocol is more in line with international guidelines than the national treatment guideline. The later was issued on March 2020. The Libyan National Essential Medicines' List contained 25 out of 50 medications of the comprehensive list based on the last update in April 2019. This study recommends that national treatment guidelines and National Essential Medicines' list require updating. Not all medications used in COVID-19 inpatient management were available in local treatment centers, although, the Emergency Management Department of Ministry of Health in Libya is responsible for the supply of the required medical supplies and medications to the COVID-19 treatment centers.

Introduction

At the end of December 2019, a wide number of idiopathic pneumonia cases have been reported in as a novel coronavirus [1]. This causative virus has

Wuhan, China. A few days after the incident, the causative agent of this pneumonia was determined been named as severe acute respiratory syndrome

coronavirus-2 (SARS-COV-2) and the relevant infectious disease has been identified as coronavirus disease-2019 (COVID-19) by the International Committee for Taxonomy of Viruses and World Health Organization (WHO) [2, 3]. By January 2020, COVID-19 has spread internationally to become a pandemic that mainly targets the respiratory system. On 24th March, 2020, the National Center for Disease Control reported the first case of coronavirus disease-2019 in Libya. By the middle of March 2020, Libyan authorities decided to close the borders, suspend classes in public and private schools and universities throughout the country and activate the country's lockdown. In response to providing medical management to the diagnosed cases, Ministry of health and through its emergency management activated designated COVID-19 treatment centers across all of Libya. In Tripoli, Tripoli Central Hospital and Zawiat-Al-Dahmani centers were firstly activated followed by Mitiga center and Souq-Altholatha center to contain the outbreak and deliver healthcare services and medical management for the confirmed COVID-19 cases requiring hospitalization. Currently, there are six COVID-19 treatment centers in Tripoli. At the early beginning of the pandemic, there was no well-established treatment protocol for the emerging disease but soon after declaring it as a global pandemic, WHO has issued guidelines for clinical management guideline. It was all started as a symptomatic treatment then evidence-based treatment recommendations developed. Therefore, some medications were withdrawn from COVID-19 treatment guidelines after they were used at the beginning of the pandemic. These medicines have proved no clinical improvement or serious side effects and it is now recommended against their use. At the same time, other treatments and medications were gaining approval and the COVID-19 treatment panel at WHO recommends their use. WHO encourages countries to have updated national standard treatment guidelines (nSTG) with medications included in an updated National Essential Medicines' list. On the other hand, local healthcare facilities are expected to adopt the national standard treatment guidelines in

their local standard treatment protocols. In addition, these facilities are expected to extract their local medicines' list from the national medicines' list. This study aimed to assess and evaluate the pharmaceutical situation of medications used in the pharmacological management of hospitalized COVID-19 patients in Tripoli using WHO availability indicators.

Materials and methods

This is a prospective observational assessment study. It was conducted in Tripoli, Libya during the period from October to the middle of December, 2021.

Study design: WHO operational package for assessing, monitoring and evaluating country pharmaceutical situation was used to determine the targeted indicators and the specific forms were accordingly modified and adjusted for the purpose and scale of the study [4]. The study involved multiple steps including documents reviewing, data collection, physicians' interviews and data analysis. The following indicators were defined for this study: availability of standard treatment guidelines, availability of medications in National Essential Medicines' list (nEML), WHO Essential Medicine List (WHO EML) and British National Formulary (BNF), as well as availability and affordability of medicines in public COVID-19 treatment Centers.

Study indicators

Availability of standard treatment guidelines: An online search was conducted to obtain Libyan pharmacological management protocol for hospitalized COVID-19 patients. WHO guidelines for treating COVID-19 hospitalized patients was also used and to be able to generate a comprehensive list of medicines for hospitalized COVID-19 patients. Relevant guidelines and protocols from the United States, United Kingdom, Ireland and Germany were also attained. Local treatment protocol from designated COVID-19 treatment centers was planned to be obtained via an

official request letter. An official letter requesting ‘the treatment guidelines used by physicians for hospitalized COVID-19 patients’ was oriented to one of these centers in Tripoli. It was confirmed that all centers apply the same treatment protocol. All of the above mentioned pharmacological management protocols and guidelines were reviewed and compared. A comprehensive list of medications used in the management of hospitalized COVID-19 patients was also generated.

Availability of medications in the nEML, WHO eML and BNF: Medications that are included in the adopted comprehensive list of medicines used in the management of hospitalized COVID-19 patients were checked for availability in the nEML, WHO EML 22nd list and BNF-81 [5, 6].

Availability and affordability of medicines in public treatment centers: The comprehensive list of medications was used to cross check their availability and pricing at the chosen designated COVID-19 treatment center.

Statistical analysis: All data obtained were entered into a Microsoft Office (2007) Excel file. A statistical descriptive included frequency and percentage of agreements and disagreements in availabilities were used.

Results

Indicator 1: *Availability of standard treatment guidelines:* A total of seven protocols and guidelines have been obtained, six of them were documented and available online (WHO, US, UK, Irish, German and National treatment guidelines [7]). Whereas, the local treatment protocol from designated COVID-19 treatment center was

obtained via an official letter requesting ‘the treatment guidelines used by physicians for hospitalized COVID-19 patients. Because of the sensitive nature of the specialty of these centers and their highly restricted accessibility, it was only feasible to deal with one center. However, they orally confirmed that all COVID-19 designated treatment centers in Tripoli apply the same treatment protocol. Although they did not have an official written internal document of this protocol to share to us in response to our request, instead they were able to reply with actual treatment applied for certain cases. The analysis of the seven protocols and guidelines revealed that total of 50 medications are used in the pharmacological management of COVID-19 in-patients. They were all registered in a comprehensive list of pharmacological used in the management of hospitalized COVID-19 patients. The distribution of these medications per each guideline and percentage of agreement and disagreement are shown in **Tables 1** and **2**. All guidelines have agreed about the use of the three medications: remdesivir, methylprednisolone and enoxaparin. These medications represent one of each main class of medications used in COVID-19 management. Local treatment center protocol and National Treatment Guideline have eight medications in common. It is also evident from the results that the local treatment center’s protocol is more in-line with other international guides than the national COVID-19 management guidelines.

Indicator 2: *Availability of medications in nEML, WHO eML and BNF:* The nEML (LML), WHO EML and BNF-81 have been obtained. The comprehensive COVID-19 medications list was compared against these documents and the results about their medications availability and inclusion are shown in **Tables 3** and **4**.

Table 1: Distribution of COVID-19 medications among treatment guidelines and protocols

	Local Treatment Center	National Treatment Guideline	US Guidelines	UK Guidelines	Irish Guidelines	German Guidelines	WHO Guidelines
No. of Medications per total (%)	24/50 48.0%	16/50 32.0%	23/50 46.0%	25/50 50.0%	18/50 36.0%	27/50 54.0%	30/50 60.0%
VTE prophylaxis (9)	05 (55.6%)	02 (22.2%)	03 (33.3%)	04 (44.4%)	05 (55.6%)	07 (77.8%)	05 (55.6%)
Systemic Corticosteroids(6)	02 (33.3%)	01 (16.7%)	06 (100%)	06 (100%)	05 (83.3%)	05 (83.3%)	06 (100%)
Antibiotics (11)	06 (54.6%)	02 (18.1%)	02 (18.2%)	07 (63.6%)	02 (18.2%)	08 (72.7%)	11 (100%)
Antiviral and MABs (6)	01 (16.7%)	02 (33.3%)	04 (66.7%)	03 (50.0%)	04 (66.7%)	04 (66.7%)	04 (66.7%)
IL-2 receptor blockers (1)	NIL	NIL	01 100%	NIL	NIL	NIL	01 100%
IL-6 receptor blockers (2)	0.00%	01 (50.0%)	02 (100%)	02 (100%)	01 (50.0%)	01 (50.0%)	02 (100%)
Vitamins and supplements (6)	04 (66.7%)	03 (50%)	04 (66.7%)	NIL	NIL	01 (16.7%)	NIL
Others* (9)	05 (55.6%)	05 (55.6%)	01 (11.1%)	01 (11.1%)	NIL	NIL	01 (11.1%)

*Others: Hydroxychlorquine, Colchicine, Ipratropium bromide, hypertonic saline solution, N-acetylcystein, Omeprazole, Famotidin, Bromhexine.

Table 2: Availability of COVID-19 medications in different protocols and guidelines

	Local Treatment Center Protocol	National Treatment Guidelines	US Guidelines	UK Guidelines	Irish Guidelines	German Guidelines	WHO Guidelines
Local treatment Center Protocol	24/24 (100%)	8/16 (50.0%)	10/23 (43.5%)	12/25 (48.0%)	7/18 (38.9%)	15/27 (55.6%)	13/30 (43.3%)
National Treatment Guidelines	8/24 (33.3%)	16/16 (100%)	8/23 (34.8%)	6/25 (24.0%)	4/18 (22.2%)	7/27 (25.9%)	8/30 (26.7%)
US Guidelines	10/24 (41.7%)	8/16 (50.0%)	23/23 (100%)	17/25 (68.0%)	14/18 (77.8%)	13/27 (48.2%)	19/30 (63.3%)
UK Guidelines	12/24 (50.0%)	6/16 (37.5%)	17/23 (73.9%)	25/25 (100%)	16/18 (88.9%)	18/27 (66.7%)	21/30 (70%)
Irish Guidelines	7/24 (29.2%)	4/16 (25.0%)	14/23 (60.8%)	16/25 (64.0%)	18/18 (100%)	15/27 (55.6%)	17/30 (56.7%)
German Guidelines	15/24 (62.5%)	7/16 (43.8%)	13/23 (56.5%)	18/25 (72.0%)	15/18 (83.3%)	27/27 (100%)	24/30 (80.0%)
WHO Guidelines	13/24 (54.2%)	8/16 (50.0%)	19/23 (82.6%)	21/25 (84.0%)	17/18 (94.4%)	24/27 (88.9%)	30/30 (100%)

Table 3: Distribution of COVID-19 medications among the medicine's lists

	National Essential Medicine's List nEML (2018-2019)	WHO Essential Medicine's List WHO EML (2021)	British National Formulary (BNF 81, March 2021)
No. of medications per total (%)	26/50 (52.0%)	28/50 (56.0%)	42/50 (84.0%)
VTE prophylaxis (9)	2/9 (22.2%)	6/9 (66.7%)	7/9 (77.8%)
Systemic corticosteroids (6)	5/6 (83.3%)	5/6 (83.3%)	6/6 (100%)
Antibiotics (11)	9/11 (81.8%)	9/11 (81.8%)	11/11 (100%)
Antiviral and MABs (6)	NIL	1/6 (16.7%)	3/6 (50.0%)
IL-6 receptor Blockers (2)	1/2 (50.0%)	NIL	2/2 (100%)
Vitamins and supplements (6)	3/6 (50.0%)	2/6 (33.3%)	5/6 (83.3%)
Others* (9)	6/9 (66.7%)	5/9 (55.6%)	8/9 (88.9%)
*Others: Hydroxychloroquine, Colchicine, Ipratropium bromide, hypertonic saline solution, N-acetylcystein, Omeprazole, Famotidin, Bromhexine.			

Table 4: Comparing availability of COVID-19 medications in different medicines lists with percentage of agreement

List	National Essential Medicine's List	WHO Essential Medicine's List	British National Formulary (BNF 81)
National Essential Medicine's List	26/26 (100%)	20/28 (71.4%)	26/42 (61.9%)
WHO Essential Medicine list	20/26 (76.9%)	28/28 (100%)	27/42 (64.3%)
British National Formulary	26/26 (100%)	27/28 (96.4%)	42/42 (100%)

The BNF-81 has most of the medications listed in the comprehensive COVID-19 medications list representing of 84.0% (42 out of 50). While the WHO and the National EML included 56.0% and 52.0% of medications listed in the comprehensive COVID-19 medications list, respectively. The number of medications in common between WHO EML, nEML and BNF-81 was 21, representing 42.0% of the 50 medications intended for use for COVID-19 in-patient pharmacological management. However, six medications that were not listed in WHO EML, nEML nor BNF, namely: LMWH certoparin, vitamin C IV, bromhexien, casirivimab, imdevimab and favipiravir.

Indicator 3: Availability and affordability of medicines in public treatment centers: COVID-19 medications for in-patients were surveyed for availability in one treatment center, it is reported that the pharmacy store at the surveyed center had 24 medications available out of 50 (48.0%). The availability of medications used in the treatment protocol of the designated treatment center reached to 75.0% (18/24). All of the treatment center management medications are listed in the BNF-81 [6], while WHO EML and nEML contained 16/24 (66.7%) and 15/24 (62.5%), respectively. The affordability could not be extensively studied because the medication prices results are not

conclusive. However, the affordability of treatment is illustrated through case of pharmacological management and treatment for one day. This clinical case details has been obtained from the treatment center with the pharmacological management applied. Thus, a case study is male patient age is not reported who is a known case of hypertension and diabetes mellitus type II was admitted because of COVID-19 diagnosis confirmed by PCR on admission and his vital signs and laboratory investigations were as follows:

Temperature: 37 °C, Sp O₂: 88.0%, Blood pressure: 140/90 mmHg, D Dimer: 1500, PCT: - 0.350, CRP: 110. The pharmacological management of the case involved: anti-inflammatory medication: methylprednisolone 50 mg IV 1 x 2, antibiotics: meropenem 1 gm IV 1 x 3 and ciprofloxacin 200 mg IV 1 x 2. Anti-coagulant: enoxaparin 6000 IU SC 1 x 2. Paracetamol 1 gm IV 1 x 3 and insulin sliding scale. The cost of the pharmacological treatment for one day is 293 LYD, and in case of early diagnosis and remdesivir is added, the cost would be 1173 LYD (based on prices from the private sector).

Discussion

After reviewing and analyzing the seven guidelines, the comprehensive list of medications used in the management of hospitalized COVID-19 patients has contained 50 medications. The national treatment guidelines revealed the least percentages of agreement with the other guidelines. The lowest percentage of agreement was between the Irish guideline and the national treatment guideline. The reason is that the Irish guideline and the national treatment guideline have the least total number of medications 18 and 16 medications respectively, therefore their probability of matching is the least.

Highest percentage of agreement was between the Irish guideline and the WHO guideline. This is expected knowing that WHO guideline contains wide range of medications and the Irish guidelines is last updated in July 2021. On the other hand, the national treatment guideline [7] which has not been updated since March 2020, has 16 medications and only eight of which are present in the WHO guideline. The local treatment protocol at the

treatment center have overall higher percentage of medications-inclusion agreement with other international treatment guidelines compared to that of the national COVID-19 treatment guideline. It is evident that treatment protocol in the local treatment center is more in-line with others (WHO and international guidelines) than the national treatment guideline. This is because the national treatment guideline has not been updated while the local treatment center's physicians were up to date with recent medications added or withdrawn from the WHO guidelines. The national treatment guideline and the local treatment center protocol have eight medications in common. According to physicians at the treatment center, methylprednisolone showed beneficial effect with severe and critical COVID-19 hospitalized patients with inflammatory responses in addition to dexamethasone. However, methyl prednisolone was much more available in the treatment center's store. Whereas, other guidelines are flexible recommending dexamethasone, prednisolone, methylprednisolone or hydrocortisone, having dexamethasone as first-line for the treatment of critical cases in their advanced stages. Although, national treatment guidelines included two anticoagulants; enoxaparin and tinzaparin, the COVID-19 treatment center protocol included five different medications as anticoagulants for thromboprophylaxis. On the other hand, there were only unfractionated heparin and fondaparinux available in the stores because these anticoagulant medications are approved in the current nEML. The treatment center protocol and the national treatment guideline included the antiviral remdesivir, which was first granted approval by the Food and Drug Administration of the US to be used for the treatment of COVID-19 hospitalized patients, however, WHO published conditional recommendation against the use of remdesivir in hospitalized COVID-19 patients on 20th November 2020. The panel explained the reasons as the absence of conclusive evidence on the effect on mortality, need for mechanical ventilation, recovery from symptoms and other patient-important outcomes [8]. This medication is available in the local treatment center stores

although it is not on the nEML nor the WHO EML for the reasons explained above. The national treatment guideline included favipiravir, although at the time of its issue there was no international professional bodies recommend the use of favipiravir for the treatment of COVID-19. A systematic review and meta-analysis suggested that in in-patients with mild-to-moderate COVID-19, favipiravir can stimulate viral clearance within seven days and clinical improvement within 14 days yet recommended further investigation to assess the effect in patients with different levels of disease severity and the different doses and durations of therapy [9]. IL-6 receptor blocker are newly emerging classes in the management of hospitalized COVID-19 patients and up to the date of this research, tocilizuma and sarilumab are strongly recommended for use in COVID-19 patients by the WHO [8]. Monoclonal antibodies; sarilumab and imdevimab are also not used for COVID-19 in-patients in Tripoli. There are multiple factors that should be considered before recommending these agents' inclusion in the national treatment guideline and nEML, two of which are cost effectiveness and health equity. IL-2 receptor blockers are only mentioned as class of medication in the US guideline [10] and the WHO guideline [8]. The findings confirmed that the BNF-81 [6] included most of medications used in COVID-19 management for hospitalized patients, because it is updated regularly. nEML represented the lowest percentage of inclusion (52.0%), its last update was in April, 2019 which explains the absence of new medications recently approved for COVID-19 treatment such as remdesivir. Although WHO EML edition was updated in 2021, the percentage of medication inclusion was 56.0% medications included. This is because some high cost medications are not listed in the WHO EML and limited to treatments that the panel strongly recommends their use. The WHO EML, nEML and BNF-81 have 21 medications (42.0%). For the same above explained reasons, it was found that all of the treatment center management medications are listed in BNF-81 [6] but lower number of them are in WHO EML (65.0%) and the nEML (60.0%). Further comparison between the comprehensive

COVID-19 medications list and the three essential medicine's lists (nEML, WHO EML and BNF-81) confirmed that there are six medications are not listed in all of them. Casirivimab and imdevimab were approved in September 2021, therefore it is very possible that they are listed in the BNF-82 (September 2021 edition) as they are included in the UK guideline (October, 2021). They are not listed in WHO EML (October 2021) probably because they have conditional recommendation [8] and of their high cost. Favipiravir is still under clinical trials and this is more likely reason for not being listed. The reasons for certoparin, vitamin C and bromhexien not being listed are not certainly known but it is possible that there is no enough supporting evidence for their use or the presence of more cost effective alternatives. Certoparin was present in the Irish and German COVID-19 treatment guidelines only.

The availability of COVID-19 management medications was checked in the treatment center stores, about 50% of the medications are available. The treatment center stores had 75% of the center's protocol medications. Central public supply stores do not directly supply the designated COVID-19 treatment centers, the reason why the treatment center stores included remdesivir when it is not on the nEML. The emergency management department at ministry of health supplies the treatment centers with medications but because of time constrain it wasn't possible to obtain regarded information for comprehensive central availability and affordability analysis. The cost of pharmacological treatment for one day of a specific case is calculated as 293 LYD if remdesivir is not used otherwise it will be 1173 LYD. This cost does not include the clinical management cost required. This cost is calculated according to the private stores prices and it is relatively expensive to be maintained by patients in private sector. This emphasizes the urgency to maintain continues supply of medications to the stores at the treatment centers with the required medications stocks.

Conclusion: This study succeeded to report WHO availability indicators as part of assessing and evaluating the pharmaceutical situation of the pharmacological treatment of the COVID-19. This

study proved that the applied local treatment center protocol is more in-line with the international guidelines. However, they are required to document their up to date treatment protocol to support internal auditing and reviewing. In addition, there is urgent

need to update the nEML and the national COVID-19 treatment guidelines. This would encourage application of cost effective and evidence based practices and bring best utilization of human and financial resources.

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Ethical issues: Including plagiarism, informed consent, data fabrication or falsification and double publication or submission have completely been observed by authors.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon

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