

**ORIGINAL ARTICLE**DOI: <https://doi.org/10.3329/mediscope.v11i1.71638>**Current Pharmaco-therapeutic Approach on COVID-19 Admitted Patients in a Corona-dedicated Hospital in Khulna*****B Islam¹, SD Haque²****Abstract**

Background: The COVID-19 pandemic has been demanding possible pharmaco-therapeutic options to reduce the mortality associated with the disease by trying out the clinical efficacy of various therapeutic agents. **Objective:** Our purpose of the study was to explore the current pharmaco-therapeutic approaches to COVID-19 patients in different clinical categories. **Methods:** This is a descriptive observational study where 300 clinically diagnosed COVID-19-positive patients were included following inclusion & exclusion criteria at the study center. Patients' demographic profiles and treatment plans were obtained using a specially designed form. The data were collated and analyzed using a Microsoft Excel spreadsheet and results were expressed in percentages. **Results:** Remdesivir, moxifloxacin, dexamethasone, meropenem, enoxaparin and other supportive drugs with different percentages in mild, moderate, severe & critical cases were frequently prescribed. Besides non-invasive oxygen therapy has been given in almost all patients. **Conclusion:** Antiviral, LMWH, broad-spectrum antibiotics, corticosteroids and other symptomatic drugs are the major treatment options for different clinical categories of COVID-19 patients.

Keywords: Pharmacotherapy, Supportive drugs, COVID-19.

Introduction

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a Global Public Health Emergency. It began in Wuhan, China, in December 2019, and has now spread worldwide and declared as a global pandemic.^{1,2} Mortality rates of Coronavirus Disease 2019 (COVID-19) have been estimated to be 5-27%^{2,3} which is more prevalent in vulnerable populations, including children, older people, pregnant women & patients with existing co-morbidities like DM, HTN, IHD, CVD, Asthma, etc.¹⁻⁷ No specific pharmacological treatment or vaccine has been invented against SARS-CoV-2 to save the people

yet.^{8,9} Various "repositioned" drugs (indicated for other uses) have been proposed for COVID-19 treatment. Empirical applications of anti-malarial (chloroquine and hydroxychloroquine), antibiotics, antivirals (remdesivir, lopinavir/ritonavir), interleukins, interferon- β (treatment for multiple sclerosis), and antirheumatic drug (tocilizumab), immunosuppressant, convalescent plasma, anticoagulants and many more are currently underway to explore a quick effective treatment due to their antiviral or immunomodulatory effects.^{1,2,8-11}

Though these therapies have been assumed to work with success, without having a clinical trial,

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they cannot be approved to ensure a rapid and effective cure. WHO has given general guidelines for symptomatic management of COVID-19.^{1,2,11,12} The treatment may vary across countries. As such, the treatment of patients varies based on disease severity and consideration of underlying medical conditions.^{2,13} COVID-19 may range from asymptomatic and mild illness to severe illness. Bangladesh govt. has been established a national guideline for the management of COVID-19 published on 5th November 2020 where the six syndromes of COVID-19 have been categorized into mild, moderate, severe, and critical cases. Mild cases represent Influenza-like illness (ILI), moderate with pneumonia (CRB 65 score 0), patients with severe pneumonia, sepsis, and with ARDS, septic shock developed in those, considered as critical cases.¹⁴ Treatment guidelines are plotted below:¹⁴

According to the guidelines symptomatic patients in risk groups (like DM, HTN, IHD, Prior Asthma/COPD/ILD patients, Known CKD, CLD, Known Malignancy, High-risk pregnancy, Obesity (BMI>25)) should be admitted in isolation ward and will be treated as follows:

- Tab Paracetamol (500mg) 1 tab if temp is more than 101° F
- Antihistamine if there is rhinorrhoea
- Antitussive if there is dry cough
- Thromboprophylaxis: For Mild COVID-19 cases with risk factors: Enoxaparin 40 mg, SC, once daily (for obese patients, 40 mg BID). Adjust dose when CrCl < 30ml/min or start Unfractionated heparin 5000 unit SC /day. • Monitor closely.

Moderate cases of hospital-admitted patients will be treated by following treatment protocol.

Mild symptomatic Treatment Protocol Plus • Oxygen through a nasal cannula (Maximum 5 L/min) if required. • Proning- Prone position at least 4-6 hrs/day • LMW heparin (Inj enoxaparin) Enoxaparin 1mg/kg SC twice daily/ day (dose adjust with CrCl < 30ml/min) Or if LMWH cannot be given or contraindicated • Inj Unfractionated heparin (UFH): 60U/kg bolus+12units/kg/hr infusion-for ACS 80U/Kg bolus +18units/kg/hr

infusion-for VTE and AF • Thromboprophylaxis should be given until symptom resolves or improves and followed by Tab rivaroxaban 10 mg once daily for 1 month • Antiviral: For moderate to severe cases who need oxygen therapy and/or are hospitalization, Inj Remdesivir has been advocated. Dosage of Remdesivir: 200 mg IV infusion (within 30 min-2 hours) on Day 1 followed by 100 mg infusion (within 30 min to 2 hours) from Day 2 to Day 5. If Remdesivir is started, then other antiviral (e.g. favipiravir) should be stopped. Remdesivir should be used at the discretion of the consultant working in the hospital and can be used in the treatment of all hospitalized adult and pediatric patients (>12 years old) with suspected or laboratory-confirmed COVID-19, irrespective of the severity of the disease. • Any Moderate case on treatment – if no response or deterioration at 24 hours in hospital: Oral Dexamethasone 6 mg/day in single or two divided doses for 10 days (market formulation is 0.5 mg and so for adult 12 tab is needed) or Oral Methylprednisolone (60-80 daily) in single or two divided doses for 7 days with antiulcerant coverage and antihelminthic coverage.

Patients with severe cases of respiratory symptoms will be managed by following this schedule:

Management of Moderate case protocol (Except oral steroid) Plus • Steroids- Inj Dexamethasone 6 mg daily for 10 days or Inj Methylprednisolone-250 mg daily for 5 days (switch to IV from oral if already started) • Maintain euvolaemia (Avoid fluid load) • Early Norepinephrine for hypotension • Broad spectrum antibiotics— IV drug at the discretion of consultant • Consider for cytokine storm/ HLH (Hemophagocytic lymphohistiocytosis) picture: 1. Tocilizumab* 2. Convalescent Plasma therapy.

In this study, we assessed pharmacological agents relevant to COVID-19-specific medications including remdesivir^{15,16}, favipiravir¹⁷, systemic corticosteroids^{2,18}, tocilizumab^{19,20} and agents that may be used for supportive care in patients with COVID-19 including statins²¹, anti-infective agents like anti-biotics, anti-fungal and anti-viral drug for

other specific viruses²², anticoagulants^{23,24}, inhalers/nebulizers²⁵, proton pump inhibitors.² However, these drugs are employed due to their proven efficacy either individually or in combination, according to their national healthcare guidelines, though there is no specific drug available to treat the contagion.⁹ We aimed to explore the current therapeutic approaches in the treatment of COVID-19 in the inpatient settings.

Materials and methods

After obtaining ethical approval from the institutional ethics committee, this descriptive observational study was conducted on 300 patients admitted to Gazi Medical College, Khulna from January to June 2021 with positive results on a real-time reverse-transcriptase polymerase chain reaction (RCT-PCR) assay of nasal or pharyngeal swab specimens for SARS-CoV-2.

RCT-PCR positive patients with all age groups of both sexes with or without co-morbidities like diabetes, hypertension, ischemic heart disease, cerebrovascular disease, asthma, excess obesity, kidney & liver disease, etc were included in this study where patients with pregnancy and lactation & those having RCT-PCR negative findings were excluded from this study. According to the National Guidelines on Clinical Management of COVID-19 of Bangladesh published on 5th November 2020, the six

syndromes of COVID-19 have been categorized into mild, moderate, severe and critical cases. In this study, critical cases were treated as severe categories due to the lack of mechanical ventilation support in hospital. Initially, critical cases were referred to another hospital where mechanical ventilation support was available. But they refused to shift from this hospital and were willing to take the treatment as like severe category. Informed written consent has been taken from the patient's attendant. Demographic information of the patient and medical treatment are recorded in a customized form. All the data from different treatment groups were compiled in the form of tables & figures by using a Microsoft Excel 2007 spreadsheet and the result was expressed in percentages.

Results

Among all the recruited patients in the study group, male 170 (56.66%) were more affected than female 130 (43.33%). The majority of the participants were aged between 38 to 57 years (42.66%) followed by more than 57 years (35%) with fewer individuals in other age groups. Among the admitted patients majorities 205m(68.33%) have co-morbidities in which diabetes was the most common 67 (32.68%) and second most common was hypertension 51 (24.87%) followed by other comorbidities. Only 53 patients (17.66%) were vaccinated whereas maximum patients 247 (82.33%) were not vaccinated. All these demographic features are shown in Table 01.

Table 01: Demographic characteristics of the population

Characteristics of the participants		Number of participants (n=300)	Percentage (%)
Gender	Male	170	56.66%
	Female	130	43.33%
Age (years)	< 18	02	0.67%
	18-37	65	21.66%
	38-57	128	42.66%
	>57	105	35%

Coexisting disorders	Absent	95	31.66%
	Present (n=205)	205	68.33%
	Diabetes	67	32.68%
	Hypertension	51	24.87%
	Asthma	28	13.65%
	Coronary heart disease	25	12.19%
	COPD	16	7.80%
	Chronic renal disease	12	5.85%
Vaccination status	Cerebrovascular disease	06	2.92%
	Vaccinated	53	17.66%
	Non-vaccinated	247	82.33%

Out of 300 admitted patients in the hospital, 95 patients were treated as a mild case (31.66%), 142 patients as moderate (47.33%), 55 patients as severe (18.33%), and only 8 patients were admitted as critical case (2.66%) which is shown in Figure 01.

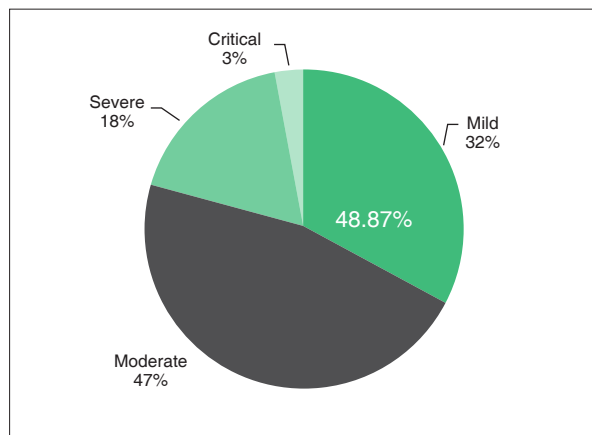


Figure 01: Categories of the patient based on severity

In our study, patients received non-invasive oxygen therapy either in the form of traditional/low-flow oxygen (up to 16 L/min) or high-flow oxygen (16 to 60 L/min). Mild cases received 80 (84.21%) traditional/low flow oxygen & 15 (15.78%) high flow oxygen. High-flow oxygen was given in the moderate & severe groups with higher percentages of 66.19%, and 90.90% respectively. A hundred percent (100%) of patients in critical cases received high-flow oxygen. These findings are shown in Figure 02.

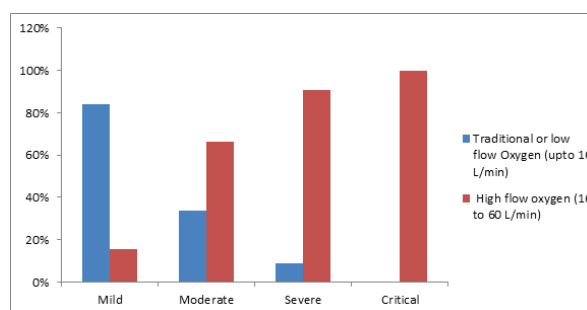


Figure 02: Oxygen therapy in different categories of COVID patients

A list of drugs for supportive therapy in different clinical categories of COVID-19 is shown in Table 02. Antivirals, monoclonal antibodies, steroids, antibiotics, and low molecular weight heparin were used mainly in critical, severe and some moderate cases. Mild cases with co-morbidities are also included under these supportive drugs. All categories were prescribed according to our national guidelines. Among antivirals, all the critical cases (100%) and 95.77% of moderate cases received remdesivir, whereas 4.22% of moderate patients received favipiravir. Tocilizumab was used as monoclonal antibody in 9.52% of cases (severe & critical). Among different groups of steroids, dexamethasone (36.84% in mild cases, 88% in moderate cases, and 79.36% in severe & critical cases), was used in the highest percentages in all categories. Budesonide (90% in mild cases and 100% in severe & critical cases) was used commonly in the form of nebulization. Patients received

methylprednisolone, hydrocortisone and prednisolone with fewer percentages also. Moxifloxacin (42.10% in mild cases and 100% in severe & critical cases) was a frequently used drug among different types of antibiotics prescribed. Moreover, meropenem was used in all (100%) severe & critical cases. Some other antibiotics such as amoxicillin & clavulanic acid, ceftriaxone, piperacillin & tazobactam combination, ceftazidime, linezolid, etc were prescribed in different categories with significant

percentages. All severe & critical patients (100%) received enoxaparin as an anticoagulant. Salbutamol & ipratropium bromide combination are used in the form of nebulization in all severe and critical patients. Each patient also received various supportive drugs with different percentages like bronchodilators, antihistamines, leukotriene receptor blockers, antiulcerants, paracetamol, anxiolytics, antiemetics, cough suppressants, immunity boosters like vitamin D, vitamin C, and zinc along with these drugs.

Table 02: List of Drugs for supportive therapy in COVID-19

List of drugs		Mild cases (n=95)	Moderate cases (n=142)	Severe+critical cases (n=63)
Antiviral	Remdisivir	Nil	136 (95.77%)	63 (100%)
	Favipiravir	Nil	06 (4.22%)	Nil
Antibody	Tocilizumab	Nil	Nil	06 (9.52%)
Steroids	Dexamethasone	35 (36.84%)	125 (88.02%)	50 (79.36%)
	Methylprednisolone	22 (23.15%)	14 (9.85%)	06 (9.52%)
	Hydrocortisone	04 (4.21%)	03 (2.11%)	07 (11.11%)
	Prednisolone	09 (9.47%)	Nil	Nil
	Budisonide(local/topical)	86 (90.52%)	142 (100%)	63 (100%)
Antibiotics	Moxifloxacin	40(42.10%)	142(100%)	63(100%)
	Meropenem	Nil	122 (85.91%)	63(100%)
	Amoxicillin+ clavulanic acid	76(80%)	26(18.30%)	Nil
	Ceftriaxon	10(10.52%)	12(8.45%)	26(41.26%)
	Piperacillin+Tazobactam	13(13.68%)	07(4.92%)	Nil
	Ceftazidime	Nil	04(2.81%)	08(12.69%)
	Linezolid	Nil	05(3.52%)	03(4.76%)
Anticoagulant	Enoxaparin	29(30.52%)	142(100%)	63(100%)
	Rivaroxaban	06(6.31%)	Nil	Nil
Bronchodilator	Salbutamol + Ipratropium bromide	50(52.63%)	142(100%)	63(100%)
	Doxofylline	52(54.73%)	110(77.46%)	48(76.19%)
	Salmeterol+fluticasone	16(16.84%)	24(16.90%)	35(55.55%)
	Salbutamol	25(26.31%)	07(4.92%)	Nil
Antihistamine	Fexofenadine	95(100%)	30(21.12%)	Nil
Leucotriene antagonists	Montileucast	95(100%)	142(100%)	45((71.42%)
Others	Antiulcerants	95(100%)	142(100%)	45(71.42%)
	Vit D	80(84.21%)	115(80.98%)	33(52.38%)
	Zinc	73(76.84%)	112(78.87%)	20(31.74%)

[N.B: In most cases, the patient received more than one drug of the same group. So percentages were more than a hundred.]

Discussion

In this observational study of 300 individuals hospitalized with positive SARS-CoV-2 tests in a corona-dedicated hospital in Khulna, Bangladesh, we explored the current pharmacological treatments for COVID-19 in different clinical categories.

The majority of the male patients 56.66% are more affected than females 43.33% which is consistent with other studies done by Lin K. J. et al., Cen Y. et al., Sanders J. M. et al., Cantudo Cuenca M.D. et al., Alam M.T. et al.^{2,6,26-28} We found most of the patients (42.66%) were in the age group of 38 to 57 years during our data collection period. Another study done by Alam M.T. et al. showed most patients' age group between the ages of 21 to 40 years.²⁸ A larger proportion of the patients (68.33%) have coexisting diseases along with COVID-19. Among them, the most common co-morbidities were diabetes (32.68%) and hypertension (24.87%) followed by asthma (13.65%), coronary heart disease (12.19%) and fewer percentage of other co-morbidities. It is concomitant with another study done by Lin K. J. et al.² But this is dissimilar with other studies done by Dalan R et al., Cantudo Cuenca M.D. et al. where hypertension was predominant.^{5,27}

Almost all the patients required oxygen therapy at the time of admission to the hospital. Low & high flow of oxygen was given to the patients according to their different clinical categories. Mild cases received traditional or low-flow oxygen (84.21%) whereas moderate (66.19%), severe (90.90%) & critical cases (100%) received high-flow oxygen. Lin K.J. et al., Grein J. et al., and Beige J.H. et al., have shown that supplemental oxygen may help identify early respiratory deterioration.^{2,15,16}

For the treatment of COVID-19, several antiretroviral drugs are considered. Remdesivir acts as RNA dependent RNA polymerase inhibitor and was frequently prescribed drug in moderate, severe & critical cases in our study.

Some other studies also revealed that remdesivir could be a promising antiviral and may be more widely available in the upcoming weeks.^{2,8,11,13,15,16,29} But it is varying with other studies where lopinavir/ritonavir was the preferred antiviral.^{12,27,30} Some studies showed that other antivirals like darunavir/ cobicistat, ribavirin, favipiravir, umifenovir, oseltamivir can play an important role in the treatment of COVID-19.^{4,9,12,13,22,27,30}

A few patients (severe & critical cases) received tocilizumab (9.52%) as monoclonal antibody, IL-6 receptor antagonist, which is FDA-approved to treat cytokine release syndrome. It may have a beneficial role in severe and life-threatening illness.^{13,11,19,20,30} In China a study done by Xu X. et al. reported that most of the patients who received only one dose of tocilizumab, 400mg was associated with clinical improvement and successful discharge.³¹

Almost all patients received steroids in different dosage forms. Budesonide, dexamethasone, methylprednisolone, and hydrocortisone are commonly used steroids using varying percentages in different categories of patients. Another study showed the uses of steroids in varying percentages.¹¹ The WHO currently recommends against the routine use of corticosteroids in the treatment of patients with COVID-19, due to the potential for delayed viral clearance and other adverse effects such as avascular necrosis and psychosis.¹³

Almost all the admitted patients received antibiotics. Many of them got more than one antibiotic. The consumption rate of moxifloxacin was more than other antibiotics. All the moderate, severe & critical cases received moxifloxacin (100%). Meropenem (100% in severe & critical cases) was the second most common antibiotic used followed by amoxicillin-clavulanic acid, and ceftriaxone. Some antibiotics used in the lowest percentage like piperacillin-tazobactam combination, ceftazidime, linezolid, etc. Some other clinical studies done by Hendaus M. A. et al., Chen T. et al., and Huang C. et al have shown

positive therapeutic outcomes of antibiotic therapy.³²⁻³⁴ Huang C. et al showed cephalosporins, carbapenems, and quinolones are good initial choices for COVID-19 patients.³⁴

In our study, among 300 patients, all the moderate, severe & critical and mild cases with co-morbidity patients received LMWH and enoxaparin. Heparin treatment appears to be associated with better prognosis in severe COVID-19 patients with coagulopathy with significantly elevated D dimer.^{1,11} To validate this finding, more forward-looking experiments are required.

Almost all the patients received bronchodilator agents. Among them, salbutamol & ipratropium bromide combination in nebulization form was broadly used (100% in moderate, severe & critical and 52.63% in mild cases). Secondly, methylxanthine derivatives doxophylline were also frequently used drugs. Patients got salmeterol & fluticasone combination and salbutamol in inhaler form in different percentages. Some other studies done by Lin K. J. et al. & Ari A. also found that bronchodilators may have a beneficial role in patients with different clinical categories of COVID-19.^{2,25}

Besides these drugs, physicians also prescribed antihistamines; fexofenadin, leukotriene receptor blocker; montelukast, antiulcerants;(omeprazole, esomeprazole), immunity booster agents like vitamin D and zinc along with these drugs with varying percentages. Some other symptomatic drugs include paracetamol, anxiolytics, antiemetics, cough suppressants (butamirate citrate, acetylcysteine, dextromethorphan), and piperfenidone with few percentages. A similar finding was found in another study conducted by Perveen R.A. et al.⁸ Additionally some purposeful drugs like antidiabetic, antihypertensive, anti-asthmatic, antianginal, etc. were prescribed in patients with co-existing diseases.

Limitations & recommendations

Due to time constrain, there was evidence of

inappropriate subgroup analysis like adults and children, different formulations, dosages and duration of drugs, etc. Furthermore, the study is needed to provide up-to-date insight into the current therapeutic approaches according to guidelines for the management of COVID-19 patients.

Conclusion

We concluded our study by addressing the pharmaco-therapeutic approaches where antiviral, LMWH, broad-spectrum antibiotic, corticosteroid and other symptomatic drugs were the mainstream treatment for different clinical categories of admitted COVID-19 patients.

Conflict of Interest

None of the co-authors declared any conflict of interest regarding this article

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