Original Article

Cotrimoxazole in the domiciliary management of patients with severe COVID-19 : A case series

Khawer Naveed Siddiqui[1], Mrinal Kanti Das[2], Alapan Bandyopadhyay[3]

Background : COVID-19 pandemic has resulted in nearly 55,000 deaths in India and over 800,000 deaths worldwide. Despite several clinical trials there is no effective proven treatment currently available for this condition and the mainstay of management is only supportive.

Methods : Data from successive patients presenting to a telemedicine clinic between May and August 2020 with severe COVID 19 and receiving domiciliary treatment with oral cotrimoxazole in addition to standard therapy was collected and retrospectively analyzed.

Results : 14 patients received cotrimoxazole in addition to standard therapy. Following start of the treatment regimen, all of the patients showed marked improvement in their clinical parameters including fever and oxygen requirements, following which all of them made complete recoveries. Only one patient required hospital admission for a transient period.

Conclusion : This observation warrants an urgent clinical trial. If the above results are replicated in future trials it may change the way in which we manage patients with this potentially life-threatening condition.

[*J Indian Med Assoc* 2020; **118(10):** 34-8]

Key words **: Severe COVID-19, Cotrimoxazole, Domiciliary treatment, Telemedicine.**

Over the course of December of 2019, a cluster of patients with clinical presentations similar to viral pneumonia of unknown origin was reported in Wuhan, China[1]. Analysis from lower respiratory tract samples of the patients, all of whom were connected to the Hunan Seafood Wholesale Market[2] indicated that the disease was caused by a novel coronavirus[3]. By the second week of March 2020, the disease quickly spread throughout China and crossed international borders to infect more than 100,000 people and kill over 4000 in over 100 countries worldwide[4]. Subsequently, the WHO declared the disease, named COVID-19, a pandemic[5]. The causative organism of the disease, was initially named nCOV-2019[6], however, its name was subsequently changed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) because of its genetic relation with the Coronavirus strain responsible for the 2003 SARS outbreak[7]. As of August, 2020, more than 20 million people have been reported to be infected by the SARS-CoV-2 in more than 210 countries and international territories, with a death toll of over 800,000. The disease has infected more than 2.9 million in India with more than 55,000 confirmed deaths[8].

Editor's Comment :

- **COVID-19 may have potential life threatening complications including acute respiratory failure from ARDS in a minority of cases.**
- **Early recognition and treatment of severe COVID-19 is vital to saving lives.**
- **The use of oral cotrimoxazole may be considered as a potential treatment option in patients with severe COVID-19.**
- **This may be due to its antimicrobial and anti-inflammatory properties. Urgent clinical trials are recommended.**

A respiratory infection of zoonotic origin, COVID-19 is transmitted from human to human through respiratory droplets[9]. The disease generally presents with respiratory symptoms, with fever, fatigue, myalgia, dry cough and dyspnea being the commonest[10,11]. It has been seen that people with co-morbidities like, diabetes, cardiovascular, and cerebrovascular diseases, cancers and preexisting lung diseases like Chronic Obstructive Pulmonary disease have a higher risk of developing severe forms of the disease[11]. In people with severe disease, this symptoms might progress to septic shock, coagulation disorders, Acute Respiratory Distress Syndrome (ARDS) multi-organ failure and even death[12]. However, being an emerging

[1]MBBS, MD, FACC, FESC, Chief Coordinator, Ruby Cardiac Research Division, Ruby General Hospital, Kolkata 700107 and Corresponding Author

[2]MBBS, MD, DM, FICP, FICC, FCSI, FACC, Consultant Cardiologist, C K BIRLA Hospitals (BMB, CMRI), Kolkata 700027

[3]MBBS, PGT (MD), Department of Community Medicine, North Bengal Medical College, Darjeeling 734012

Received on : 26/08/2020

Accepted on : 04/09/2020

disease, till date there has been no clear consensus regarding the management of the disease, with different countries and health bodies using their own sets of criteria and management guidelines.

Materials and Methods

Data from successive patents presenting to a telemedicine clinic between May and August 2020 with severe COVID 19 and receiving domiciliary treatment with oral cotrimoxazole in addition to standard therapy was collected and retrospectively analyzed. The patients were diagnosed as severe COVID according to the WHO diagnostic criteria of fever and suspected respiratory infection, with any one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or $SpO_2 \leq 93\%$ on room air from their diagnosis[13]. All of the consultations and follow-ups were made through tele-consultancy. All the patients were treated at home as they declined hospital admission. Informed consent was obtained from each patient regarding initiation of cotrimoxazole and collection, analysis and publication of the anonymous data.

Statistical Analysis

Continuous data will be presented using mean and standard deviation. Comparisons between two groups for continuous data will be made using the t-test. Categorical data will be presented as number of patients or percentage of patients. A p-value of <0.05 is considered to be significant.

Results

The demographic and clinical characteristics of the patients are presented in Table 1. The mean age of the patients was 57 ± 8.1 years. Males constituted 9 of the 14 patients consulted (64%) and the rest were female. Of the 14 patients treated, 4 (29%) had Type 2 Diabetes, 3 (21%) had Ischemic Heart Disease, 1 (7%) had Bronchial asthma and 6 (48%) had controlled hypertension and 2 patients has no co-morbidities. High-grade fever (100%) was the most common symptom with which the patients presented themselves (Table 2). The next most common symptoms were shortness of breath (93%) and persistent cough (93%). Only 2 patients among the 14 developed sore throats. The mean duration of symptoms for the patients was 4±2 days.

Laboratory parameters of the patients were similar (Table 3). The mean oxygen saturations at room air was 87 ± 5 %. Mean WBC count was 6620.7 ± 1918.7. Only 3 patients (21%) tested negative on RT-PCR of nasopharyngeal swabs for COVID-19 with strong clinical, biochemical and radiological suspicion of

Table 1 — *Demographic and clinical characteristics of patients (n=14)*

Characteristic	Patients (n = 14)	Percentage
Age in years (mean ± SD)	57 ± 8 years	
Sex		
Male	9	64%
Female	5	36%
Risk factors[a]		
Type 2 Diabetes Mellitus	4	29%
Ischemic Heart Disease	3	21%
Bronchial Asthma	1	7%
Controlled hypertension	6	43%
None	2	14%
Treatment Duration (mean ± SD)	9.7 ± 2.9 Days	

[a]More than one risk factors were present in multiple patients

Table 2 — *Symptom profile of patients (n = 14)*

Symptoms[a]	Patients (n = 14)	Percentage
Fever	14	100%
Shortness of Breath	13	93%
Cough	13	93%
Sore throat	2	14%

[a]More than one symptom was present in multiple patients

Table 3 — *Clinical and biochemical parameters of patients at presentation (n = 14)*

Patient	Duration of symptoms (days)	SpO_2 at Room Air	Temperature at presentation (°F)	TLC	Neutrophil (%)	Lymphocyte (%)	CRP	RT-PCR for COVID
1	4	81%	101.5	11000	87	9	128	Negative
2	2	90%	101	5180	63	27	NA	Positive
3	3	92%	102	4430	70	15	NA	Negative
4	5	90%	102	6500	55	38	NA	Positive
5	4	93%	102	6140	65	28	NA	Positive
6	3	84%	103	5100	77	18	71.2	Positive
7	4	89%	102	7500	64	34	125	Negative
8	7	74%	103	5900	76	18	35	Positive
9	3	91%	101.5	6600	62	33	41.7	Positive
10	4	88%	102	5200	65	29	5.87	Positive
11	3	91%	101	6900	67	27	5.8	Positive
12	8	82%	103	10340	73	23	158	Positive
13	3	89%	102.5	5200	60	35	19.6	Positive
14	3	91%	104	6700	66	27	3.4	Positive
Mean	4	87	102	6620.7	67.9	25.8	59.4	-
SD	2	5	0.8	1918.7	8.2	8.3	57.9	-

COVID-19. Chest X-Rays were done for 9 patients (64.3%). Rest could not be done due to the ongoing restrictions of all travel/ home isolations. All of the Chest radiographs showed lung infiltrates, with bilateral infiltrates being the most common (Table 4). Only one patient had a high IL6 count of 37.5.

Of the patients, only one required hospitalization for 2 days. All of the rest were cared for at home, with regular follow-up through tele-medicine facility. All of the patients were given oral Cotrimoxazole (960 mg twice daily for 7 to 10 days) and Azithromycin (500 mg once daily). Moist Oxygen Inhalation was provided to 11 (79%) patients. Other drugs that were given to patients are shown in Table 5. The mean duration of treatment for the patients was 10 ± 3 days.

All of the patients made full recovery, with resolution of the presenting symptoms. Statistically significant increase was seen with regards to the mean SpO_2/FiO_2 ratio on presentation and at second measurement 48-72 hours later (mean±SD:417±26 *versus* 451±12, *p*-value <0.001,Table 6). In addition majority of the patients required oxygen for upto 5 days (n=8) from the initiation of treatment. Only a minority of patients required oxygen for a longer period (two patients for 8 days and 1 patient for 6 days). Moreover there was significant improvement of body temperature 48-72 hours after initiation of treatment with cotrimoxazole (mean ± SD: 102±0.8°F versus 98.5±0.6°F, p-value <0.001, Table 7). Furthermore the mean time taken for the fever to completely subside after initiation of treatment with cotrimoxazole was 69±19 hours. Finally significant improvement was seen on repeat chest radiographs (n=7) at one to two weeks after intervention with cotrimoxazole.

Table 4 — *Chest X-Ray PA View findings (n = 14)*

Chest Radiograph Findings	Patients	Percentage
Bilateral Infiltrates	5	36%
Left Lower Lobe involvement	2	14%
Right lower lobe involvement	2	14%
Not Done	5	36%

Table 5 — *Treatment and outcomes of patient with severe COVID-19 (n = 14)*

Parameters	Patients	Percentage
Medications[a]		
Cotrimoxazole 960 mg PO*	14	100%
Azithromycin 500 mg PO	14	100%
Moist Oxygen Inhalation[b]	11	79%
LMWH 60 mg SC	7	50%
Ivermectin 12 mg PO	7	50%
Doxycycline 100 mg PO	3	21%
Methylprednisolone 30 mg PO	1	7%
Piperacillin-Tazobactam 4.5 g IV	1	7%
Favipavir 200 mg PO	1	7%
Outcome		
Hospitalization	1	7%
Home-based care	13	93%
Death	0	0%
Recovered	14	100%

[a]More than one medication was used in each patient
[b]As per required
PO: Per Oral; SC: Subcutaneous; IV: Intravenous; LMWH: Low Molecular Weight Heparin
* Cotrimoxazole was given orally at a dose of 960mg twice daily for 7-10 days

Table 6 — *SpO_2/FiO_2 (S/F) ratio comparisons at presentation and after 48-72 hours*

Patient	S/F ratio at presentation	S/F ratio after 48-72 hours
1	386	438
2	429	457
3	438	462
4	429	471
5	448	448
6	400	433
7	424	462
8	352	429
9	433	457
10	419	443
11	433	452
12	390	447
13	424	457
14	433	452
Mean	417	451
SD	26	12

Discussion

In this report we have shown that patients with severe COVID-19 (COVID-19 with mild to moderate hypoxia) were reviewed and followed up by a physician via a telemedicine clinic and were provided with domiciliary treatment with cotrimoxazole in addition to standard therapy showing excellent outcomes.

Recent studies have indicated that the envelope spike protein receptor binding domain of the SARS-CoV-2 binds with the angiotensin converting enzyme 2 (ACE2) receptors of the host cells, generally the epithelium of the respiratory system and alveolar pneumocytes type 2 (AT2)[14,15]. The virus then causes lysis of the infected cells, setting into motion the inflammatory immune response of the host by triggering release of proinflammatory cytokines like interleukin (IL) IL1, IL2, IL6, IL 7, interferon gamma, macrophage

Table 7 — *Body temperature comparisons at presentation and after 48-72 hours*

Patient	Body temperature at presentation	Body temperature after 48-72 hours
1	101.5	98.3
2	101	98.2
3	102	100
4	102	99.5
5	102	98
6	103	98.3
7	102	98.1
8	103	98.4
9	101.5	97.8
10	102	98
11	101	97.8
12	103	99.2
13	102.5	99.2
14	104	98.2
Mean	102	98.5
SD	0.8	0.6

inflammatory proteins, tumor necrosis factor alpha etc[2]. In patients with severe forms of the disease, the excessive immune response by the host coupled with the continued lysis of the infected cells generate a cytokine storm syndrome (CSS). Damage Associated Molecular Patterns (DAMPs) released following mitochondrial injury in host cells lead to the stimulation of Formyl Peptide Receptors (FPRs) situated on the outer surface of the cell membrane of the neutrophils and monocytes, which in turn cause the recruitment of these cells to the lung. When stimulated, FPRs cause the release of Reactive Oxygen Species (ROS) in the tissue, leading to the release of even more cytokines[16,17]. This leads to extensive tissue damage, causing rapid progression of mild respiratory symptoms like dry cough and fever into Acute Respiratory Distress Syndrome followed by multiple organ failure in susceptible patients[2]. The key to managing severe COVID-19 is preventing this cytokine storm from taking place, in addition to making sure that there are no superimposed secondary bacterial infections in the already compromised lungs of the patient.

Cotrimoxazole is a commonly used antibiotic used to treat a wide range of diseases ranging from Urinary and Respiratory tract infections to opportunistic pneumocystis pneumonia and toxoplasmosis in people with HIV/AIDS. Composed of one-part Trimethoprim and five parts Sulfamethoxazole. Cotrimoxazole is a cheap drug with excellent efficacy and a high safety profile[18]. This has led it to being enlisted in the WHO list of essential medicines[19] and being available as a generic medication[20]. Research done *a priori* suggest that Cotrimoxazole can block the FPRs, leading to the prevention of inflammatory cell recruitment, release of cytokines and ROS in the damaged tissue[21,22]. Cotrimoxazole have also been found to be effective at the reduction of pro-inflammatory cytokines like IL-1, 2, 6, 8 and Tumor Necrosis Factor –α[23]. This might lead to prevention of the progression of the clinically severe COVID-19 into ARDS by thwarting the impending CSS. Furthermore, the drug is highly effective in the treatment of nosocomial and opportunistic infections. This might also have an effect in averting the progression of COVID to ARDS by preventing any secondary bacterial infection. The addition of this drug to standard therapy showed substantial improvement in the course of the disease. Low Molecular Weight Heparin was used in some patients with large number of co-morbidities and/or more severe disease to prevent venous thromboembolism commonly seen in patients suffering from COVID-19[24]. The rapid and complete recoveries that all of the 14 patients treated with Cotrimoxazole made thus lends credence to this idea that cotrimoxazole may be an effective drug to combat the disease and is in keeping with a recent report by Quadery and colleagues[25].

Another important aspect of the reported cases is that 13 out of the 14 patients were managed in **a** domiciliary setting through telemedicine, without needing admission to a specialized in-patient setup. Only one patient was hospitalized with a duration of stay of 2 days. In countries of South and South-East Asia, high population density, poor healthcare infrastructure, high out of pocket healthcare expenses, and rampant poverty makes it hard for a large part of the populace to avail and access healthcare[26]. In this scenario, a domiciliary treatment regimen along with tele-medicine consultation that can help manage clinically severe COVID-19 in an out-patient setup and lessen the need to admit the patient in intensive care has the potential to alleviate a lot of burden not only from the patients but also from the healthcare facilities, whose resources are stretched thin in order to combat the pandemic. As all of the drugs forming the treatment regimen for the management of these 14 patients are common, widely used and inexpensive, they can be easily accessible to the patient population. Most of them are easily self-administrable (except for LMWH which may need a help or video supervision by a doctor during administrating the drug), and which makes them ideal for home-based care. In countries where there is a dearth of specialized setups for the management of COVID-19, such a regimen that can reach patients in hard to reach areas by virtue of being prescribed and followed up through telemedicine can be of immense help, especially in the context of public health and healthcare delivery systems.

Conclusions

In this case series for the first time we are able to demonstrate excellent outcomes by adding oral Cotrimoxazole to standard therapy in patients with severe COVID-19 in a domiciliary setting where the patients were reviewed and followed up via a telemedicine facility. However, further research using comparison groups need to be done to substantiate and validate the findings reported in this report.

Funding : None

Conflict of Interest : None

References

1 WHO — Novel Coronavirus–China. Jan. 2020; 12.

2 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020 Feb 15; **395(10223):** 497-506.

3 February 26, 2020. [Internet] [Archived from original February 27, 2020; Cited August 10, 2020]. Available from: https://web.archive.org/web/20200227094018/http://china.caixin.com/2020-02-26/101520972.html
4 World Health Organization — Coronavirus disease 2019 (COVID-19): situation report, 50. [Internet]. March 11, 2020. [Cited August 10, 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200310-sitrep-50-covid-19.pdf?sfvrsn=55e904fb_2
5 McKay B, Calfas J, Ansari T — Coronavirus declared pandemic by World Health Organization. *The Wall Street Journal* 2020; Mar 11.
6 Nature — Coronavirus: the first three months as it happened. [Internet]. Nature. April 22, 2020. [Cited August 10, 2020]. Available from: https://www.nature.com/articles/d41586-020-00154-w
7 World Health Organization — Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. WHO. February 11, 2020. [Cited August 10, 2020] Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
8 World Health Organization— Coronavirus disease 2019 (COVID-19): situation report, 194. [Internet]. August 1, 2020. [Cited August 10, 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200801-covid-19-sitrep-194.pdf?sfvrsn=401287f3_2
9 World Health Organization — Q&A on coronaviruses. *Global Alert and Response (GAR)* 2020; Feb 2; 552.
10 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y — Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* 2020; **323(11):** 1061-9.
11 Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Yu T — Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet* 2020; **395(10223):** 507-13.
12 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z — Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020; **395(10223):** 497-506.
13 World Health Organization — Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected, Interim Guidelines. [Internet]. WHO. March 13, 2020. [Cited August 10, 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-eng.pdf?sequence=1&isAllowed=y
14 Wan Y, Shang J, Graham R, Baric RS, Li F — Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of Virology 2020; **94(7):**
15 Hamming I, Timens W, Bulthuis ML, Lely AT, Navis GJ, van Goor H — Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: *A Journal of the Pathological Society of Great Britain and Ireland* 2004; **203(2):** 631-7.
16 Li L, Chen K, Xiang Y, *et al* — New Development in Studies of Formyl-Peptide receptors: Critical Roles in Host Defense. *J Leukoc Biol* 2016; **99(3):** 425-35.
17 Barnes BJ, Adrover JM, Baxter-stoltzfus A, Borczuk A, Cools-LartigueJ, *et al* — Targeting Potential Drivers of COVID-19: Neutrophil Extracellular Traps. *J Exp Med* 2020; **217(6):** 1-7.
18 British National Formulary: https://bnf.nice.org.uk/drug/co-trimoxazole.html
19 World Health Organization — World Health Organization model list of essential medicines: 21st list 2019. Geneva: World Health Organization. 2019.
20 Brown D, Edwards H, Seaton L, Buckley T — Lewis's Medical-surgical Nursing: Assessment and Management of Clinical Problems. Elsevier Health Sciences; 2015 Jan 29.
21 Varney V, Smith B, Quirke G, *et al* — The effects of oral cotrimoxazole upon neutrophil and monocyte activation in patients with pulmonary fibrosis and healthy controls; does this relate to its action in idiopathic pulmonary fibrosis? *Thorax* 2017; **72:** A109
22 RobertsDE, Curd JG — Sulfonamides as antiinflammatory agents in the treatment of wegener'sgranulomatosis. *Arthritis & Rheumatism* 1990; **33:** 1590-1593. doi:10.1002/art.1780331020
23 Ohtake T, Kobayashi S, Honjou Y, *et al* — Generalized Wegener's Granulomatosis Responding to Sulfamethoxazole-trimethoprim Monotherapy. *Internal Medicine* 2001; **40(7):** 666-70. https://doi.org/10.2169/internalmedicine.40.666
24 Kow CS, Hasan SS — Use of low-molecular-weight heparin in COVID-19 patients. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2020 Jun 17.
25 Quadery SR, John T, Samuel T, *et al* — Improved outcomes with trimethoprim or cotrimoxazole in patients with severe COVID-19 : A district hospital experience. (Preprint) https://ssrn.com/abstract=3626443
26 World Bank — OOP expenditure as % of total health expenditure, 2014. [Internet]. World Bank. 2014. [Cited August 10, 2020] Available from: http://data.worldbank.org/indicator/SH.XPD.OOPC.TO.ZS.

This is a pilot study with promising results. The study is to be undertaken with adequate sample size in multiple centres along with control group.