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Improved Recovery and Survival with Trimethoprim or Cotrimoxazole in Patients with Severe COVID-19: A Retrospective Analysis

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ABSTRACT

Background: COVID-19 may become a life-threatening illness as a result of acute respiratory distress syndrome with the mainstay of management supportive, although dexamethasone and serum from recovered patients look helpful in reducing mortality in oxygen dependant patients.

Methods: We retrospectively analysed data from 22 patients with severe COVID-19 treated with trimethoprim (TMP) or cotrimoxazole (CTX) added to standard therapy antibiotics (ST) and compared this with anonymized data from 22 patients with COVID-19 of similar severity receiving ST alone.

Results: Patients receiving additional TMP or CTX showed clinical improvement within 48 hours with reduced fever (p= 0.001), C-reactive protein levels (p=0.002) and oxygen requirements (SpO2/FiO2, p<0.001). Mortality was reduced (to 5% versus 32% for ST, p=0.022) and the need for ventilatory support (3 versus 16 patients on ST, p<0.001) and hospital length of stay (mean: 9 days versus 22 days on ST p<0.001).

Discussion: This benefit may be due to combined antimicrobial and immunological effects of TMP and CTX. Both drugs block stimulation of the formyl peptide receptors (FPR's) on the surface of circulating neutrophils and monocytes. When stimulated, FPR's cause homing of neutrophils to the lung and trigger the release of Reactive Oxygen Series driving cytokine production and therefore a possible cytokine storm. Stressed neutrophils can extrude their nuclear content as 'external nets' (NETosis) to trap infectious agents, these nets can block the pulmonary alveolar bed giving severe hypoxia and death as seen in post mortems from COVID-19 patients. Blocking of neutrophil FPR's by these drugs may be the mechanism by which they protect the lung in COVID-19.

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Abbreviations

TXM-Trimethoprim
CTX- Cotrimoxazole
ST-Standard Treatment (benzylpenicillin & clarithromycin)
SpO_2/FiO_2- oxygen saturation percentage/inspired oxygen fraction
CRP-c-Reactive Protein
ROS-Reactive Oxygen Series
FPR-Formyl Peptide Receptors
NETosis- Neutrophil Extracellular Nets
ARDS-Acute respiratory Distress Syndrome
MRSA-Methacillin Resistant Staph Aureus
MSSA-Methacillin Sensitive Staph Aureus
MERS-Middle East Respiratory Virus
CT Scan- Computerised Tomography Scan
WHO-World Health Organisation
NLR-Neutrophil to Lymphocyte Ratio
IQR-Interquartile Range

Keywords: Severe COVID-19, ARDS, ventilatory support, Neutrophil NETosis, Trimethoprim, Cotrimoxazole, formyl peptide receptors.

Background

The Corona virus (COVID-19) pandemic has affected over 16.7 million people resulting in more than 661,000 deaths. While the disease is self-limiting for many, for those with severe disease effective treatments are limited. Risk factors for more severe disease include male sex, obesity, ethnicity and diabetes alongside prior cardiac or respiratory diseases. Recent studies have shown that Hypertension is not an independent risk factor for COVID-19. Subgroups of patients with severe COVID-19 have unremitting fevers; blood cytopenia's and 50% may develop pulmonary involvement associated with over stimulation of the Immune response to the virus [1-5]. Respiratory failure and acute respiratory distress syndrome (ARDS) are the most serious complications of pulmonary involvement with the mainstay of treatment being

oxygen therapy. Patients who require non-invasive or invasive ventilatory support have a higher mortality. Secondary bacterial infections are often seen in patients with viral pneumonia, with Staphylococcus aureus being the commonest pathogen in Influenza A and influencing prognosis. MRSA (methicillin resistant staph aureus) and Stenotrophomonas maltophilia are commonly seen in ventilated patients with Severe Acute Respiratory Syndrome. Co-trimoxazole (a combination of trimethoprim and sulphamethoxazole) has anti-folate and bactericidal properties, and is indicated for the treatment of hospital acquired pneumonia in the UK. It is effective against a number of microorganisms including Methicillin sensitive Staphylococcus Aureus (MSSA), Methicillin resistant Staphylococcus Aureus (MRSA), Klebsiella pneumoniae, Haemophilus influenzae B and Stenotrophomonas maltophilia. Trimethoprim is licensed for the treatment of respiratory tract infections in the UK and has comparable efficacy with a better safety profile than cotrimoxazole and both drugs may have anti-inflammatory effects. The medical literature contains case reports describing clinical recovery after the Middle East Respiratory Syndrome (MERS) with acute respiratory distress following the use of cotrimoxazole [6-10]. Here we report our observations with trimethoprim and cotrimoxazole added to standard therapy in patients with severe COVID-19 compared with historical data from record reviews of patients with confirmed severe COVID-19 receiving standard therapy alone.

Case series: Methods

We retrospectively analysed case series data obtained from electronic case records of patients admitted to our hospital trust between 17 March 2020 and 18 April 2020. These patients were not eligible for the UK National Recovery Trial at the time of initiation of cotrimoxazole or trimethoprim. Data was collected, anonymized and stored securely for later review. Patients admitted with increasing fever, cough and breathlessness were commenced on standard therapy of clarithromycin and benzyl penicillin for possible super infection secondary to COVID-19 as per hospital guidelines. Chest-X-rays (± CT chest scans) confirmed lung infiltrates in a pattern consistent with a radiological diagnosis of COVID-19. All patients met the WHO criteria for severe COVID-19 on clinical grounds and oxygen saturations < 90% on room air at rest [11]. Patients demonstrating a poor initial response to standard therapy (within 24-72hrs of admission) were considered to be at risk of further deterioration due to increasing fevers and oxygen requirements were given either oral Cotrimoxazole (CTX; 160mg of trimethoprim and 800mg sulphamethoxazole) 12hrly (n=4) or oral Trimethoprim (TMP; 200 mgs) 12hrly (n=18) for 5 days following discussion of their condition and our concerns about further deterioration. This followed the General Medical Council guidance on good medical practice and was used in accordance with the patient's best interests in order to reduce the risk of mortality from possible staph aureus super-infection along with any additional anti-inflammatory effects of these drugs to offset the risk of severe ARDS [12]. The clinical data from the 22 patients who received additional trimethoprim or cotrimoxazole were analysed. Of these 15 patients (68%) subsequently tested positive for COVID-19. Historic data from anonymized record reviews selected a further 22 patients with confirmed COVID-19 of comparable severity who received standard antibiotic therapy alone (ST) for a comparison. Mortality and progression to ventilatory support, lengths of hospital stay and changes in C-reactive protein, body temperature and oxygen requirements were compared. Most admitted patients had been shielding for 7 or 8 days at home and were admitted because they were increasingly unwell. "Day 0" was time of initiation of trimethoprim or cotrimoxazole and was generally within 24-72hrs of hospital admission. For patients receiving standard therapy alone, "Day 0" corresponded with the first 24hr time period following admission, when oxygen requirements and severity matched those of the patients who commenced TMP OR CTX. Comorbidities for all patients were recorded.

Ethics and Patient Consent

The anonymized case series presented from this retrospective review and comparison of cases did not require R&D approval or patient consent. The COVID-19 pandemic waived usual research approvals in the UK until Sept 30th 2020 [12].

Statistical Analysis

Data is presented using mean and standard deviation. Comparisons between the two groups of patient were by Mann Whitney U test and Wilcoxon signed rank test for non-parametric data as indicated on the tables. Categorical data is presented as the number or percentage of patients between the 2 groups with statistical methods used indicated on the tables. Survival was assessed by the Kaplan–Meier method. Comparisons between two groups were performed using the log-rank test. A p-value of < 0.05 was considered to be significant. The statistical software SPSS was used for the analysis.

Funding and approval

No funding was involved in this case series and the authors declare no conflict of interests.

Case series: Results

Baseline characteristics from anonymized record reviews are shown (table 1) for standard therapy patients and those with TMP or CTX added to standard therapy. The patient groups were comparable for mean age, sex, ethnic group, diabetes, chronic lung disease, ischaemic heart disease and chronic kidney disease. Hypertension was lower in the TMP or CTX added group at 14% compared with standard therapy at 50%. A raised BMI >35 was present in 23% of the TMP/CTX group compared with 14% for ST group. Baseline observations were similar for oxygen requirements (FiO_2), respiratory rate, C-reactive protein, body temperature and lung infiltrates (table 1). All patients had neutrophil to lymphocyte ratios (NLR) >7.3, with a NLR ratio >3.3 considered a poorer prognosis. The SpO_2/FiO_2 ratio (peripheral oxygen saturations ÷ inspired oxygen fraction) correlates with acute lung injury, with likely ARDS associated with a ratio below 315 in non-ventilated patients. For both patient groups this ratio was <250, confirming the clinical impression of ARDS [13,14]. At 48hrs (table 2) patients with added TMP or CTX showed a significant reduction in fevers, C- reactive protein, respiratory rate and oxygen requirements (FiO2). The SpO_2/FiO_2 ratio had also improved to a mean of 320 consistent with improvement. The standard therapy patients showed no overall changes in any of these parameters (table 2**).**

Table 1: Baseline characteristics of patients with severe COVID-19 receiving trimethoprim (TMP) or cotrimoxazole (CTX) with standard therapy or standard therapy antibiotic therapy only

Table 1 baseline data	TMP/CTX + standard therapy	Standard therapy alone	p-value*
+ Subjects	22	22	
Age, mean (range)	59 (26-93yr)	60 (40-80)	0.760
Male	59%	68%	0.531
***Ethnicity**			
Asian	23%	14%	0.615
Afro-Caribbean	9%	9%	
Mixed	13%	5%	
Caucasian	55%	72%	
***Comorbidities**			
Hypertension	14%	50%	0.010
Diabetes Mellitus	18%	27%	0.472
Ischemic Heart Disease	9%	14%	0.635
Chronic obstructive pulmonary disease	23%	9%	0.412
Chronic kidney disease > 2	9%	23%	0.412
BMI % of cases >35	23%	14%	0.52
Baseline observations: Day 0			
+ Clinical parameters	mean ± SD	mean ± SD	
Days from admission to Day 0	3 ± 3	1 ± 3	0.180
Fraction of inspired oxygen (FiO_2)	0.45 ± 0.17	0.44 ± 0.10	0.760
Oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratio	244 ± 97	220 ± 49	0.690
Respiratory rate (breaths/min)	24 ± 9	21 ± 5	0.952
Body temperature (°C)	37.6 ± 0.8	37.8 ± 1	0.638
C-Reactive Protein (mg/L)	120 ± 74	148 ± 74	0.307
*Neutrophil Lymphocyte ratio (NLR)	7.8 ± 9.8	7.4 ± 2.4	0.029
% of subjects with infiltrates on the Chest X-Ray	91%	100%	0.488
Comparison between continuous variables and categorical variables was made by the + Mann-Whitney U Test and *Fishers exact test. A p-value of <0.05 was considered statistically significant. +SD= Standard Deviation			

Table 2: Primary outcomes and observations on day 0 and day 2 in patients with severe COVID-19 receiving trimethoprim (TMP)/cotrimoxazole (CTX) with standard therapy or standard therapy alone

Table 2 Primary Outcomes			
***Outcome Measures, Number of cases (%)**	**TMP/CTX + standard therapy**	**Standard therapy alone**	**p-value***
Discharged	21 (95%)	15 (68%)	0.416
Died	1(5%)	7 (32%)	0.046
Ventilatory support	3 (14%)	16 (73%)	<0.001
Continuous positive airway pressure	2 (9%)	11(50%)	0.001
Mechanical ventilation	1 (5%)	5 (23%)	0.185
+ Length of stay in days (mean ± SD)	9 ± 4	22 ± 13	<0.001
Observations on Day 0 and Day 2: TMP/CTX + standard therapy (number of cases =22)			
	mean ± SD	mean ± SD	
Clinical parameters	Day 0	Day 2	p-value
+ Fraction of inspired oxygen (FiO_2)	0.45 ± 0.17	0.33 ± 0.13	0.001
+ Oxygen saturation/fraction of inspired oxygen (SpO_2/FiO_2) ratio	244 ± 97	320 ± 104	<0.001
+ Respiratory rate (breaths/min)	24 ± 9	20 ± 2	0.035
+ Body temperature (°C)	37.6 ± 0.8	36.7 ± 0.6	0.001
+ C-Reactive Protein (mg/L)	120 ± 74	69 ± 42	0.002

Observations on Day 0 and Day 2: Standard therapy alone (number of cases =22)			
	mean ± SD	mean ± SD	
Clinical parameters	Day 0	Day 2	p-value
+ Fraction of inspired oxygen (FiO2)	0.44 ± 0.10	0.44 ± 0.14	0.864
+ Oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratio	220 ± 49	241 ± 98	0.286
+ Respiratory rate (breaths/min)	21 ± 5	21 ± 5	0.965
+ Body temperature (°C)	37.8 ± 1	37.2 ± 0.9	0.097
+ C-Reactive Protein (mg/L)	148 ± 74	186 ±104	0.040
*Comparison using Wilcoxon Signed ranks test, +Mann-Whitney U test and *Fishers exact test. A p-value of <0.05 was considered statistically significant. +SD = standard deviation			

Figure 1 shows day-0 to day-5 changes (means, standard deviation and 95% confidence intervals) for oxygen requirement FiO2, SpO_2/FiO_2 ratio, body temperature and C- reactive protein. This demonstrated continuing improvement for patients receiving TMP or CTX in addition to standard therapy. While ST only cases showed only a reduction in body temperature, but oxygen requirement FiO_2, CRP and SpO_2/FiO_2 ratios remained unchanged. 21 out of 22 patients with added TMP or CTX were discharged well without oxygen after a mean stay of 9 days (table 2), there was one death (4.5%) due to ARDS occurring at day 6 following admission with mechanical ventilation at day 4. Data from the patients receiving standard therapy alone, showed that 7 patients died (32%) from ARDS with a mean time to death following admission of 7 days (IQR range 5-20 days). The mean length of hospital stay for the 15 surviving ST patients was 22 days. UK data suggests that mortality for ventilated patients with COVID-19 was 33% at that time period [6]. Figure 2 shows the Kaplan Meier plot for survival versus days from admission for the 2 groups of patients (standard therapy only (ST) and TMP/CTX with ST). Follow-up CXR (taken 8-12 weeks after discharge) for 18 patients in the CTX/TMP group showed 16 were now clear of infiltrates with 2 improving with 3 CXR still pending. For the 15 surviving ST patients, CXR (taken 8-12 weeks after discharge) showed 10 had resolution of changes, with 3 improving with 2 patients CXR still pending.

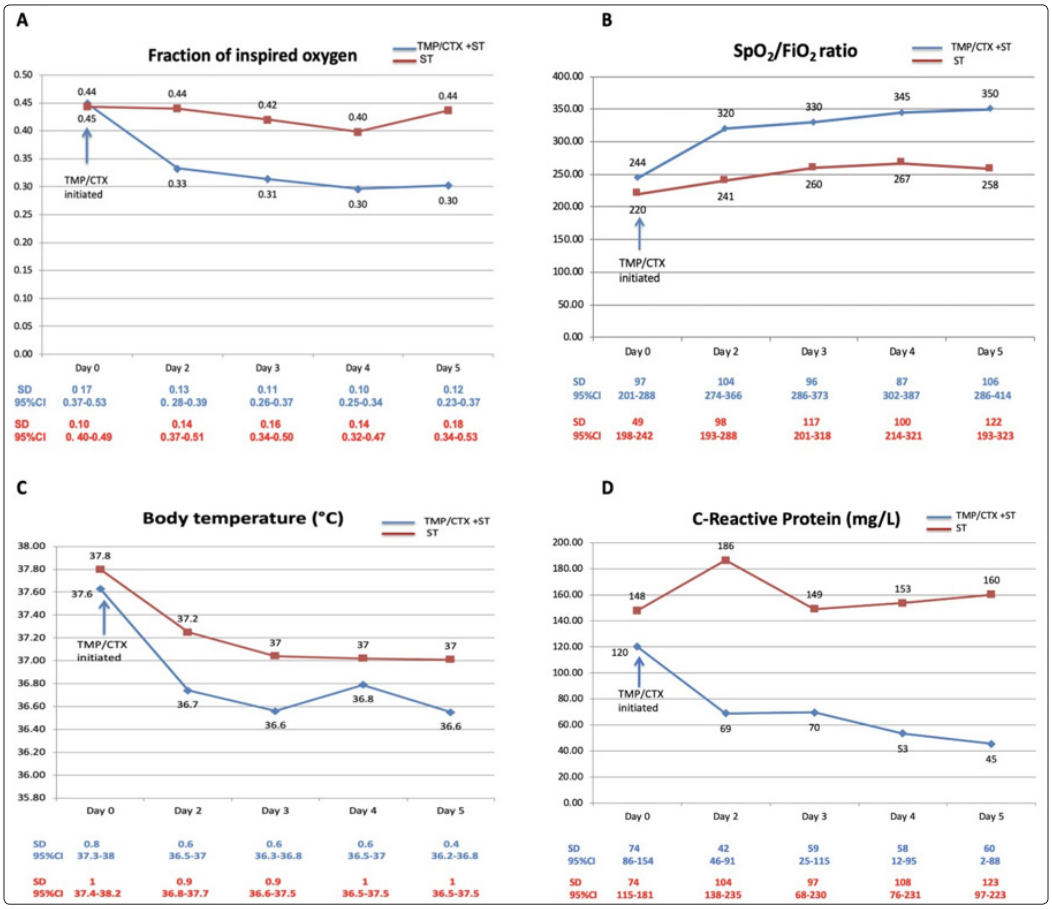

Figure 1: Observations between Day 0 and Day 5 in patients with severe COVID-19 receiving Trimethoprim (TMP) or Co-trimoxazole (CTX) with standard therapy (ST) or ST alone: A) Fraction of inspired oxygen (FiO_2), B) SpO_2 /FiO_2 ratio, C) Body temperature and D) C-Reactive Protein

Definition of abbreviations: Figure 1

SpO_2=peripheralcapillaryoxygensaturation;SD=standarddeviation;95%CI=95%confidence interval;
Data represents mean ± SD(standard deviation) and 95% CI(confidence intervals)

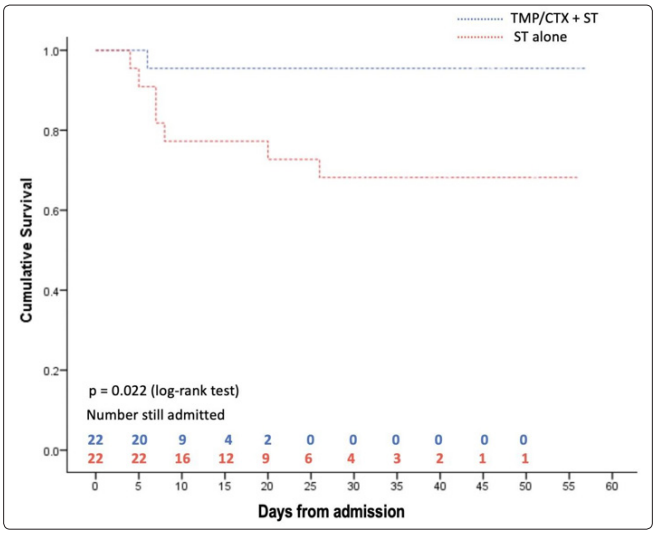

Figure 2: Kaplan-Meier estimates of survival from date of admission comparing outcomes in patients with severe COVID-19 receiving Trimethoprim (TMP) or Co-trimoxazole (CTX) with standard therapy (ST) or ST alone

Discussion

Data presented suggests that the addition of oral TMP or CTX may reduce acute lung injury in patients with severe COVID-19, thereby reducing the need for ventilatory support and improving outcomes. The ST cases as a comparison group are open to criticism, as they were not randomised which increases bias, but this data indicates the need for further investigation. TMP/CTX has no direct anti-viral effects but may offer protection against ARDS from their antimicrobial, anti-inflammatory and immunomodulatory effects. The beneficial effects of TMP/CTX were apparent within 12 hours of the first dose, likely reflecting their excellent absorption and lung penetration. ARDS is a life-threatening complications of COVID-19 thought to be associated with a hyper-immune response to the virus. Co-trimoxazole and trimethoprim block stimulation of the formyl peptide receptors (FPR's) which are abundantly expressed on the surface of circulating neutrophils and monocytes and normally regulate their function [15-19]. When FPR's are stimulated, they trigger the release of both intracellular and extracellular Reactive Oxygen Series (ROS) which can in turn drive cytokine production both inside and outside the neutrophil. Released ROS can further activate the surface FPR's causing an escalating inflammatory response or cytokine storm. The FPR's are linked to the homing of neutrophils and monocytes to the lung, where high levels of ROS can stress the neutrophil and cause it to undergo neutrophil NETosis [17,18]. In this process, highly stressed neutrophils extrude their nuclear content as Neutrophil Extracellular Traps (or NETs) that form 'external nets' in an attempt to trap and kill infectious agents; but platelets, debris , fibrin and other cells can become trapped and block off the pulmonary alveolar bed as seen in post mortems from COVID-19 patients [20]. Neutrophil nets have a high procoagulant potential that could explain the microvascular thrombosis seen in lungs, heart and kidney and brain in COVID-19, leading to the risk of hypoxic injury and death Excessive neutrophil and platelet activation gives dysregulated immuno-thrombosis and microvascular thrombi with neutrophil NETosis now recognised in recent post-mortem data [16,18-21]. The ability of cotrimoxazole and trimethoprim to block this process via the FPR's could reduce or reverse these escalating immune processes and protect the lung from injury. Published data shows that cotrimoxazole has anti-cytokine effects reducing interleukin-1, 2, 6, 8 and tumour necrosis factor-α production [22-24].Several of these cytokines are shown to be raised in the cytokine storm associated with COVID-19. This offers a possible explanation for the observed clinical benefit of these drugs in reducing Immune system activation leading to a reduction in the risk of ARDS [22-24]. Timely recognition of any clinical deterioration due to an escalating cytokine storm syndrome is important, as delayed treatment may reduce the ability of these drugs to act before blockade of the alveolar capillary bed by neutrophil NETosis and fibrin clots occur, with the risk of profound hypoxemia that may be difficult to reverse. Trimethoprim or cotrimoxazole are inexpensive drugs indicated for use in respiratory infections and are available worldwide and may have benefit in preventing acute lung injury in this pandemic. Cotrimoxazole may have advantages over trimethoprim due to the additional anti-inflammatory effects of sulphamethoxazole along with an intravenous preparation for use in deteriorating patients.

Conclusion

These observations require confirmation in a larger group of patients with severe COVID-19 infections, so benefit to mortality and the need for ventilatory support may be fully assessed along with the potential to save many thousands of lives worldwide. To date a randomized control trial with cotrimoxazole in severe COVID-19 has commenced (ClinicalTrials.gov Identifier NCT04470531) and results are awaited [25].

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