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BRIEF REPORT

Rapid Implementation of a Multidisciplinary COVID-19 Cytokine Storm Syndrome Task Force

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Objective. Patients with coronavirus disease 2019 (COVID-19) can progress to a state of unregulated inflammation called cytokine storm syndrome (CSS). We describe formation and operation of a COVID-19 multidisciplinary consultation service that was allowed to individualize treatment for critically ill patients with COVID-19 during the pandemic.

Methods. Institutional experts from different subspecialties formed a COVID-19 CSS task force at Montefiore Medical Center, Bronx, NY. They agreed on a set of four clinical and six laboratory parameters that can help early identify COVID-19 CSS. We describe the formation and implementation of the COVID-19 task force. The case series description of the COVID-19 CSS consultation cohort highlights consultation volume, baseline characteristics, clinical and laboratory parameters, and how biologic treatments were allocated to these patients.

Results. Between April 4,2020, and May 7,2020, the COVID-19 CSS task force was formed, consisting of adult and pediatric rheumatologists and allergy and immunology physicians. The task force evaluated a total of 288 patients, of whom 197 (68%) were male, the median (interquartile range [IQR]) age was 62 (51-70) years, 122 (42%) were Hispanic, and 88 (31%) were Black or African American. The common presenting symptoms in all referred patients were dyspnea (85%) and diarrhea (80%). Thirty-one patients who received biologic therapy were younger, with a median (IQR) age of 53 (32-63) years, as opposed to 62.5 (52-70) years in the nonbiologic group ($P = 0.008$). A higher proportion receiving biologics was in the critical care setting (26 [84%] vs 151 [59%]; $P = 0.006$).

Conclusion. To the best of our knowledge, this is the first multidisciplinary collaborative effort to provide individualized patient recommendations for evaluation and treatment of patients with COVID-19 who may have CSS. This working model helped to devise an approach that may have identified patients who were most likely to benefit from biologic therapy in the absence of evidence-based guidelines.

INTRODUCTION

As of December 2020, severe acute respiratory syndrome coronavirus 2 has affected more than 9.2 million individuals in the United States (1). New York City has become an epicenter for coronavirus disease 2019 (COVID-19), with more than 269,000 cases and 24,013 deaths (2). In May 2020, Bronx County, with 2921 positive cases per 100,000, had the highest proportion of cases in New York City (2); and a majority of the hospitalized patients in this borough were treated at Montefiore Medical Center (MMC).

COVID-19 has a wide spectrum of presentations, from mild upper respiratory symptoms, to adult respiratory distress syndrome, to an exaggerated inflammatory response due to unregulated cytokine release termed cytokine storm syndrome (CSS) (3,4). A multidisciplinary approach is needed to address these presentations because of the complexity and multisystem involvement of the syndrome (3). COVID-19 CSS shares many similar features with secondary hemophagocytic lymphohistiocytosis (sHLH), in that an exaggerated inflammatory state causes multiorgan failure. Rheumatology and allergy and

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATION

- We summarize our novel approach and experience in the formation and functioning of a coronavirus disease 2019 (COVID-19) cytokine storm syndrome (CSS) task force at the peak of the first wave of the COVID-19 pandemic, with the goal of early identification of patients progressing toward COVID-19 CSS and provision of timely management
- Rheumatologists and Allergy and Immunology (AI) physicans have expertise in treating CSS and using biologic therapy, their perspective and input in the management of COVID-19 cytokine storm is valuable.
- Between April 4, 2020, and May 7, 2020, the CSS task force evaluated a total of 288 patients for possible COVID-19 CSS. This multidisciplinary initiative allowed us to triage consultations quickly and to individualize treatments for each patient in the absence of evidence-based guidelines.

immunology (AI) physicians are well versed in managing sHLH and have an in-depth understanding of this immune-mediated disease process.

Although there is currently no proven immunomodulatory treatment for COVID-19 infection, the utility of interleukin-6 (anti IL-6) and interleukin-1 inhibitors (anti IL-1) have been studied in COVID-19-CSS, with preliminary encouraging results (5,6). Recognizing the role of rheumatologists and AI physicians in managing immune-mediated complications of COVID-19, a multidisciplinary task force was formed at MMC in the Bronx, NY, to assist in the management of patients with COVID-19 CSS.

Here, we summarize our novel approach and experience in the formation and functioning of a COVID-19 CSS task force. The task force consisted of adult and pediatric rheumatologists and AI, infectious disease (ID), and critical care medicine (CCM) physicians, and the goal of the task force was to provide recommendations for COVID-19 CSS. This collaborative, multidisciplinary initiative allowed us to triage consultations quickly and individualize treatments for each patient in the absence of evidence-based guidelines.

MATERIALS AND METHODS

Formation and launching of the COVID-19 CSS task force/consultation service. On March 20, 2020, MMC doubled its hospital capacity to accommodate for the surge of patients with COVID-19 at three adult hospitals and one children's hospital. Subsequently, adult and pediatric rheumatology and AI divisions started receiving consultations for CSS secondary to COVID-19. Anticipating a large consultation volume for COVID-19 CSS, a process was urgently needed to evaluate these patients. The CSS task force was immediately created within a week, and criteria for early identification of COVID-19 CSS were developed by institutional experts from adult and pediatric rheumatology and AI.

Table 1. Clinical and laboratory parameters based on consensus recommendations of the COVID-19 CSS task force

Clinical parameters	Laboratory parameters
Persistent fever ≥101°F for 48 hours	Ferritin level ≥1000 μg/l
Systolic BP ≤90 (not responding to IV fluids)	CRP level ≥30 mg/dl or change in CRP level ≥15 mg/dl
PaO_2/FIO_2 ≤200 in intubated patients or increasing oxygen requirement in nonintubated patients	AST level ≥150 IU/l
...	Hemoglobin level ≤9 g/l
...	Platelet count ≤100,000/μl
...	Absolute neutrophil count ≤7700/μl

Abbreviations: AST, aspartate aminotransferase; BP, blood pressure; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CSS, cytokine storm syndrome; FIO_2, fraction of inspired oxygen; IV, intravenous.

The task force reviewed the available literature to decide on the parameters to guide the early diagnosis and management of COVID-19 CSS. Because there are many known similarities between sHLH and COVID-19 CSS, the task force considered parameters from the scoring systems used in the hemophagocytic lymphohistiocytosis (HLH) 2004 criteria and 2014 H-Score (7–9). ID and CCM specialists within the task force discussed their early clinical experience in caring for critically ill patients with COVID-19 and added additional parameters seen in patients suspected of having CSS that may not be reflected in sHLH scoring systems.

By consensus, a set of four clinical parameters and six laboratory parameters were identified to provide a framework for early identification of patients with COVID-19 believed to be progressing toward CSS (Table 1). Laboratory parameters, such as IL-6, D-dimer, lactate dehydrogenase, and procalcitonin, were considered but excluded on the basis of a lack of specificity, processing time, unclear clinical significance, and cost. The task force members agreed that these clinical and laboratory parameters would be reviewed periodically and that amendments could be made to these criteria in the future with availability of more information.

During the pandemic, the health care teams taking care of patients with COVID-19 were made aware of these criteria through the daily hospital communication emails that included COVID-19–related updates. The inpatient teams followed these criteria for early identification of patients progressing toward CSS and timely consultation with the CSS task force for further evaluation and management. On April 4, 2020, within 2 weeks of convening, the COVID-19 CSS task force officially started operating as a consultation service. The case series discussion of the COVID-19 CSS consultation cohort highlights the consultation volume, baseline characteristics, clinical and laboratory parameters, and how biologic treatments were allocated to these patients. This project was approved by the Albert Einstein College of Medicine Institutional Review Board.

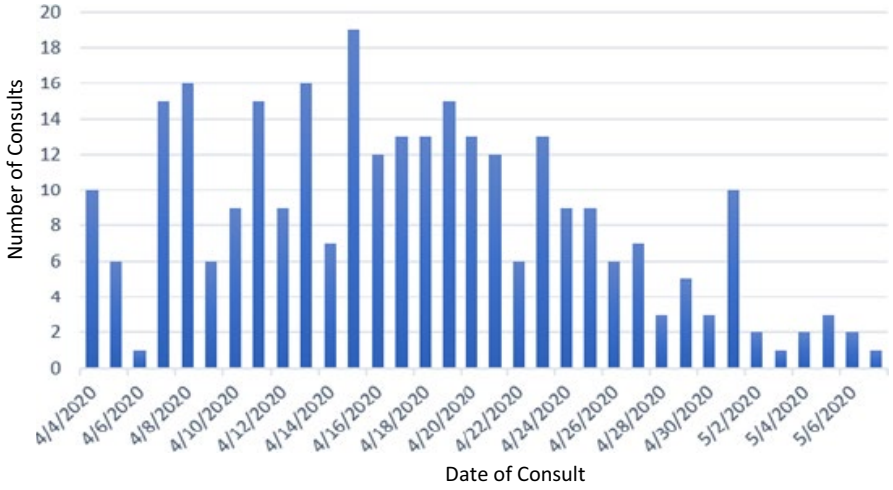

Figure 1. Total number of consultations for COVID-19 CSS task force.

Statistical analysis. Descriptive statistics were used to describe clinical, demographic, and COVID-19–related characteristics of the electronic consultations (e-consultations) evaluated by the CSS task force. Univariate statistics were used to compare patients who were recommended to receive biologic therapy with those who were not recommended to receive biologic therapy. Wilcoxon–Mann–Whitney tests were used to compare continuous variables. Pearson's χ^2 tests (or Fisher's exact test when appropriate) were used to compare categorical variables. Statistical analyses were performed by using Stata statistical software (version 15; StataCorp LLC).

RESULTS

Formation and implementation of the COVID-19 CSS task force experience. On April 4, 2020, a CSS e-consultation order was created in our electronic health record to streamline the workflow. These were completed as e-consultations per MMC policy during the COVID-19 pandemic. Every e-consultation was reviewed by a subspecialist (rheumatology or AI) and discussed in a daily multidisciplinary virtual conference. The primary consulting physician gathered information on the basis of a chart review and discussions with the primary team. The information presented at these conferences included clinical status, clinical and laboratory parameters, medications, and prognosis. Based on this information, consensus recommendations were made regarding steroid therapy or IL-6 or IL-1 inhibitor therapy, if deemed appropriate. All biologic therapy recommended by the CSS task force required a final review and approval from a designated physician from ID or CCM.

Initially, all e-consultations were discussed during conference calls, but later, as consultants became more familiar with the presentations, only complicated patients were discussed. This was important as the number of e-consultations increased, and it was necessary to adapt to the challenging additional responsibilities and deployment of some of the subspecialists to COVID-19 units.

As time progressed, the CSS task force consultants developed more experience evaluating and managing patients with COVID-19 CSS. As our consultation numbers increased, we modified our working flow to confine our conference call discussions to patient who were admitted to the critical care units on mechanical ventilation and pressor support and those patients who had secondary infections.

COVID-19 CSS consultation cohort. Between April 4, 2020 and May 7, 2020, the CSS task force evaluated a total of 288 patients for possible COVID-19 CSS (Figure 1). The CSS task force evaluated 288 patients of which, 197 (68%) were male, median (interquartile range [IQR]) age was 62 (51-70) years, 122 (42%) were Hispanic, and 88 (31%) were Black or African American. The common presenting symptoms in all referred patients were dyspnea (85%) and diarrhea (80%). Two hundred five (71%) patients had symptoms for less than or equal to 7 days. One hundred seventy-one (59%) patients had preexisting hypertension, and 133 (46%) had diabetes (Table 2). The median (IQR) body mass index was 29.5 (25-34). At the time of consultation,177 (61%) patients were admitted to the critical care units; 177 (61%) were on mechanical ventilation, 113 (46%) required vasopressor support, and 60 (21%) required new-onset renal replacement therapy.

The CSS task force recommended biologic therapy for 31 patients (11%). Patients who received biologic therapy were younger compared with patients who did not (median [IQR] age: 53 [32-63] years vs 63 [52-70] years; $P = 0.008$). A higher proportion of patients who received biologics were in the critical care setting (26 [84%] vs 151 [59%]; $P = 0.006$) and on mechanical ventilation (26 [84%] vs 146 [57%]; $P = 0.003$) and vasopressors (22 [71%] vs 111 [43%]; $P = 0.003$). Patients who received biologics were more likely to have a higher median (IQR) C-reactive protein value (24 [14-29] mg/dl vs 16.8 [9-27] mg/dl; $P = 0.027$) and a longer median (IQR) duration of steroid therapy (12.5 [6-15] days vs 8 [5-12] days; $P = 0.01$). There was no difference in the

Table 2. Characteristics of COVID-19 patients evaluated by the CSS task force

Variable	Total (N = 288)	Biologic therapy (n = 31)	No biologic therapy (n = 257)	*P*
Age, median (IQR), years	62 (51-70)	53 (32-63)	62.5 (52-70)	0.01
Male sex, No. (%)	197 (68)	22 (71)	175 (68)	0.75
Ethnicity, No. (%)				0.63
Non-Hispanic	149 (52)	15 (48)	134 (52)	...
Hispanic	122 (42)	13 (42)	109 (42)	...
Race, No. (%)				0.56
Black or African American	88 (31)	9 (29)	79 (31)	...
White	25 (9)	1 (3)	24 (9)	...
Asian	24 (8)	2 (6)	22 (9)	...
Presenting symptoms, No. (%)				
Subjective fever	197 (68)	26 (84)	171 (67)	0.05
Cough	188 (65)	20 (65)	168 (65)	0.86
Dyspnea	245 (85)	27 (87)	218 (85)	0.74
Hyperglycemia	109 (38)	16 (52)	94 (37)	0.21
Acute kidney injury	116 (40)	13 (42)	103 (40)	0.86
Diarrhea	230 (80)	5 (16)	51 (20)	0.81
Duration of presenting symptoms prior to hospital admission, No. (%)				0.87
≤7 days	205 (71)	21 (68)	184 (72)	...
>7 and ≤14 days	64 (22)	8 (26)	56 (22)	...
>14 days	19 (7)	2 (7)	17(7)	...
Comorbidities, No. (%)				
Diabetes mellitus	133 (46)	9 (29)	124 (48)	0.04
Hypertension	171 (59)	14 (45)	157 (61)	0.08
Respiratory illness (asthma, COPD, or ILD)	37 (12.8)	2 (6.5)	35 (14)	0.26
ESRD, on dialysis	32 (11.1)	3 (9.7)	29(45.8)	0.79
Liver cirrhosis	3 (1.)	0	3 (1.2)	0.54
Rheumatic illness	17 (5.9)	2 (6.5)	15 (5.8)	0.88
Active malignancy	14 (4.8)	1 (3.2)	13 (5.1)	0.66
History of organ transplant	17 (6)	3 (10)	14 (5)	0.4
HIV, on treatment	6 (2)	0	6 (2)	0.65
Cognitive impairment	20 (7)	6 (19)	14 (6)	<0.01
Clinical features during current admission, No. (%)				
DVT	20 (7)	1 (3)	19 (7)	0.39
PE	9 (3)	2 (7)	7 (3)	0.26
CVA including hemorrhagic stroke and ischemic stroke	15 (5)	1 (3)	14 (5)	0.60
Required ICU admission	177 (61)	26 (84)	151 (59)	0.01
Persistent fever >101 F	81(28)	16 (52)	65 (25)	<0.01
Fever >40.6°C	6 (2)	1 (3)	5 (2)	0.64
Oxygen requirement				
Non-rebreather mask	71 (25)	4 (13)	67 (27)	0.23
High-flow nasal canula	47(16)	4 (13)	43 (17)	0.51
Mechanical ventilation	172 (60)	26 (84)	146 (57)	<0.01
Hypotension (SBP <90 mm Hg), on vasopressors	113 (46)	22 (71)	111 (43)	<0.01
Laboratory parameters at time of consultation, median (IQR)				
Ferritin, ng/ml	1491 (904-2847)	1818 (821-2909)	1456.5 (905.5-2842.5)	0.55
C-reactive protein, mg/dl	17.6 (9.5-27)	24 (14-29)	16.8 (8.9-26.8)	0.03
Absolute neutrophil count, ×1000/mm^3	11 (7.1-15.5)	12.4 (7.9-17)	10.8 (7-15)	0.28
Absolute lymphocyte count, ×1000/mm^3	0.8 (0.5-1.1)	0.7 (0.5-1.0)	0.8 (0.5-1.1)	0.61
Hemoglobin, g/L	11.2 (9.9-13.2)	11.9 (10.7-13.7)	11.2 (9.7-13.2)	0.19
Platelet count, ×1000/μl	249 (173-332)	271 (170-374)	246.5 (175-329)	0.52
Aspartate Aminotransferase, IU/l	49 (30-83)	41 (28-58)	47 (29.5-81)	0.05
Procalcitonin, ng/ml	1 (0.2-5.2)	0.9 (0.2-3.9)	1 (0.2-5.7)	0.74
LDH, U/L	576 (439-783)	577 (461-831)	574 (439-781)	0.96
IL-6, pg/ml	61.2 (24.4-156.2)	85.9 (40.6-164.6)	24.3 (14.9-155.3)	0.21
Patients with a reported D-dimer level >3 μg/ml, No. (%)	184 (66)	17 (59)	167 (67)	0.4
CSS consultation steroid recommendations, No. (%)				0.361
No steroids	61 (21)	5 (16)	56 (22)	...
Continue same steroid regimen	133 (46)	17 (55)	116 (45)	...
New steroid initiation	49 (17)	8 (26)	41 (16)	...

(Continued)

Table 2. (*Cont'd*)

Variable	Total (N = 288)	Biologic therapy (n = 31)	No biologic therapy (n = 257)	*P*
Increase steroids	16 (6)	0	16 (6)	...
Decrease steroids	29 (10)	1 (3)	28 (11)	...
Pulse steroids	1 (<1)	0	1 (<1)	...

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CSS, cytokine storm syndrome; CVA, cerebrovascular accident; DVT, deep vein thrombosis; ESRD, end-stage renal disease; IL-6, interleukin 6; ILD, interstitial lung disease; IQR, interquartile range; LDH, lactate dehydrogenase; PE, pulmonary embolism; SBP, systolic blood pressure.

two groups in terms of their comorbidities or other laboratory parameters at the time of the consultation (Table 2).

DISCUSSION

We describe a novel experience at our institution where a multidisciplinary COVID-19 CSS task force was created quickly to manage an emerging need to triage large consultation load of potential COVID-19 cytokine storm patients. In most hospitals, patients with COVID-19 are treated by hospitalist, ID, and CCM teams. The patient surge during the pandemic has stretched their working limits. At MMC, we used a collaborative approach and involved our multispecialty expertise to decide on the parameters for early identification of COVID-19 CSS. Because COVID-19 can lead to an uncontrolled inflammatory response, involvement of rheumatology and AI adds an important perspective in managing this subset of patients at risk of CSS. During the pandemic, when resources and biologic supplies were limited and costly, the task force played a critical role by evaluating patients in a judicious and careful way to identify those thought most likely to benefit from biologic therapy. Because there were no formal guidelines or recommendations for management of COVID-19 CSS, the task force helped provide individualized, timely multidisciplinary guidance.

To the best of our knowledge, this is the first multidisciplinary collaborative effort to provide individualized patient recommendations for the evaluation and treatment of patients with COVID-19 who may have CSS. This model allowed to wisely use limited resources when there were no guidelines and to efficiently manage the workload. We acknowledge that the parameters used by the task force to make recommendations were not validated in a formal fashion; however, further studies are planned to evaluate outcomes. Our hospital serves a large African American and Hispanic population, and subspecialty services of adult and pediatric rheumatology and AI are available around the clock. This may limit generalizability to other populations, cities, or hospitals. However, this was an important initiative in a high-volume center that serves a typically underserved and critically ill population. As we were able to set up this multidisciplinary task force in a busy center amidst a pandemic, this model could have its implications beyond COVID-19, for other multisystemic diseases like Steven Johnson's syndrome and HLH. The urgent need created by the pandemic led to the rapid development of a task force to manage a new disease entity with no formal guidelines.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bibi Ayesha had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ayesha, Broder, Kumthekar, Wahezi, Rubinstein, Ramesh.

Acquisition of data. Ayesha, Kumthekar, Jain, Patel, Ramesh, Ferastraoaru, Hudes, Karagic, Zafar, Bartash, Vasquez-Canizares, Kitsis, Tagoe, Wahezi, Rubinstein, Broder.

Analysis and interpretation of data. Broder

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