CHEST Online Supplement

Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized Patients With Coronavirus Disease 2019

Survival and Clinical Outcomes

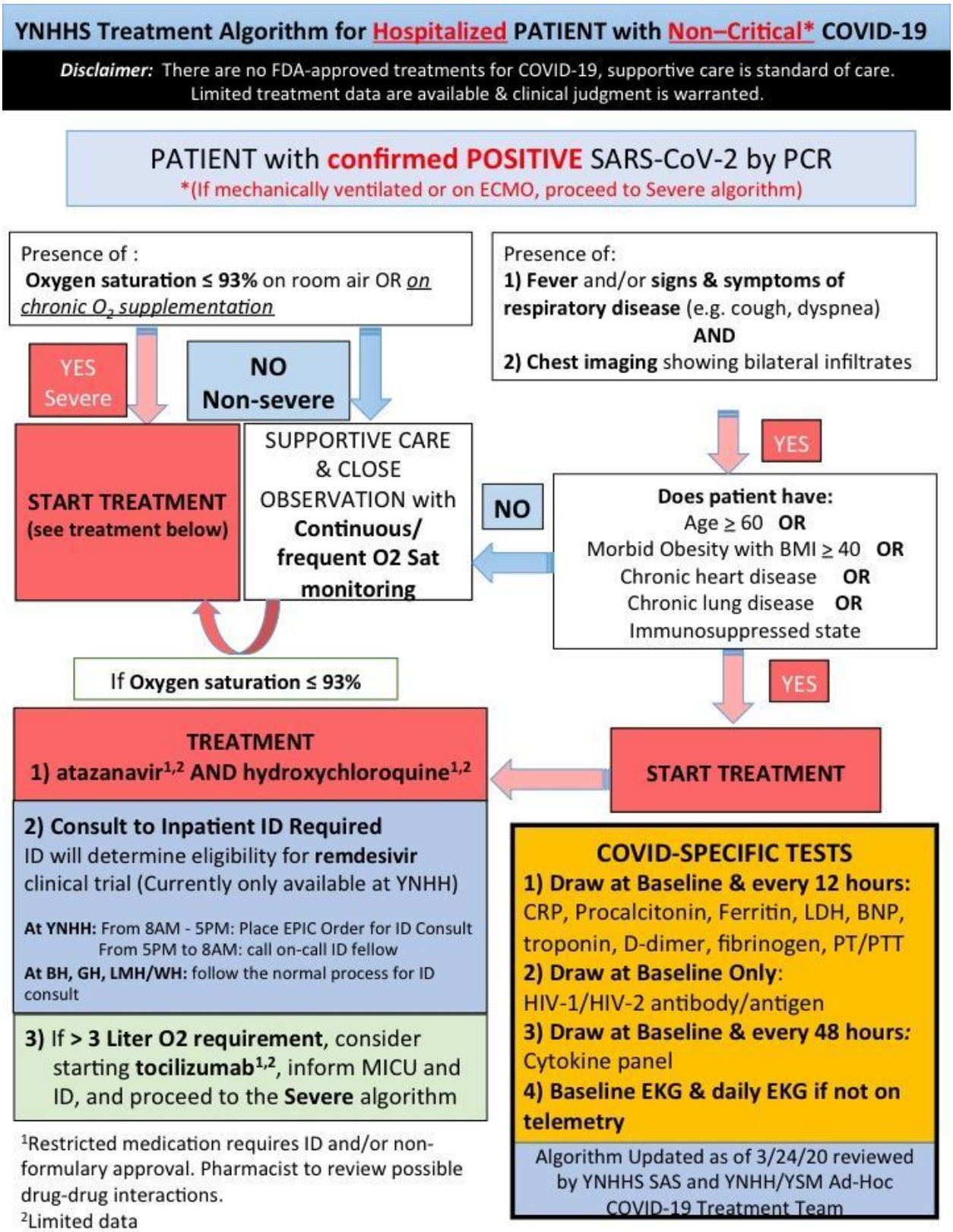
Christina C. Price, MD; Frederick L. Altice, MD; Yu Shyr, PhD; Alan Koff, MBBS; Lauren Pischel, MD; George Goshua, MD; Marwan M. Azar, MD; Dayna Mcmanus, PharmD; Sheau-Chiann Chen, PhD; Shana E. Gleeson, MD; Clemente J. Britto, MD; Veronica Azmy, MD; Kelsey Kaman, MD; David C. Gaston, MD, PhD; Matthew Davis, PharmD; Trisha Burrello, MS; Zachary Harris, MD; Merceditas S. Villanueva, MD; Lydia Aoun-Barakat, MD; Insoo Kang, MD; Stuart Seropian, MD; Geoffrey Chupp, MD; Richard Bucala, MD, PhD; Naftali Kaminski, MD; Alfred I. Lee, MD, PhD; Patricia Mucci LoRusso, DO, PhD; Jeffrey E. Topal, MD; Charles Dela Cruz, MD, PhD; and Maricar Malinis, MD

CHEST 2020; 158(4):1397-1408

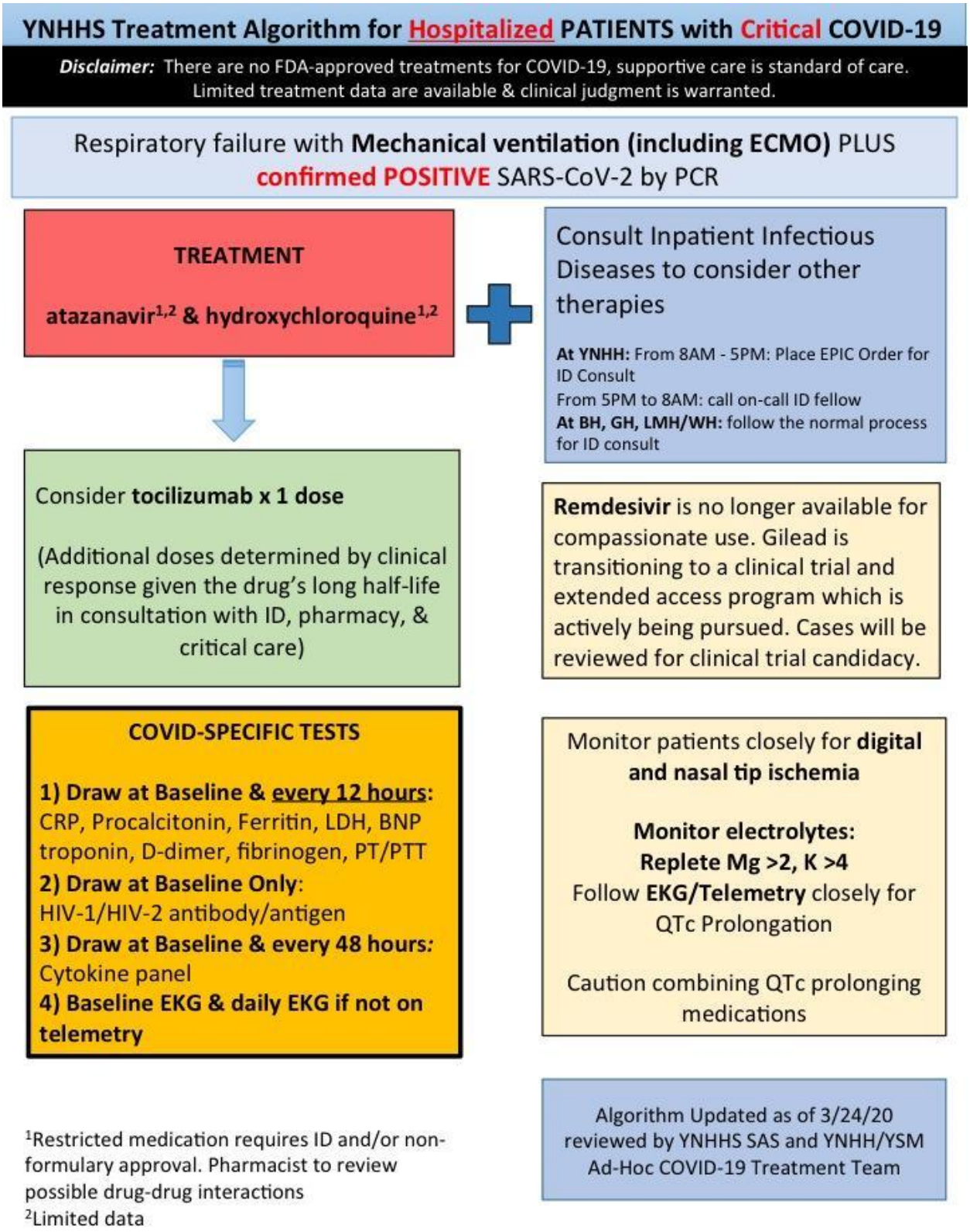
 DOI: 10.1016/j.chest.2020.06.006

CHEST Online Supplement

e-Appendix 1: Initial YNHH COVID-19 Treatment algorithm*



CHEST™ Online Supplement



* Patients who began to develop findings of CRS, evidenced by increased oxygenation needs, markedly elevated or increasing hsCRP levels, could also receive tocilizumab.

e-Appendix 2: Risk factors Supplemental and definition of Immunosuppression

Age ≥ 60, BMI ≥ 40

Hypertension

Diabetes

Chronic heart disease

Chronic lung disease

Immunosuppressed: Cancer treatment within 1 year, the use of immunosuppressive drugs (biologics, chronic prednisone ≥20mg daily), solid organ transplant, bone marrow transplantation, HIV/AIDS (regardless of CD4 count), leukemia, lymphoma, SLE, or vasculitis.

e-Appendix 3: Treatment protocol laboratory panel and clinical monitoring

The COVID-19 lab panel consisted of hsCRP (high sensitivity C-reactive protein), procalcitonin, ferritin, troponin, lactate dehydrogenase, pro-brain natriuretic peptide, fibrinogen and prothrombin time every 12 hours. Additionally, a baseline HIV test was ordered given the use of a single anti-retroviral agent, and a cytokine panel was drawn every 48 hours. Cytokine panel included soluble Interleukin 2 Receptor (sIL2R or CD25), Interleukin 12, Interferon gamma, Interleukin 4, Interleukin 5, Interleukin 10, Interleukin 13, Interleukin 1 beta, Interleukin 6, Interleukin 8, Tumor Necrosis Factor-alpha, Interleukin 2, and Interleukin 17. Cytokine panel tests were performed via a quantitative multiplex bead assay by a CLIA-certified diagnostic lab in Salt Lake City, Utah. Lower limit of detection was 5pg/mL. Laboratory values were included in the analysis up to twice daily (if available) if they were twelve hours apart +/- two hours; if not then a single daily value was recorded. Chest radiographs were repeated only for worsening clinical status to reduce increased exposure.

e-Appendix 4. Oxygen data entry and definitions

The admission oxygen saturation on room air from the nursing triage note was utilized. In cases where patients arrived with a new supplemental oxygen, the oxygen saturation reported by emergency medical services (EMS) was used. Patients arriving from EMS already on supplemental oxygen reporting values such as "80's on room air" could not be included for this one variable; all of these patients had reported oxygen saturations of less than 90%. Patients on chronic oxygen therapy were included in the analysis of admission oxygen saturations so long as their oxygen requirement was at their baseline at the time of measurement. Nasal cannula values with 0.5L measurements were rounded up to the nearest liter.

Scale	Oxygen Requirement
0	Room Air
1	1L nasal cannula
2	2L nasal cannula
3	3L nasal cannula
4	4L nasal cannula
5	5L nasal cannula
6	≥6L nasal cannula OR Venti mask
7	Non-rebreather
8	High flow nasal cannula OR non-invasive positive pressure ventilation
9	Intubated with FiO2 <50% and PEEP ≤5 cmH_20
10	Intubated with FiO2 ≥50% but <70% OR PEEP >5 but <15 cmH_20
11	Intubated with FiO2 ≥70% but <100% OR PEEP ≥15 but <20 cmH_20
12	Intubated with FiO2 100% OR PEEP ≥20 cmH_20
13	Extracorporeal membrane oxygenation (ECMO)

CHEST™ Online Supplement

e-Table 1: Survival at 7, 14 and 21 days

	Overall	Non-Severe	Severe
Entire Sample	**N=239**	**N=135**	**N=134**
7 days	92 (88, 96)	97 (95-100)	86 (79, 93)
14 days	86 (81, 91)	93 (88, 99)	78 (69, 87)
21 days	81 (75, 88)	91 (84, 98)	71 (61, 83)
Tocilizumab Subgroup	**N=153**	**N=59**	**N=194**
7 days	94 (90, 98)	98 (95,100)	91 (85, 97)
14 days	86 (80, 93)	92 (83, 100)	83 (75, 92)
21 days	82 (74, 90)	92 (83, 100)	75 (66, 88)
No Tocililzumab Subgroup	**N=86**	**N=76**	**N=10**
7 days	89 (83, 97)	NA	NA
14 days	87 (78, 96)	NA	NA
21 days	81 (69, 95)	NA	NA
Mechanically Ventilated Subgroup	**N=53**	**N=7**	**N=46**
7 day	78 (68, 91)	NA	NA
14 day	72 (60, 86)	NA	NA
21 day	67 (55, 82)	NA	NA

e-Table 2: Clinical consequences before and after tocilizumab administration, stratified by disease severity (N=153)

		Non-severe			Severe	
		(N=59)			(N=94)	
Variables	**N**	**Statistics**	***P* Value**	**N**	**Statistics**	***P* Value**
Maximum Temperature Change, median (95%CI)	33	-1·35 (-1·65, -1)	<0·001 [a]	76	-1·35 (-1·6, -1·1)	<0·001 [a]
Pre-TCZ Temperature °C, median (IQR)	59	38·8 (38·2, 39·3)		94	39·18 (38·35, 39·4)	..
Post-TCZ Temperature °C, median (IQR)	33	37·2 (37, 37·56)		76	37·37 (37·1, 38·23)	..
D-Dimer Change, median (95%CI)	47	0·67 (0·31, 1·3)	<0·001 [a]	82	1·09 (0·62, 1·9)	<0·001 [a]
Pre-TCZ D-Dimer, mg/L FEU, mean, median (IQR)	57	0·94 (0·56, 1·35)		87	0·98 (0·62, 1·89)	..
Post-TCZD-Dimer mg/L FEU mean, median (IQR)	47	1·53 (0·71, 3·33)		82	1·71 (0·99, 4·62)	..
Absolute Lymphocyte Count Change 1, mean median (95%CI)	47	0·03 (-0·07, 0·15)	0·54[a]	79	0·21 (0·13, 0·29)	<0·001 [a]
Pre-TCZ Absolute Lymphocyte Count 1000/microL, mean, median (IQR)	57	1·01 (0·75, 1·4)		89	0·9 (0·7, 1·2)	..
Post-TCZ Absolute Lymphocyte Count 1000/microL, mean, median (IQR)	47	1·17 (0·74, 1·59)		79	1·11 (0·86, 1·42)	..
hsCRP Change, median (95%CI)	49	-15·1 (-24·5, -5·4)	0·001[a]	82	-19·15 (-28·35, -10·6)	<0·001 [a]
Pre-TCZ hsCRP mg/L max, median (IQR)	59	131·9 (84·8, 162·1)		94	137·75 (102·15, 218·15)	..
Post-TCZ hsCRP mg/L max, median (IQR)	49	113·7 (74·9, 154·4)		82	103·2 (70·5, 188·62)	..
IL-6 Change, mean median (95%CI)	26	103·12 (66·5, 165·5)	<0·001 [a]	62	136·8 (99·0, 179·6)	<0·001 [a]
Pre-TCZi IL-6 pg/ml, mean, median (IQR)	53	15·67 (6, 34)		86	19 (7, 74)	..
Post-TCZ IL-6 pg/ml, mean, median (IQR)	26	105·75 (82·95, 173·56)		62	146·62 (64·12, 254·88)	..
Change in sIL2R, mean median (95%CI)	44	338·6 (186.6, 521·8)	<0·001 [a]	77	354·2 (220.2, 490·23)	<0·001 [a]
Pre-TCZ sIL2R pg/ml, mean, median (IQR)	56	849·62 (528·3, 1451·5)		84	1114·3 (783·9, 1710·5)	..
Post-TCZ sIL2R pg/ml, mean, median (IQR)	44	1245 (802·75, 1973)		77	1416·25 (1041, 2081)	..
Chest radiograph findings at 14 days, No· (%)	129	..			..	
Improved		36 (75)	0·22 [a]		50 (62)	0·22 [a]
Unchanged		6 (12)	..		11 (14)	..
Worse		6 (12)	..		20 (25)	..

[a] Wilcoxon signed-rank test, TCZ=tocilizumab, FEU= Fibrinogen equivalent units, sIL2R=Soluble interleukin 2 receptor (CD25), TCZ=tocilizumab

e-Table 3: Safety profile of tocilizumab before and after treatment (N=153)

Variable	Pre-Treatment No· (%)	Post-Treatment No· (%)
Absolute neutrophil count (cells/mL), N=150		
≤500	2 (1)	6 (4)
Alanine aminotransferase (ALT), N=131		
Grade 0	87 (62)	43 (31)
Grade 1	47 (33)	52 (37)
Grade 2	4 (3)	21 (15)
Grade 3	3 (2)	23 (17)
Grade 4	0 (0)	0 (0)
Aspartate aminotransferase (AST), N=130		
Grade 0	25 (18)	9 (7)
Grade 1	100 (71)	84 (61)
Grade 2	12 (9)	23 (17)
Grade 3	4 (3)	21 (15)
Grade 4	0 (0)	0 (0)
Bacteremia, N=111	· ·	4 (4)
Grading system: 0 = within the normal range, 1 = within 3 times the upper limit of normal, 2 = 3-5 times the upper limit of normal, 3 = greater than 5 times the upper limit of normal, 4 = 10 times the upper limits of normal		