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Title: Dramatic clinical improvement in nine consecutive acutely ill elderly COVID-19 patients treated with a nicotinamide mononucleotide cocktail: A retrospective case series

Abstract:

Background: Nicotinamide adenine dinucleotide (NAD+) - a coenzyme found in every cell in the human body - is involved in hundreds of critical metabolic processes. However, as humans age, intracellular NAD+ levels decrease - this depletion appears to be exacerbated during complicated SARS-COV-2 infections. NAD+ depletion impairs our antiviral defense systems and our ability to optimally control inflammation.

Methods: Ten consecutive acutely-ill presumed SARS-CoV-2 infected patients older than 50 years were treated with over-the-counter nicotinamide mononucleotide (NMN), betaine, sodium chloride and zinc sulfate (NMN cocktail). Eight patients had positive nasopharyngeal SARS-CoV-2 NAA test results, one patient was clinically diagnosed with COVID-19 based on classic symptoms and one patient was excluded as Covid-19 was ruled out. The COVID-19 patients were monitored with clinical evaluations, body temperatures and room air (RA) oxygen saturation (O2 sat) levels. Serial inflammatory cytokine measurements and chest X-rays (CXRs) were done in 7/9 of the COVID-19 patients.

Results: Cases #1, 4, 7 and 10 were critically-ill with worsening O2 sats, pulmonary infiltrates and inflammation prior to administration of the NMN cocktail. Post-treatment, prompt clinical improvement was seen including fever resolution in 2-3 days (4/4), rapid CXR improvement (4/4), dramatic drops in CRP (4/4) and IL-6 (3/4) within 72 hours and hospital discharge in ≤ 5 days (3/3 cases). No patient required ICU care or intubation post treatment. Cases 5 and 8 (bilateral pneumonias but no prior CXRs) and cases 2 and 3 (symptomatic outpatients with failed trials of hydroxychloroquine (HCQ), azithromycin (AZ) and zinc (Zn) with no CXRs performed) had a strong temporal relationship between NMN cocktail use and rapid clinical improvement. One patient (#6) improved with prompt fever and symptom resolution but after premature NMN cocktail discontinuation recurrent fever and pulmonary infiltrates were noted 2 and 8 days later respectively.

Summary: The NMN cocktail resulted in rapid and dramatic clinical and laboratory improvement in older persons with complicated SARS-CoV-2 infections. NMN with and without boosters deserves further study in elderly patients with complicated COVID-19 as this treatment has a strong molecular rationale for success, can be safely administered orally at home and in critically ill hospitalized patients.

Introduction: One of the most – if not the most - transformative biologic discoveries is age reversal[1]. Significant life span enhancement has been shown with anti-aging interventions targeting 6 unique mammalian signaling pathways, each cross tested in three independent labs[2]. One promising anti-aging agent is NMN, an orally absorbed NAD+-boosting compound with remarkable abilities to reverse age-associated kidney, liver, brain, vascular and immune system decline in mice[3]. This food supplement, found in small amounts in all living cells but most notably in breast milk, tomatoes and avocados, has its own specific transmembrane transporter[4], and in Phase I and II human clinical trials, larger doses were found to be safe, well tolerated and able to raise NAD^+ levels in whole blood[56]. NAD+, the cell's hydrogen carrier, is well known for its role in reduction-oxidation (redox) reactions. More recently, it has emerged as a signaling molecule through its role as a substrate for several different families of enzymes, most notably the sirtuins. By modulating sirtuins, NAD+ controls hundreds of key processes from circadian rhythm to energy metabolism to DNA repair and cell survival, rising and falling depending on food intake, exercise, and the time of day. Sirtuins also play a major role in immune functions – including our antiviral defense systems and our ability to optimally control inflammation. However, intracellular NAD+ levels decrease with normal aging[7] and appear to further deplete during SARS-CoV-2 infection[8].

In March 2020, I cared for a hospitalized SARS-CoV-2-infected woman (patient #1) with rapid clinical deterioration – she went from having a normal CXR and O2 sats to life threatening ARDS in just 4 days. Due to strict hospital protocol, I was unable procure experimental Remdesivir or an experimental anti-IL6 drug to treat an apparent evolving cytokine storm. In my private internal medicine practice, I routinely follow elevated inflammatory markers in older patients to predict the risk of cardiovascular diseases, frailty and decline of physical and cognitive function. I had repeatedly observed cytokine levels decrease on oral OTC NMN with three boosters to possibly further optimize sirtuin enzyme action (betaine to counter NAD+ inhibition by nicotinamide[9], sodium chloride to enhance NMN absorption[10] and Zn to up regulate nuclear factor erythroid 2-related factor 2 (Nrf2) function[11]). Therefore, with no other treatment options available and after signed informed consent from the patient and family, the NMN cocktail was administered. She promptly and dramatically improved within 48 hours[12]. Based on this surprising result, I used this NMN cocktail in every subsequent older acutely ill patient I cared for with presumptive COVID-19.

Methods: Ten consecutive individuals over the age of 50 in my private practice with presumptive diagnosis of COVID-19 were treated with the OTC supplement NMN cocktail (EGA®) after signing written informed consent for participation and for their deidentified data being reported in a published case series. The NMN cocktail (83cc) was mixed with 400cc of water and consumed fasting pre breakfast and dinner in sync with the patients presumed bi-daily peaks of NAD+. Treatment was recommended for a minimum of 6 continuous days.

Four of the patients in this series were established patients, six were referrals by established patients (two being already hospitalized COVID-19 cases desiring a second opinion). No case was excluded.

Longitudinal information was entered based on review of prior hospital records and patient diaries of home temperature readings, O2 sats and the presence or absence of other COVID-19-

associated symptoms (cough, sore throat, shortness of breath, tight chest sensation, headache, diarrhea, rash or anosmia) as well as activity level (i.e. ambulatory vs. non-ambulatory). Ordering timely chest X-rays proved challenging as local outpatient radiologic facilities denied service for SARS-CoV-2 positive patients during the duration of this case series. Acute respiratory distress syndrome (ARDS) was defined as bilateral pulmonary opacities on chest radiograph, arterial hypoxemia (partial pressure of arterial oxygen [PaO2] to fraction of inspired oxygen [FiO2] ratio <300) (estimated here as O2 sat on room air < 93%), and exclusion of cardiac failure - at time of treatment[13].

Results: **Patient characteristics:** Eight patients had positive nasal-pharyngeal SARS-CoV-2 nucleic acid amplification (NAA) tests (Table 1). One patient (#3) had classic Covid-19 clinic presentation (cough, persistent daily fevers to 102ºF, severe fatigue and anosmia). One patient (#9) with fever and persistent cough was ruled out for COVID-19 based on three negative nasal-pharyngeal SARS-CoV-2 NAA tests, one negative serologic test for antibodies directed against the virus (day 18 post symptom onset) together with a normal CXR and chest CT.

Table 1. Patient Characteristics:

Patient #	1	2	3	4	5	6	7	8	10	9
Covid-19 Test	(+) PCR	(+) PCR	na	(+) PCR	(+) PCR	(+) PCR	(+) PCR	(+) PCR	(+) PCR	(-) PCR x 3
Age	55.1	60.6	72.2	79.3	52.4	78.7	61.4	59.6	62.0	56.7
Gender	F	M	F	M	F	M	F	M	M	M
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Hispanic	Hispanic	Hispanic	Hispanic	Caucasian	Caucasian
Exercise/Week	0	0	0	4	0	0	0	0	0	5
Job Physicality	0	0	0	0	1	1	0	0	0	0
Comorbidities										
BMI	30	26	24	24	29	29	26	28	24	25
Smoking Hx		past		past		past		current		
Diabetes			pre-DM2	DM2	pre-DM2	DM2	pre-DM2	pre-DM2	pre-DM2	
CAD			CAD	OSA		CAD, CABG				
HTN			HTN	HTN		HTN				
Medication		lipitor	diazide	metformin		metformin				
			crestor	lipitor		metropolol				
				lisinopril		benicar				
				allopurinol		lipitor				
Symptom onset	3/15/20	3/6/20	4/1/20	4/12/20	5/17/20	5/22/20	5/20/20	5/18/20	5/24/20	5/27/20
Symptoms	fever	fever	fever	fever	fever	fever	fever	fever	fever	fever
	cough	cough	cough	cough	cough	cough	cough	cough	cough	cough
		diarrhea	diarrhea			diarrhea	diarrhea		diarrhea	hoarseness
		HA	HA	Fatigue		nausea	nausea		Fatigue	
	chest tight	chest tight	chest tight		chest tight	dizzyness	chest tight	chest tight		
			anosmia	anosmia	anosmia	anosmia	anosmia		anosmia	
	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden	bedridden
Prior treatment	HC, A, Zinc	HC, A, Zinc	HC, A, Zinc	Convalescent plasma					HC	

The nine Covid-19 infected patients were on average 65 years old with frequent co-morbidities - 2 with diabetes, 5 with pre-diabetes, 2 with known significant coronary heart disease (CAD), 3 on baseline meds for hypertension (HTN) and 6 with body mass indexes (BMI) in the overweight category. 9/9 patients presented with fever, cough and lethargy leaving them for the most part bedridden; 6/9 reported anosmia with 5/9 initially complaining of diarrhea.

Three individuals (#1, 2, 3) took prior HCQ, AZ and Zn. One individual (#10) took a six-day course of HCQ alone. One individual (#4) received convalescent plasma.

All patients were acutely ill when treatment with the NMN cocktail was begun (range 5 to 34 days after the onset of Covid-19 symptoms) (Table 2). Two patients took treatment for only three days. At onset of treatment, seven patients had CXRs done - six patients had bilateral pulmonary opacities (#1, 4, 5, 7, 8, and 10) - four patients (#1, 4, 8, and 10) had ARDS (Table 2 blue). One patient had a normal CXR (#6).

Serial CXRs from prior to the time of treatment were available in four cases (#1, 4, 7 and 10) - every case revealed worsening CXR appearance. Oxygenation status and inflammation markers in these critically ill cases were also deteriorating immediately prior to the initiation of NMN cocktail treatment (Table 2 yellow).

Table 2. Pre-Treatment Patient Characteristics:

Patient #	1	2	3	4	5	6	7	8	10
Clinical Status:	Worsening infiltrates, hypoxia, cytokine levels	Recurrent fever, severe HA and CP several days after apparent recovery	Persistent fever, cough, abnormal O2 sat, lethargy	Worsening infiltrates, hypoxia, cytokine levels and new fever s/p convalescent plasma	Double pneumonia, risk factors for poor outcome	Severe Covid-19 symptoms, risk factors for poor outcome	Worsening infiltrates, risk factors for poor outcome	Double pneumonia, risk factors for poor outcome	Worsening infiltrates, hypoxia, cytokine levels
Days of Symptoms	12	24	9	34	8	5	7	12	16
Consecutive days fever	12	1	14	8	10	2	7	9	15
Bilateral pulmonary infiltrate	yes	unknown	suspected	yes	yes	no	yes	yes	yes
ARDS	yes	unknown	unknown	yes	no	no	no	yes	yes
Worsening Infiltrates	yes	unknown	unknown	yes	unknown	no	yes	unknown	yes
Pre-Treatment Lab Values									
RA O2 sat %	84	95	94	<74	95	98	97	92/93	92/93
CRP	201	2.6	na	211	5.7	<0.2	3.1	25	14.9
IL-6	54	na	na	19	23.1	13.3	17.4	29.7	59.2
Absolute lymphocytes	291	1100	na	920	1200	1300	1700	1400	1000
	Bilateral pulmonary infiltrates					HA - headache, CP - chest pressure			
	Worsening bilateral pulmonary infiltrates or ARDS at onset treatment								
	Cytokine levels at onset treatment consistent with poor outcome (29) (30)								

Patient Outcomes: Four patients required hospitalization, (one was treated in an emergency room then sent home). No patients required intubation. All nine patients have fully recovered.

Fevers ran an average of nine continuous days pre NMN cocktail administration - then resolved in all 9 patients in 2-3 days (Table 3). All six patients with bilateral pulmonary opacities (including the four patients who met ARDS criteria) exhibited prompt post-treatment clinical improvement, namely 2-3 days until temperature resolution (6/6), dramatic drops in CRP (7/8) and IL-6 levels (6/7) within 3-10 days, increases in absolute lymphocyte numbers at 3 (6/8) and 10 days (8/8) and discharge post treatment $\leq$ 5 days (3/3 cases). CXR improvement was noted in every patient with pneumonia at the onset of treatment (6/6), specifically those with worsening bilateral pulmonary infiltrates (patients #1, 4, 7 and 10) and bilateral pulmonary infiltrates of unknown onset (patients #5,8) with significant improvement at the first follow-up CXR. In the

two severely symptomatic outpatients with no CXRs, there was a strong temporal relationship between NMN cocktail use and prompt clinical improvement.

Patient #6, a 79-year-old man with multiple comorbidities, was symptomatic but had a normal CXR initially; he clinically improved after three days of treatment (resolved fever, symptoms better and inflammation bio-markers lowered). Due to miscommunication, he stopped the NMN cocktail after just three days and two days later he relapsed with recurrent fever and new bilateral pulmonary infiltrates (8 days later).

Observed Side Effects: Seven patients reported no adverse effects. Two patients complained of a caffeine-like jitteriness temporally associated with NMN cocktail ingestion that attenuated with repeated use (patient #1) and dose discontinuation after three days of treatment (patient #2). No other adverse symptoms or lab changes were noted.

Table 3. Patient Outcomes:

Patient #	1	2	3	4	5	6	7	8	10
Total duration treatment (d)	11	3	6	13	6	3	6	6	9
Duration Fever pre treatment (d)	12	1	14	8	10	2	7	9	15
Duration treatment till T< 99.3 (d)	2	1	2	2	3	2	3	3	2
CRP 3 d post treatment	-33%	-96%		-43%	19%	0%	87%	-60%	-19%
CRP 6 d post treatment	-87%			-85%	-49%	increased			
CRP 10 d post treatment	-96%			-100%	-98%	increased	-90%	-94%	-53%
IL6 3 d post treatment	-30%			-3%	-36%	-49%	136%	-41%	24%
IL6 6 d post treatment	-69%			-67%	-90%	47%			
IL6 10 d post treatment	-94%			-77%	-87%	-8%	-70%	-79%	354%
Abs lymphocye 3 d post	170%	18%		58%	0%	8%	24%	36%	-10%
Abs lymphocye 6 d post	275%			34%	0%	-15%			
Abs lymphocye 10 d post	319%			107%	25%	38%	106%	29%	10%
		Bilateral pulmonary infiltrates							
		Decreasing inflamation markers or increasing absolute lyphoctye count							

Detailed Patient Histories, Treatment Timelines and Serial Chest X-rays: Supplemental Individual Case Summaries:

Patient 1: A 55-year-old white SARS-CoV-2 NAA test positive female complained of seven days of myalgia, chest aching, shortness of breath, cough and high fevers (T max 102º F). Her RA O2 sats were 93-95 and her CXR was normal (Figure 1a). On day 8 her fever increased to 102.5º F and she was prescribed HCQ, AZ and Zn. On day 11 she deteriorated; her clinical status (dyspnea at rest, T max to103º F, RA O2 sat 90%) and her CXR (new infiltrates) worsened. She was hospitalized with admission labs (CRP 217 mg/L, Il-6 56 pg/mL, TNF-alpha 7.4 ng/mL and myoglobin >500 ng/mL) predicting a fatal outcome[1]. A repeat RT-PCR SARS-CoV-2 test revealed negligible (<4copies/µl) nasopharyngeal virus.

1. Qiurong Ruan et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med, 3/3/20

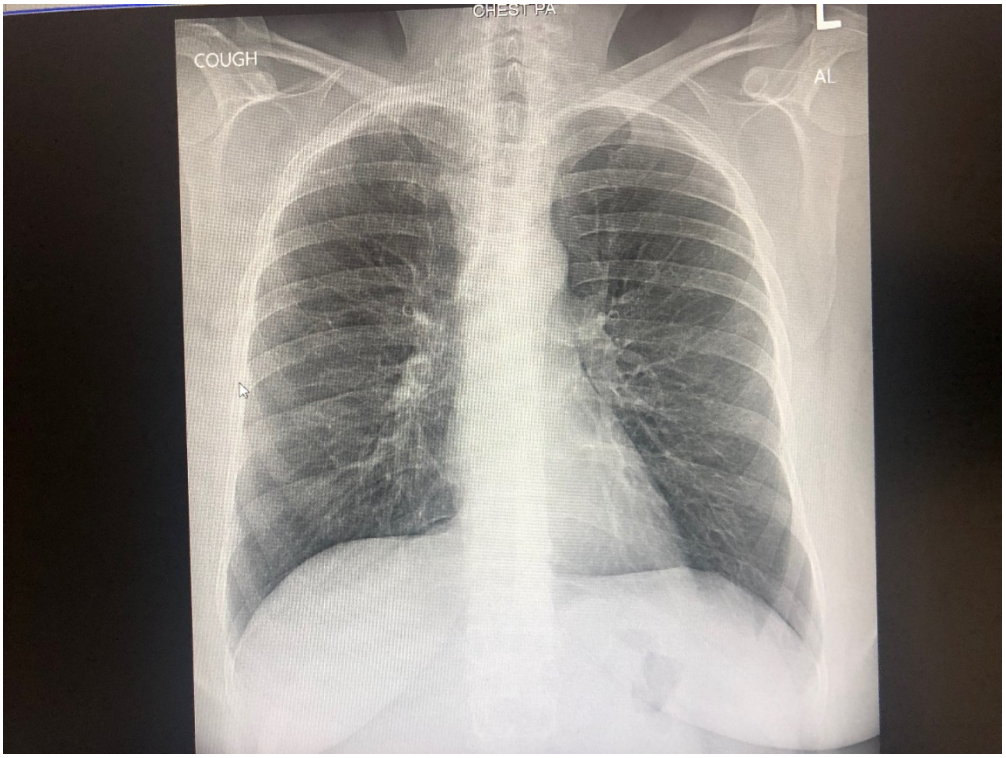

Figure 1a. Day #7 CXR: normal

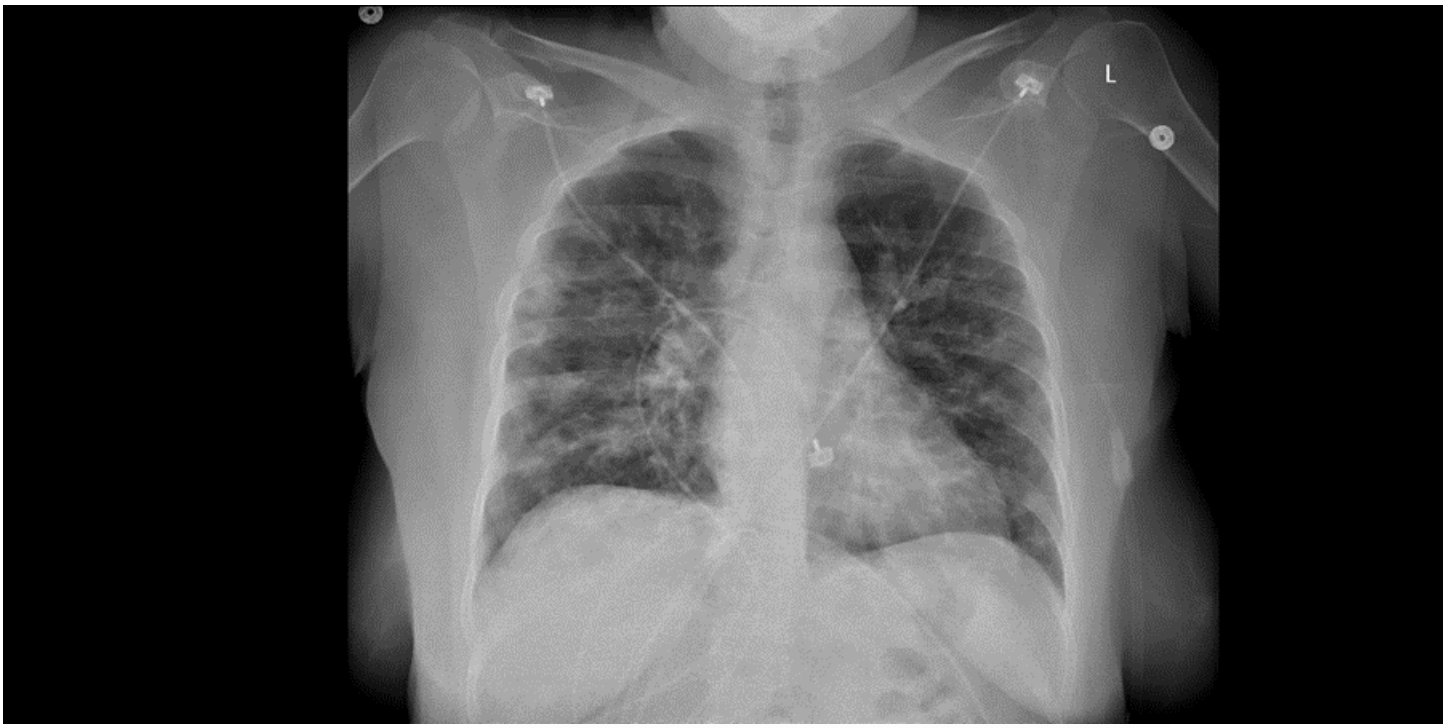

Figure 1b. Day #11 Admission CXR: new bilateral patchy infiltrates throughout both lungs

Neither Remdesivir nor Tocilizumab was available. Therefore, the NMN cocktail was begun on the evening of day #12. She was unable to sit up in bed to drink the NMN cocktail so her nurse called me to say she had held this initial treatment dose. However, I personally came to the hospital, raised the head of her bed up 30 degrees, and sat at her bedside while she slowly, over a 30-minute period, sipped the NMN cocktail thru a straw.

12 hours after the initial dose, her RA O2 sat (84%) and CXR worsened (pulmonary infiltrates consistent with ARDS) (Figure 1c). However, her absolute lymphocyte count markedly increased from 291 to 540.

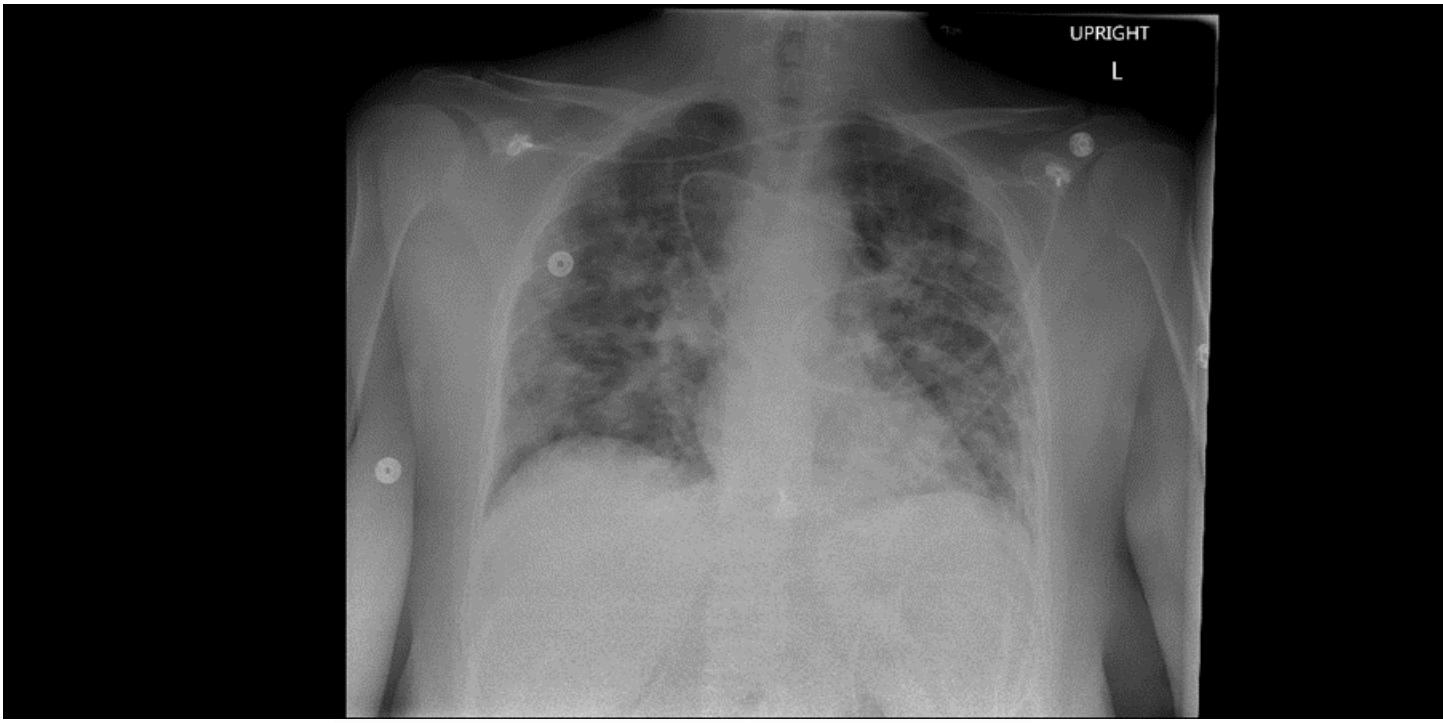

Figure 1c. Day #13 CXR: interval increase in the bilateral pulmonary opacities (12 hours after hospital admission).

36 hours after treatment began (Day #14), her clinical condition dramatically improved:

- Improved clinical condition (fatigue, SOB, cough and abnormal chest sensation were 75% better in 2-3 days, after 2 weeks her temperature resolved in 36 hrs.)
- Potent anti-inflammatory action (CRP and IL-6 both dropped 80% while absolute lymphocytes gained 250% over 5 days)
- Improved oxygenation (RA O2 sat 84 improved to 96% in just 5 days)
- Improvement of CXR in just 4 days (Figure 1c compared with 1d) with near normalization of CXR in 8 days (Figure 1e).
- CRP and IL-6 decreased to 7.4 mg/L and 3.2 pgr/mL in 7 days (- 96% and -94% respectively)

Patient # 1																							
Symptom Day #	1	2	4	6	7	8	9	10	11	12	13	14	15	16	17	18	20	22	23
Temp (Tmax)	100.2			101.5	102.0	102.5	102.6	102.8	103.0	103.0	103.1	102.3	99.0	98.9	98.3		98.8		98.6
Cough	choking cough	new chest "ache"											reduction cough						
Symptoms				bedrid	bedrid	bedrid	bedrid	bedrid	progressive dyspnea			walk	walk	walk	walk				Normal
O2 sat RA 5 min					93				89-90	88	84	88	93	94	96		97		97
Covid19 Tests		(+) PCR									(+) PCR (<4 copies/uL)						(-) PCR		(+)IgG/M Ab
Hospital															home 10am				
CXR					NL				bilat infilt		bilat infilt				bilat infilt				bilat infilt
											worse				better				better stil
Absolute Lymph									490	291	540				1029		1218		
CRP									217	201	193	205	134	69	36		7.4		
IL6									56		52						3.2		
Antibiotics						Hydroxychloraquine,			Azithromycin										
Zinc sulfate Qd						220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg
NMN/Betaine/NaCl	BID								pm on	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr

Patient #1 medical history

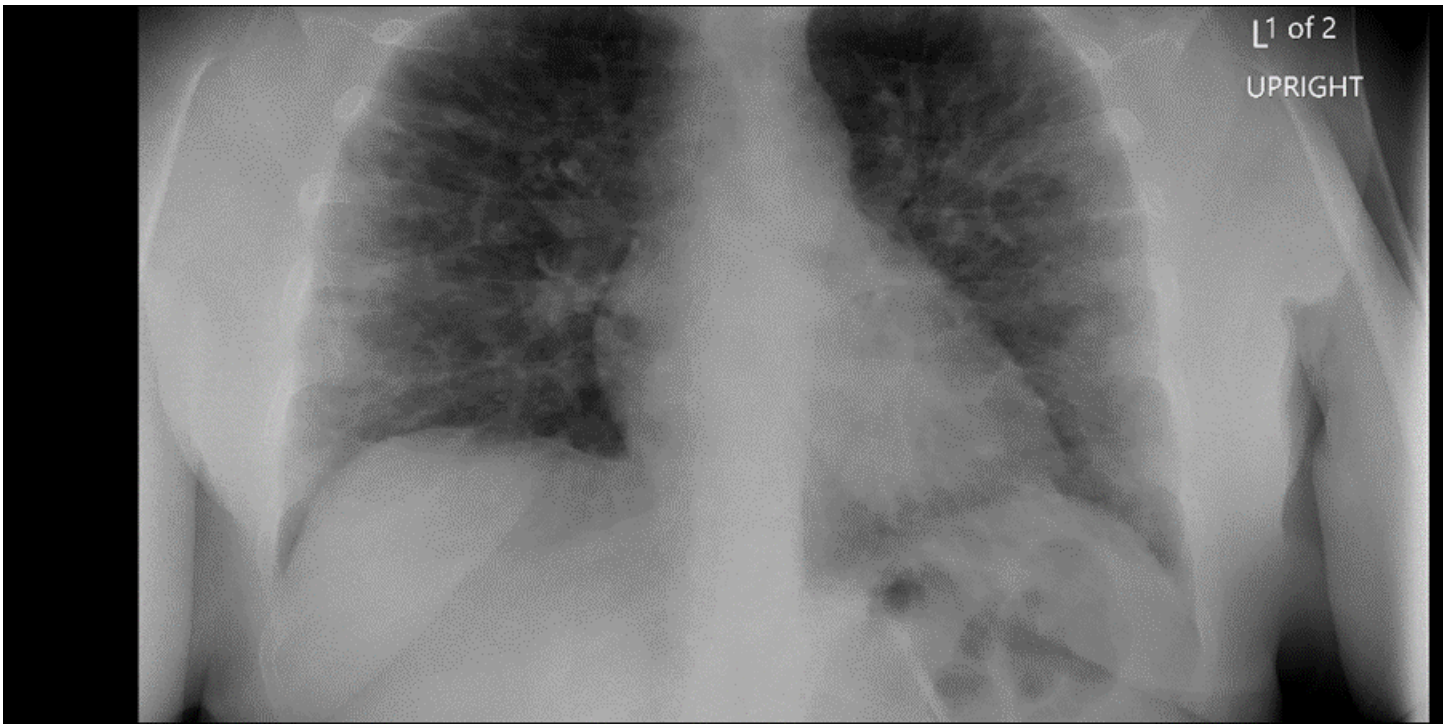

Figure 1d. Day #17 CXR: Improved interstitial and alveolar opacities compared with day #13.

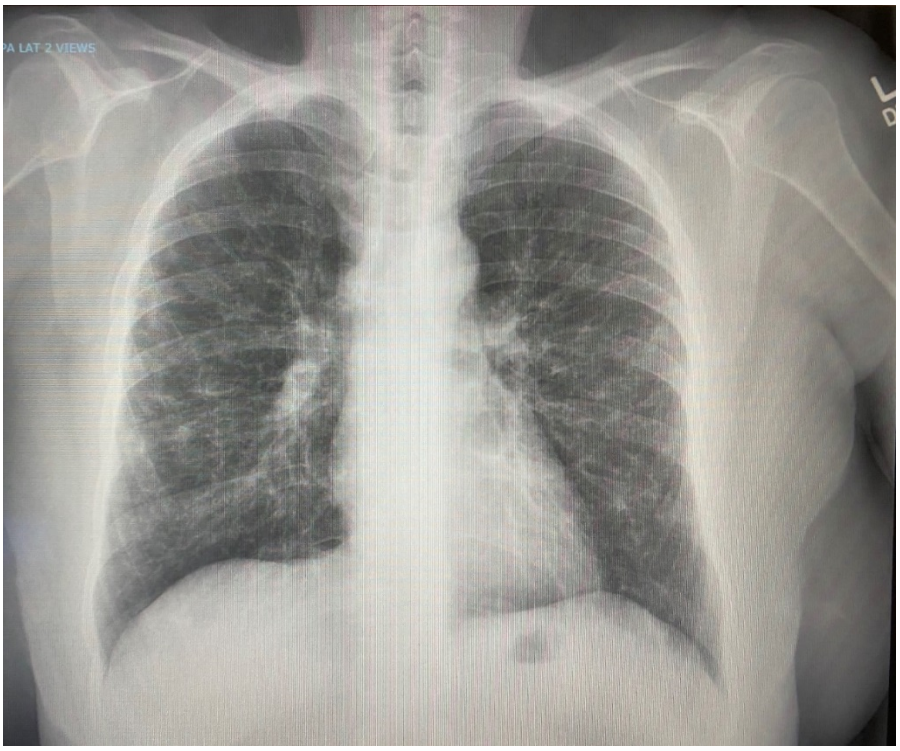

Figure 1e. Day #23 CXR: dramatically improved interstitial and alveolar opacities.

Case 2: A 56-year-old SARS-CoV-2 NAA positive man with cough, chest tightness, dyspnea, diarrhea and HA was prescribed HCQ, AZ and Zn as an outpatient on his 15th consecutive day of fever. At the completion of the 6-day course he became afebrile and his chest pressure and headache improved, however his cough and insomnia continued. Three days later, his fever, HA and chest pressure recurred. He was begun on the NMN cocktail and experienced a prompt response:

- His recurrent 2-day fever resolved within 24 hours
- His clinical condition improved in 2-3 days (resolved cough, chest pain, headache)
- Improved oxygenation in three days (RA O2 sat 95 to 96%)
- Anti-inflammatory action in 3 days (CRP dropped from 2.6 to undetectable and absolute lymphocytes increased from 1100 to 1300)
- Probable side effect: patient complained of shaky hands and a “too much caffeine” edginess. These symptoms resolved after 1-2 days off the NMN cocktail.

Patient # 2																				
Symptom Day #	1	3	5	13	15	16	17	18	19	20	21	23	24	25	26	27	28	29		
Temp (Tmax)	Febrile				100.7	101.9	100.9	100.9	100.9	afeb	afeb	afeb	100.1	100.5	afeb	afeb	Edgyness resoved			
Cough	cough, chest tightness, SOB								intense cough but less CP			recurrent cough, CP				cough, CP resolved				
Symptoms	diarrhea, HA				nausea		less HA					recurrent HA		severe HA		edgy, anxious.				
O2 sat RA 5 min					95					95				95				96		
Covid19 Tests		(+) PCR			(+) PCR					(-) PCR										
Hospital																				
CXR																				
Absolute Lymph														1.1				1.3		
CRP														2.6				<0.2		
IL6														2.8						
Antibiotics					Hydroxychloraquine, Azithromycin															
Zinc sulfate Qd					220mg	220mg	220mg	220mg	220mg					220mg	220mg	220mg				
NMN/Betaine/NaCl	BID													1.67 gr	1.67 gr	1.67 gr				

Patient #2 medical history

Case 3: A 72-year-old woman complained of fever, fatigue, sore throat, cough, HA, anosmia and diarrhea approximately 5 days after her personal assistant came down with a similar constellation of symptoms. She was clinically diagnosed as SARS-COV-2 infected. On symptom day #3, she was seen at her home and begun on HCQ, AZ and Zn. However, her O2 sat subsequently dropped from 96 to 94% and her symptoms intensified.

She was then treated with the NMN cocktail and experienced a prompt response: Her clinical condition (fourteen-day fever, cough, fatigue and headache) improved in 2-3 days.

Patient # 3																				
Symptom Day #	1	2	3	4	5	6	7	8	12	13	14	15	16	17	18	19	20	21		
Temp (Tmax)	101.0		101.5								101.1		98.5	afeb	100	100	afeb	afeb		
Cough			slight sore throat cough								persistent cough									
Symptoms	no smell/taste, diarrhea, headache, beddridden										bedridden, headache		90% better							
O2 sat RA 5 min			96								94									
Covid19 Tests																				
Hospital																				
CXR																				
Absolute Lymph																				
CRP																				
IL6																				
Antibiotics			Hydroxychloraquine, Azithromycin																	
Zinc sulfate Qd			220mg	220mg	220mg	220mg	220mg	220mg			220mg	220mg	220mg	220mg	220mg	220mg	220mg			
NMN/Betaine/NaCl	BID										PM on 1.67 gr	1.67 gr	1.67 gr	1.67 gr	1.67 gr	am only				

Patient #3 medical history

Case 4: A 79-year-old business man was hospitalized on symptom day #22 with ARDS (Figure 4a), renal failure (Cr 4.6), diabetes, myocarditis and liver failure (AST/ALT 2878/1598) with possible pulmonary embolism.

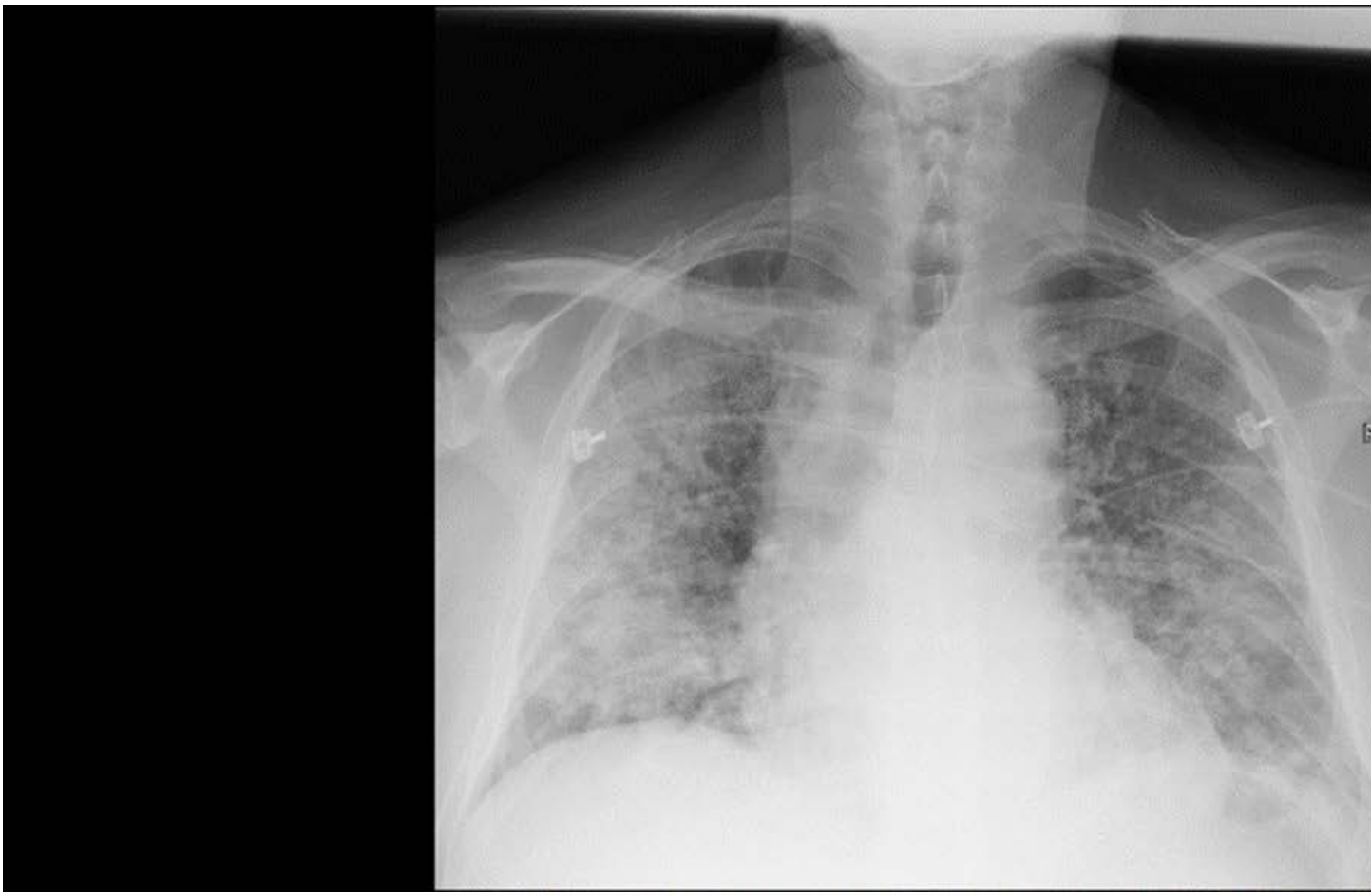

Figure 4a. Day #22 Admission CXR: Bilateral infiltrates consistent with ARDS.

He tested positive for SARS-COV-2 RT-PCR, received high flow nasal O2, empiric antibiotics, anticoagulants and was placed in a convalescent plasma trial on symptom day #24 (Remdesivir was contraindicated given his liver failure). Post convalescent plasma, his high-flow nasal O2 needs, liver failure, renal failure and inflammatory profile improved allowing transfer from the ICU to a floor bed on symptom day #27. However, over the subsequent 6 days, his condition steadily deteriorated with fever and increased inflammation - on day #32, his oxygenation and CXR (Figure 4b) worsened to the point his family was told by the hospital Covid-19 specialists that ICU transfer was imminent - they recommended Tocilizumab plus Remdesivir be started ASAP.

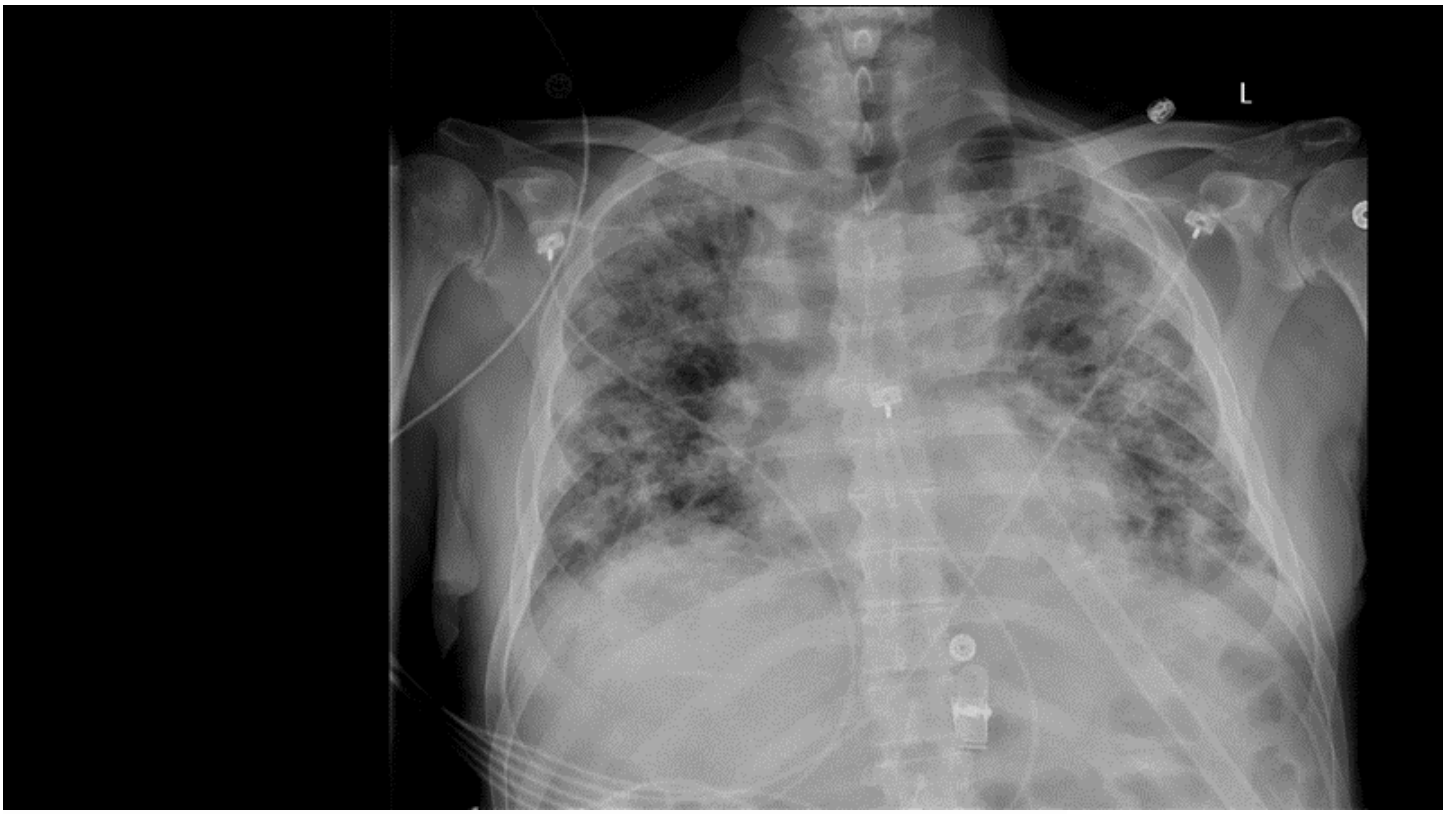

Figure 4b. Day #32 CXR: Increasing bilateral infiltrates, especially in the left lung.

The family requested a second opinion. A nasal PCR test revealed no virus, making persistent viremia unlikely and rendering the Remdesivir recommendation moot. Given the patient's fear of possible Tocilizumab side effects, the patient opted to first try the NMN cocktail. **(**Patient #4 medical history).

Patient # 4																					
Symptom Day #	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40		47
Temp (Tmax)	99.1	99.0	Afeb	Afeb	Afeb	101.0	100.0	100.2	100.0	101.8	100.5	99.6	100.8	99.9	99.2	Afeb	Afeb	Afeb	Afeb		Afeb
Cough																					
Symptoms	bedridd	bedridd	bedrid	bedrid	bedrid	bedrid	bedrid	bedrid	bedrid	bedrid	bedrid	bedrid	bedridde	bedrid	bedrid	bedrid	sitting	walk	walking		walking
O2 sat RA	88												<74	75	78	82	84	88	90		95
O2 suppl %	60	50	45	45	50	65	55	60	60	40	60	60	60	50	50	40	30	nasal canula			
L per min	40	35	35	35	35	40	35	30	30	30	30	30	30	25	25	20	20	2	1		
Covid19 Tests	(+) PCR						(+) PCR						(-) PCR	(-) PC	(+)IgG/M Ab						
Hospital	ICU ARDS, Myocarditis, probable P					transfer to floor													home		home
CXR	bilat infil				bilat infil		bilat infil				bilat infil		new	bilat infil				bilat infil			bilat infil
					worse L		same c/w day#26				worse L		medical	same c/w day#32				improved			sign improved
Absolute Lymph	600					930	920						consult	1450		1270					1900
DDimer	>20	9.9	8.6	6.2	4.3	3.4	2.8	3.2	3.2	3.1	3.1	3.7	3.7	4.1	3.4	2.8	2.3	2.2			1.1
Ferritin	34169	10054	5030	3137	2450	1992	1565	1469	1230	1287	1403	1376	1023	1005	1026	954	850	843			352
CRP	347		132	101	79	94	139	167	181		192		211	162	142	121	86.3	55	32		0.7
IL6	26										21			18.4		6.2					4.3
Antibiotics	doxycyline/ceftiaxone																				
Convelescent plasma		trial																			
Zinc sulfate Qd		infusion											220mg	220mg	220mg	220mg	220mg	220mg	220mg	22	220mg
NMN/Betaine/NaCl	**BID**												6 pm onl	1.67 gr	1.67 gr	1.67 gr	1.67 gr	1.67 gr	1.67 gr	1.	1.67 gr

Patient #4 medical history

- Improved clinical condition (after 8 days his temperature resolved in 36 hrs, after being bed ridden for 5 weeks, he was able to sit in 3 days, walk in 5 days)
- Potent anti-inflammatory action (CRP, IL-6 and D-Dimer were -43, -67 and -24% respectively in first 72 hours)
- Improved oxygenation (RA O2 sat increased from <74 to 90% in just 6 days, with CXR improvement in 5 days (Figure 4b to 4c) and near normalization in 10 days (Fig 4b to 4d)

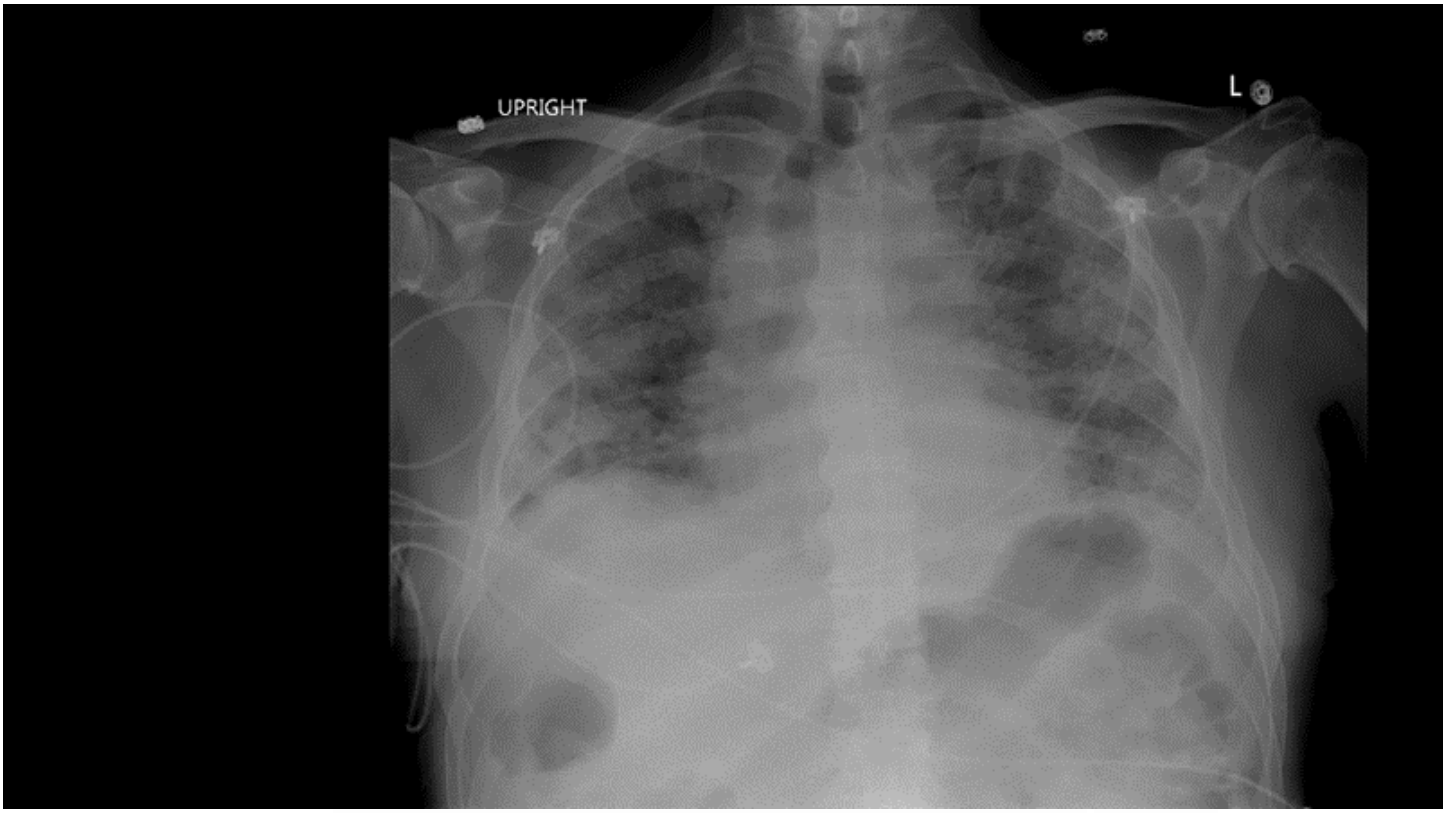

Figure 4c. Day# 39 CXR: interval improvement of the extensive bilateral pulmonary infiltrates

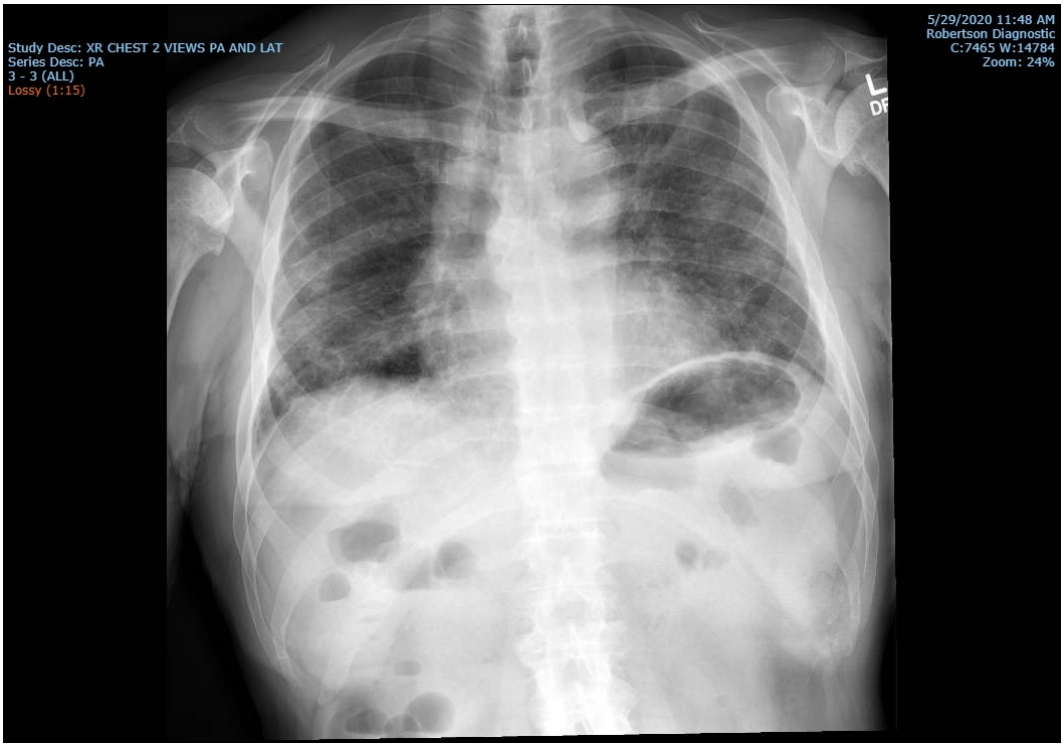

Figure 4d. Day #47 CXR: diffuse infiltrates dramatically resolved.

Case #5: A 52-year female chef (known SARS-CoV-2 NAA positive) was first seen on symptom day #10 complaining of persistent fever, SOB, headache and loss of smell and taste. Her presenting CXR revealed bilateral pneumonia (Figure 5a).

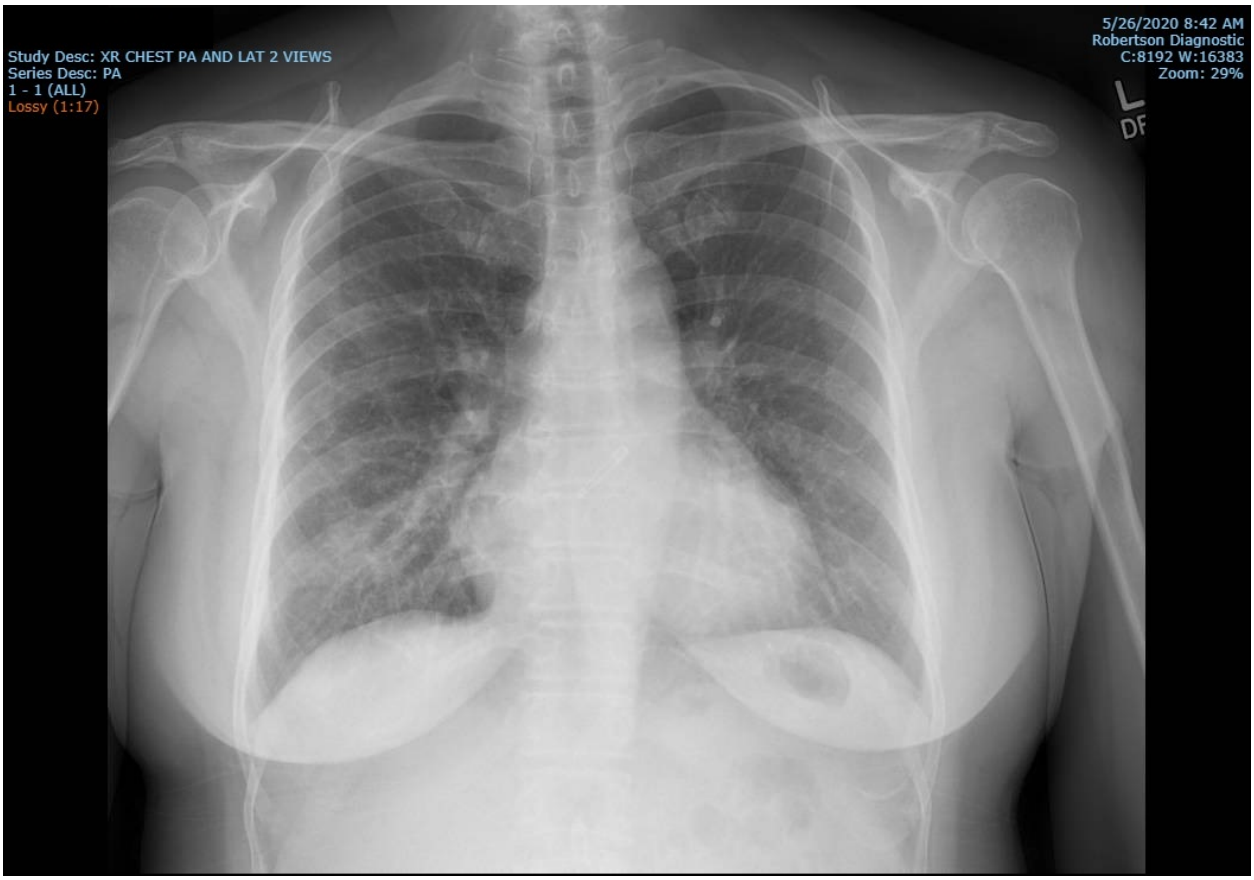

Figure 5a. Day #10 CXR: irregular marginated parenchymal opacities in the R mid and lower lobes and possibly in the left retrocardiac region.

She was begun on the NMN cocktail with a prompt and dramatic response:

- Resolution temperature (afebrile within 48 hours)
- Improved clinical condition (cough, SOB and headache improved “90%” in just 3 days)
- Potent anti-inflammatory action (CRP and IL-6 were -49 and -90% respectively in 6 days)
- Improved oxygenation (RA O2 sat from 95 to 97% in 3 days)
- Decreased CXR parenchymal opacities in 10 days (Figure 5a compared to 5b)

Patient # 5																			
Symptom Day #	1	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Temp (Tmax)	fever	fever	fever	fever	fever	fever	fever	101.0	100.7	100.6	99.3	98.8	97.7	99.0	afeb	99.3	afeb	afeb
Cough				Cough, SOB,			SOB @ 3am				sweating							
Symptoms		loss smell taste, dec appetite, headache									90% better		95% better, no taste or smell				Asymptomatic	
O2 sat RA 5 min								95			97			98				98
Covid19 Test					(+) PCR													(+) PCR
Hospital																		
CXR								B Infilt										B Infilt
																		resolve
Absolute Lymph								1200			1200			1200				1500
CRP								5.7			6.8			2.9				< 0.2
IL6								23.1			14.7			2.4				2.9
Antibiotics	none																	
Zinc sulfate Qd								220	220	220	220	220	220					
NMN/Betaine/NaCl	BID							1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr					

Patient #5 medical history

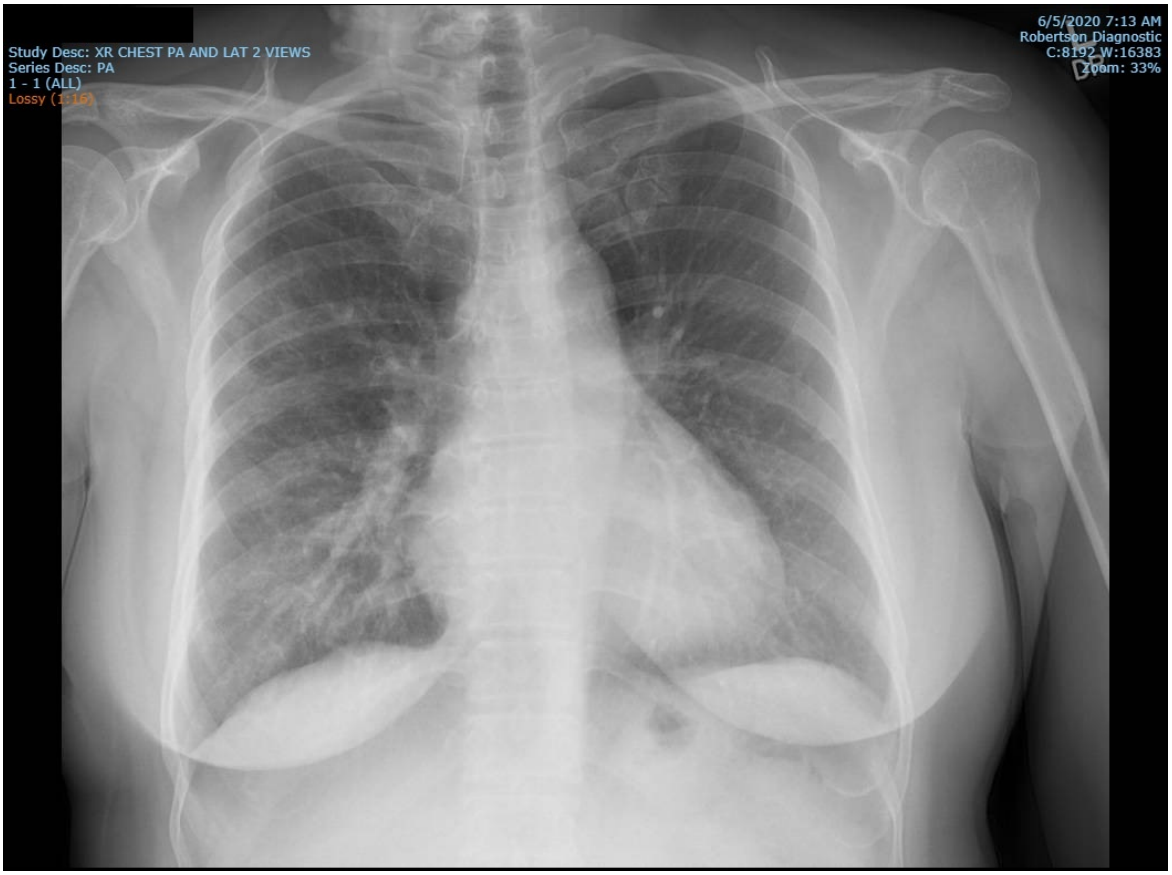

Figure 5b. Day #20 CXR: decreased parenchymal opacities in the R mid and lower lobes; L lung normal.

Case 6: A 78-year-old Latino man, regularly employed in a physically demanding job, presented after contact with known SARS-COV-2 NAA positive family members and 5 days after the onset of suspicious symptoms (new fever, cough, sore throat and diarrhea). He was a past smoker on medication for hypertension, coronary heart disease and diabetes type 2. His CXR was normal (figure 6a).

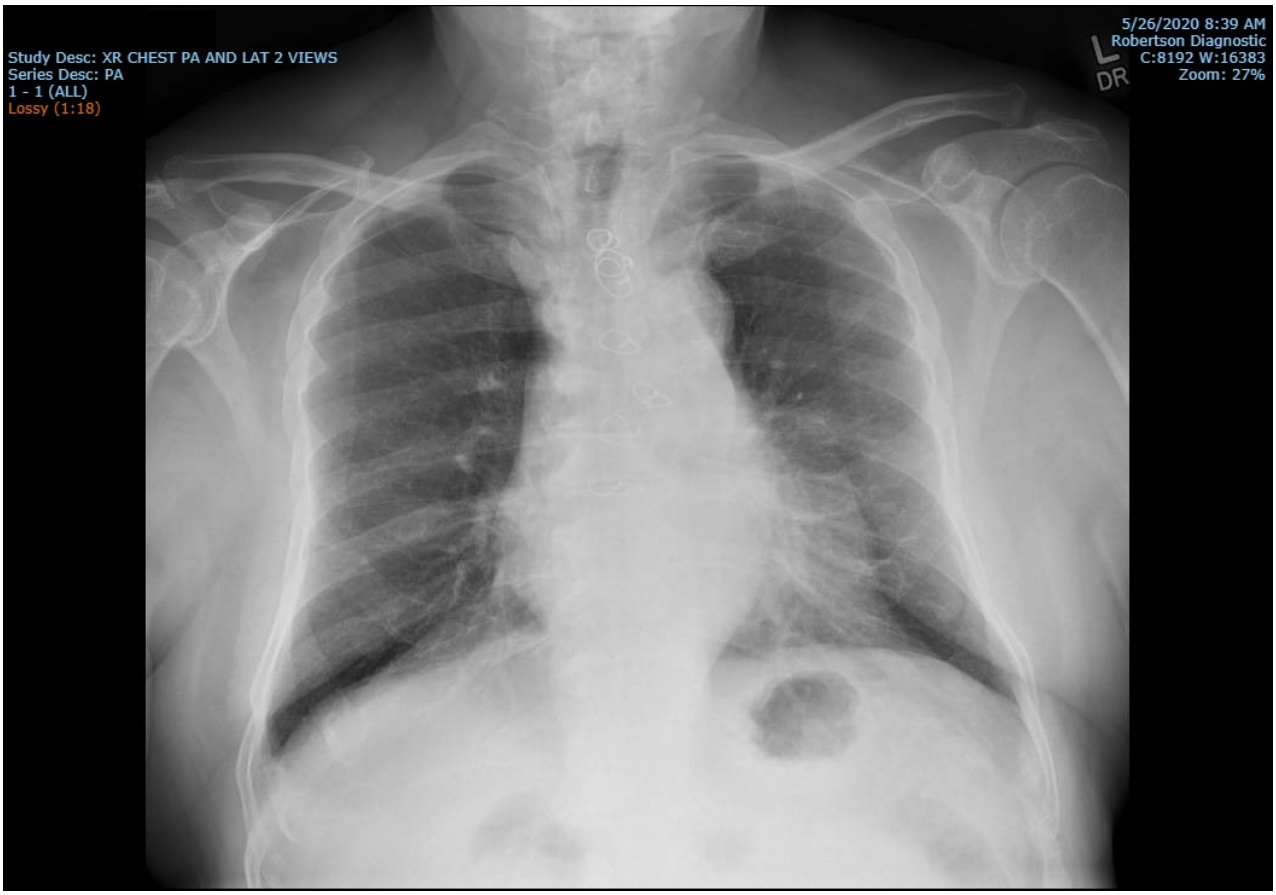

Figure 6a. Day #5 CXR: Normal.

Given his probability of being SARS-CoV-2 positive (confirmed in 72 hrs), together with his co-morbid conditions, he was placed on the NMN cocktail - he noted a prompt response:

- His fever resolved in two days
- His clinical condition partially improved - less cough - but he was still weak, lightheaded and nauseous and needing a cane (no longer walker) to ambulate.
- His oxygenation improved (RA O2 sat 95 to 97% in 3 days)
- Anti-inflammation effect (IL-6 dropped (-49%) his absolute lymphocytes increased (8%) over 3 days.

His exam on day #8 revealed orthostatic hypotension - he was asked to discontinue his blood pressure medication. On day #10, the family reported his fever had returned, he was unable to get out of bed. His examination on day #11 revealed fever, persistent nausea and benign positional vertigo. Laboratory tests revealed increasing inflammation markers. Via interpreters, he revealed day #8 when told to stop his blood pressure medications, he had also prematurely stopped his NMN cocktail. He felt better over the next several days with the exception of

persistent nausea. On day #15 he was afebrile still complaining of vertigo and nausea but was observed to walk without assistance. A CXR revealed new L mid to upper lung zone peripheral and sub pleural opacifications (Figure 6b). His metformin was discontinued. Over the next 1-2 days the patient's nausea resolved. The patient felt progressively better - on day #21 he felt essentially "100%" and returned to his physically demanding full time job.

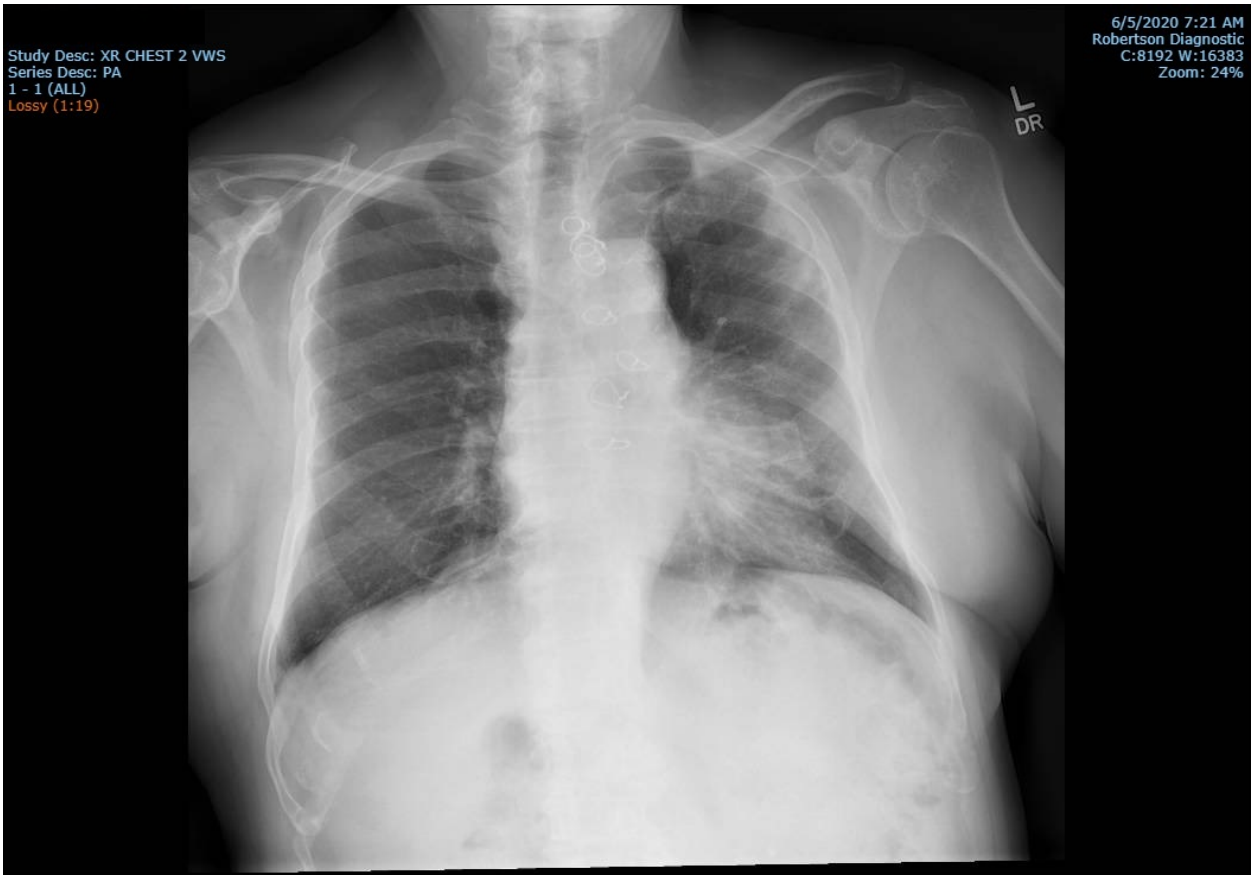

Figure 6b. Day #15 CXR: Peripheral and sub pleural irregular marginated parenchymal opacifications in L mid to upper lung zone.

Patient # 6																							
Symptom Day #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Temp (Tmax)				fever	101.0	101.0	98.9	97.6	100.7	101.1	100.0	fever	fever		98.5	afeb	afeb	afeb	afeb	afeb	afeb		
Cough					cough, sore throat			ortho hypotension			N, brief am confusion?				stronger, walking better						100% better		
Symptoms	N, diarrhea, dizzy (needs walker now!)							better, cane to walk			worse, not walking, anopsia				N (?drug SE), vertigo (?BPV)						back @ physical job		
O2 sat RA 5 min					95			97			96				97								
Covid19 Test	(-) PCR				(+) PCR			88/55			135/80				113/69								
Hospital								Metropolol DC'd			gluc 123				Metformin DC'd								
CXR					Nl CXR			HCTZ DC'd							new infiltrates								
															peripheral/subpleural infiltrates								
Absolute Lymph					1300			1400			1100				1800								
CRP					<0.2			<0.2			2				1.3								
IL6					13.3			6.8			19.6				12.3								
Antibiotics																							
Zinc sulfate Qd					220	220	220																
NMN/Betaine/NaCl BID					1.25	1.25	1.25																

Patient #6 medical history

Case 7: A 61-year-old female first presented to a local ER on symptom day #5 for fever, shortness of breath (SOB), muscle cramps, cough, nausea and diarrhea. CXR was normal (Figure 7a) but a CT chest revealed bilateral patchy peripheral regions of ground glass opacification. She tested positive for SARS-CoV-2 RT-PCR and was discharged home with no treatment.

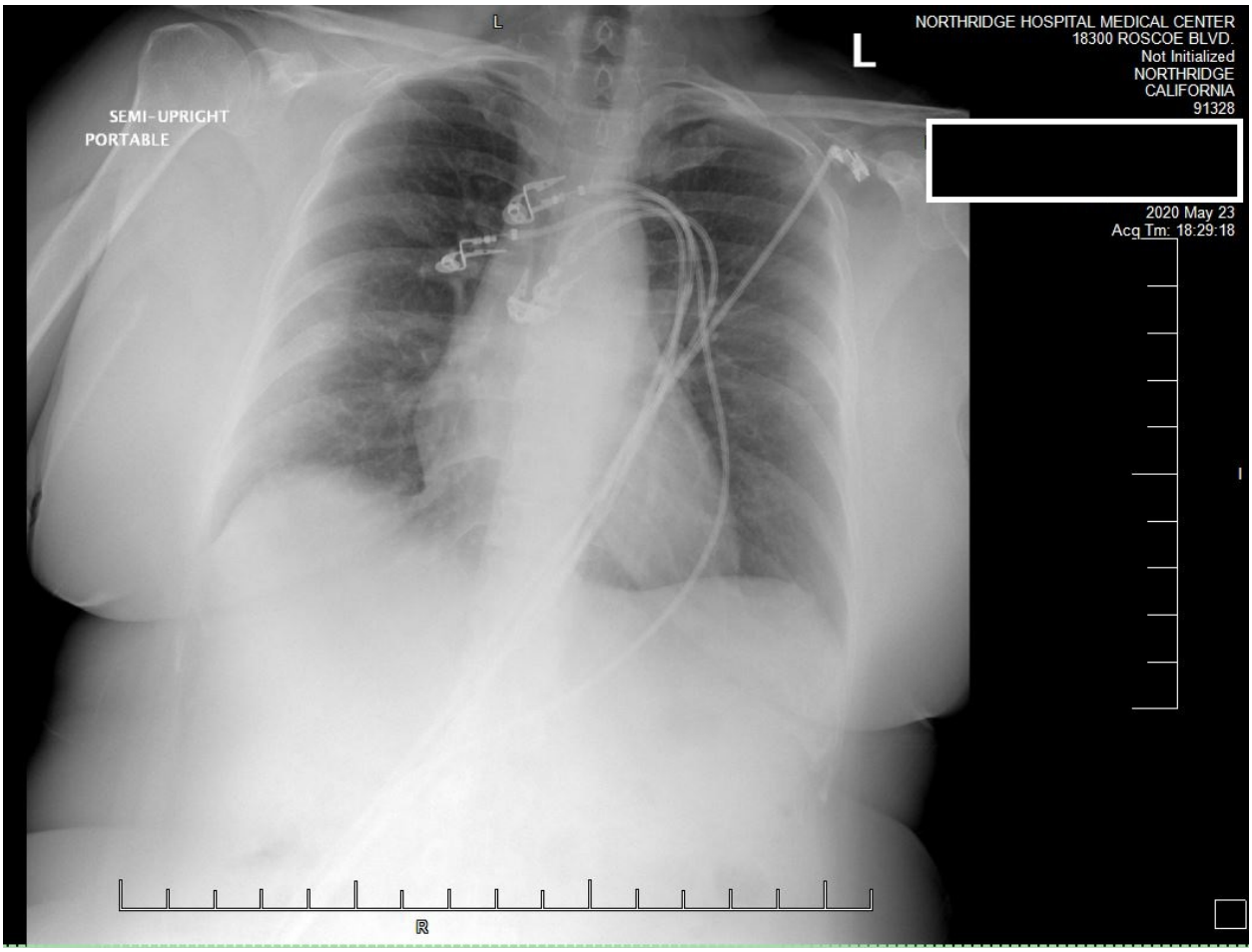

Figure 7a. ER admission CXR: normal

Her SOB, cough and fever worsened and I first saw her in consultation on symptom day #7 with T=102 and an O2 sat of 95% (Patient #7 medical history). CXR revealed new bilateral pneumonia (Figure 7b).

She was begun on the NMN cocktail with a prompt response:

- She became afebrile within 3 days.
- Her other clinical symptoms (cough, chest pressure, SOB and nausea) improved markedly in the first three days with her diarrhea nearly gone in 6 days
- Improved oxygenation (RA O2 sat 95 to 98 % in 3 days)
- Normalization of CXR by day #24 (Figure 7b compared to 7d). CXR day #17 in part better, in part worse than day #7 CXR (Figure 7b compared to 7c)
- Over the first three days her CRP and IL6 both increased. They were next tested on day #17 and were both markedly decreased

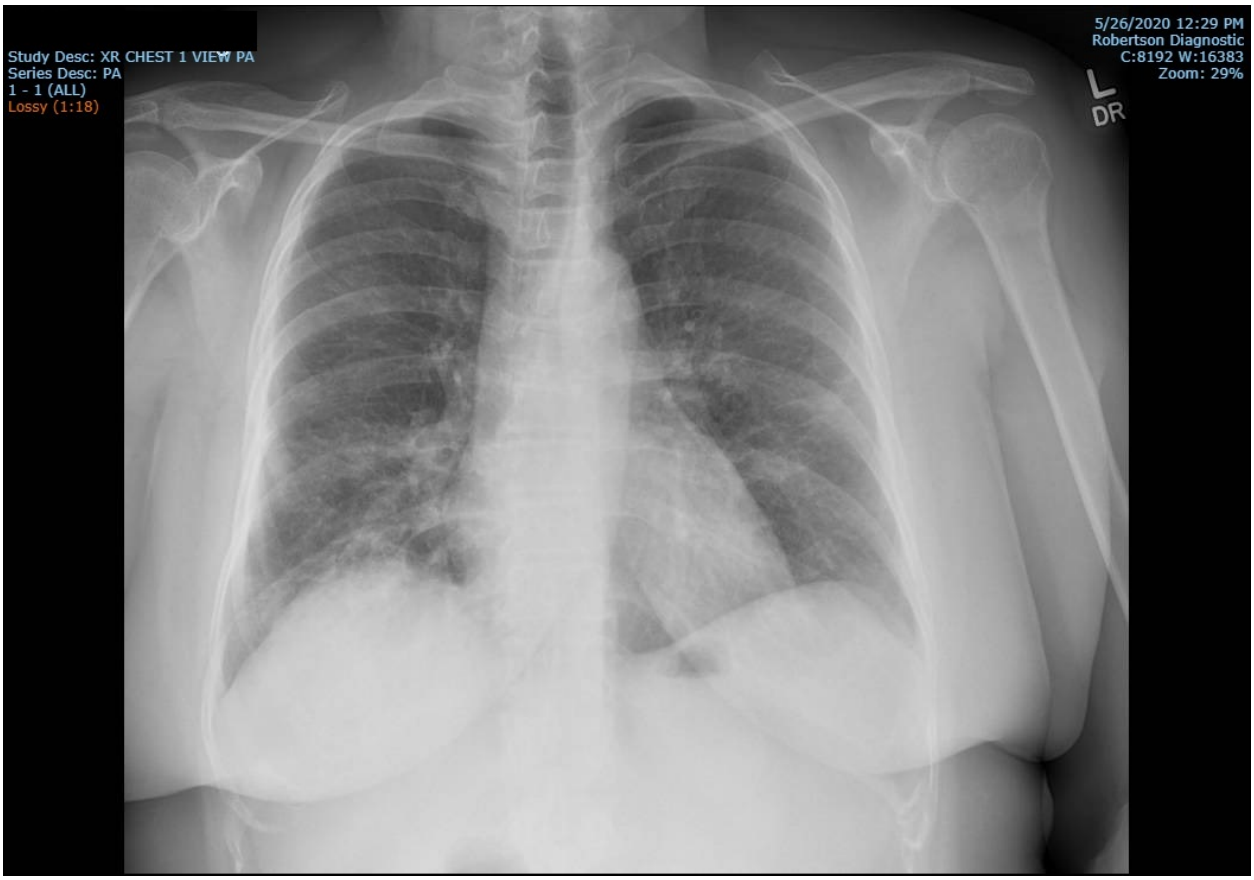

Figure 7b. Symptom day #7 CXR: irregular marginated parenchymal opacities consistent with viral pneumonia

Patient # 7																						
Symptom Day #	1	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	24
Temp (Tmax)	102.8 fever	fever	fever	fever		102.0	100.7	99.9	99.2	98.7	98.5	Afeb	Afeb	Afeb	Afeb	98.1				
Cough	cough, SOB, chest pressure					cough, CP, SOB			SOB, CP, bone pain all better							asymptomatic				
Symptoms	Nausea, diarrhea, weakness, no smell/taste								less weakness, little diarrhea and nausea											
O2 sat RA 5 min						95			98							98				
Covid19 Test				(+) PCR																
Hospital				ER: Breathing difficult, cramps																
CXR				CXR: Nl		bilat infilt										bilat infilt				bilat infil
						worse										RLL worse, LLL better				better
Absolute Lymph				CT chest		1700			2100							3500				
CRP				bilat infilt		3.1			5.8							0.3				
IL6						17.4			41.1							5.3				
Antibiotics	none																			
Zinc sulfate Qd						220 mg	220 mg	220 mg	220 mg	220 mg	220 mg									
NMN/Betaine/NaCl BID						1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr									

Patient #7 medical history

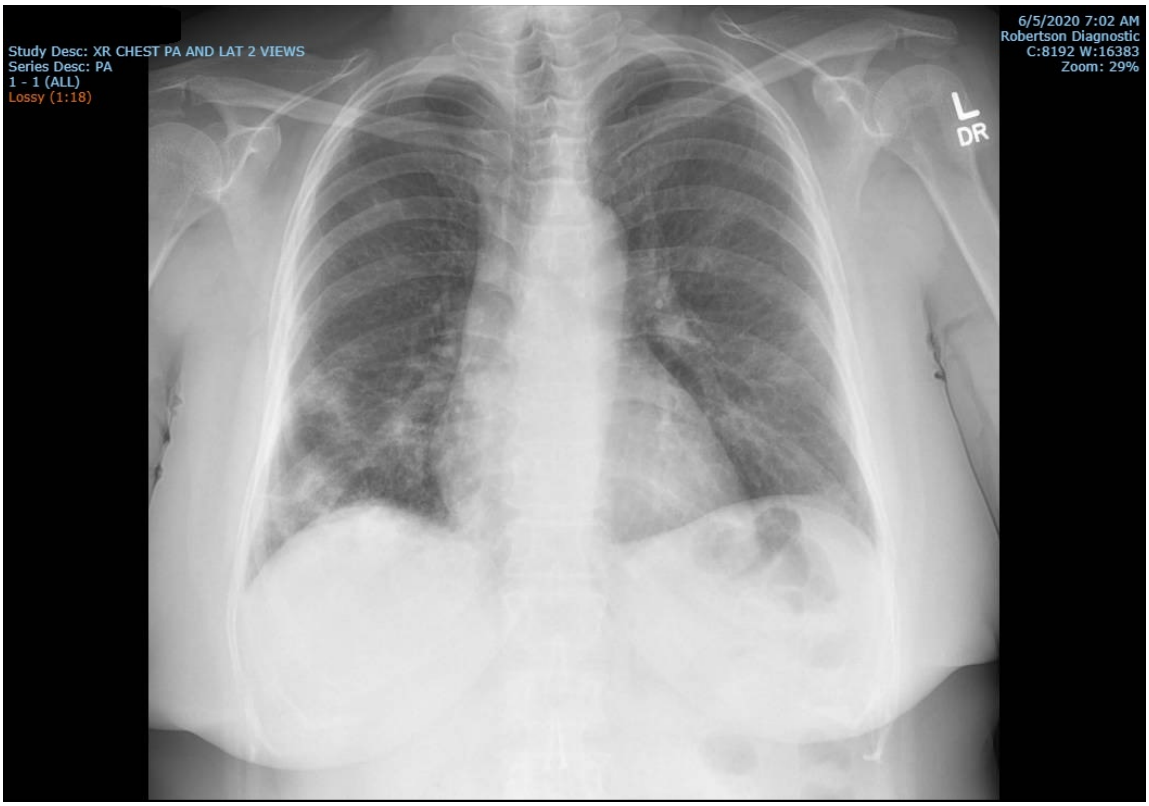

Figure 7c. Day #17 CXR: opacities in the mid to lower lung zone are decreased but increased parenchymal opacification without cavitation R lower lung zone compared with day #7.

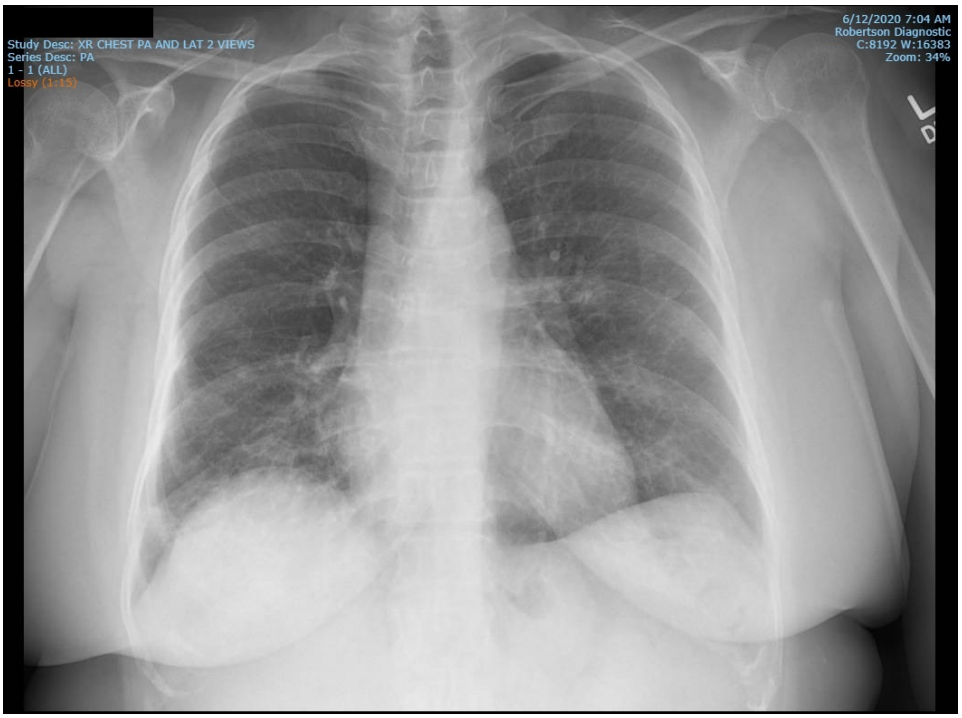

Figure 7d. Day #24 CXR: Deceased parenchymal opacification within the R mid to lower lung zone since day #17, irregular marginated parenchymal opacities.

Case 8: A 60-year-old cab driver was seen on symptom day #12 complaining of 10 days of fever, fatigue, and cough and chest pressure. A CXR revealed bilateral pneumonia (Figure 8a). His nasopharynx SARS-COV-2 NAA test returned positive (Patient #8 medical history).

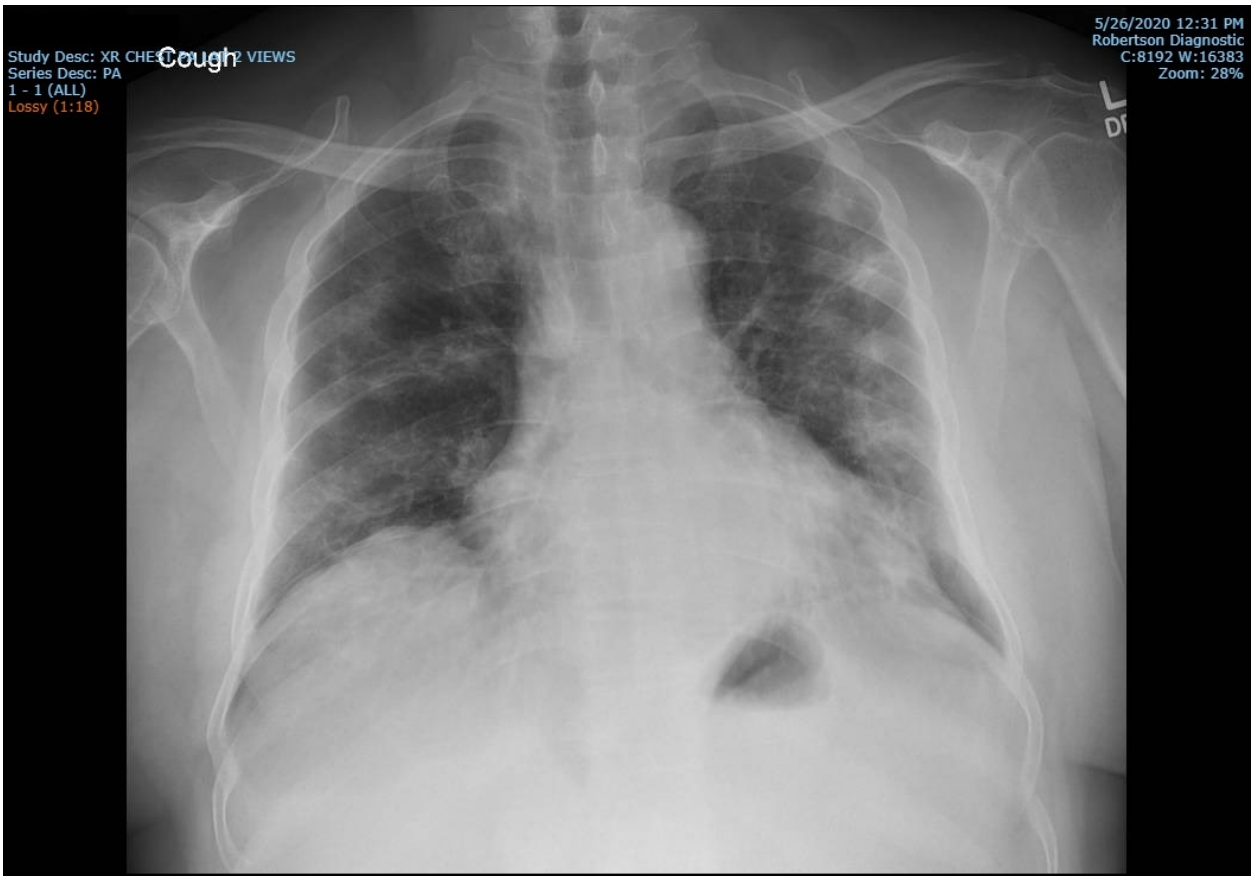

Figure 8a. Symptom day #12 CXR: irregular marginated bilateral parenchymal opacities L>R.

He was begun on the NMN cocktail with a prompt response:

- Resolved temperature (afebrile within 48 hours)
- Improved clinical condition (fatigue, SOB, cough and abnormal chest sensation were 75% better in 2-3 days)
- Potent anti-inflammatory action (CRP, IL-6 and absolute lymphocytes changed -60, -41 and 36% respectively in just 3 days)
- Improved oxygenation (RA O2 sat 93 to 94% in 3 days)
- Modest improvement of CXR in 10 days (Figure 8a compared with 8b).

Patient # 8																					
Symptom Day #	1	3	5	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Temp (Tmax)		100.9	fever	fever	fever	fever	fever	fever	100.2	100.4	99.5	98.9	98.7	98.5	98.7	afeb	afeb	afeb	98.1
Cough	dry cough, chest sensation					dry cough			dry cough			dec cough, SOB, more energy, no CP							no cough
Symptoms						SOB			fatique			"75%" better							"100%"
O2 sat RA 5 min									92/93			94							96
Covid19 Test									(+) PCR										
Hospital																			
CXR									bilat infilt										bilat infilt
																			improved
Absolute Lymph									1400			1900							1800
CRP									25			10.1							1.5
IL6									29.7			17.6							6.2
Antibiotics	none																		
Zinc sulfate Qd									220 mg	220 mg	220 mg	220 mg	220 mg	220 mg					
NMN/Betaine/NaCl BID									1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr					

Patient #8 medical history

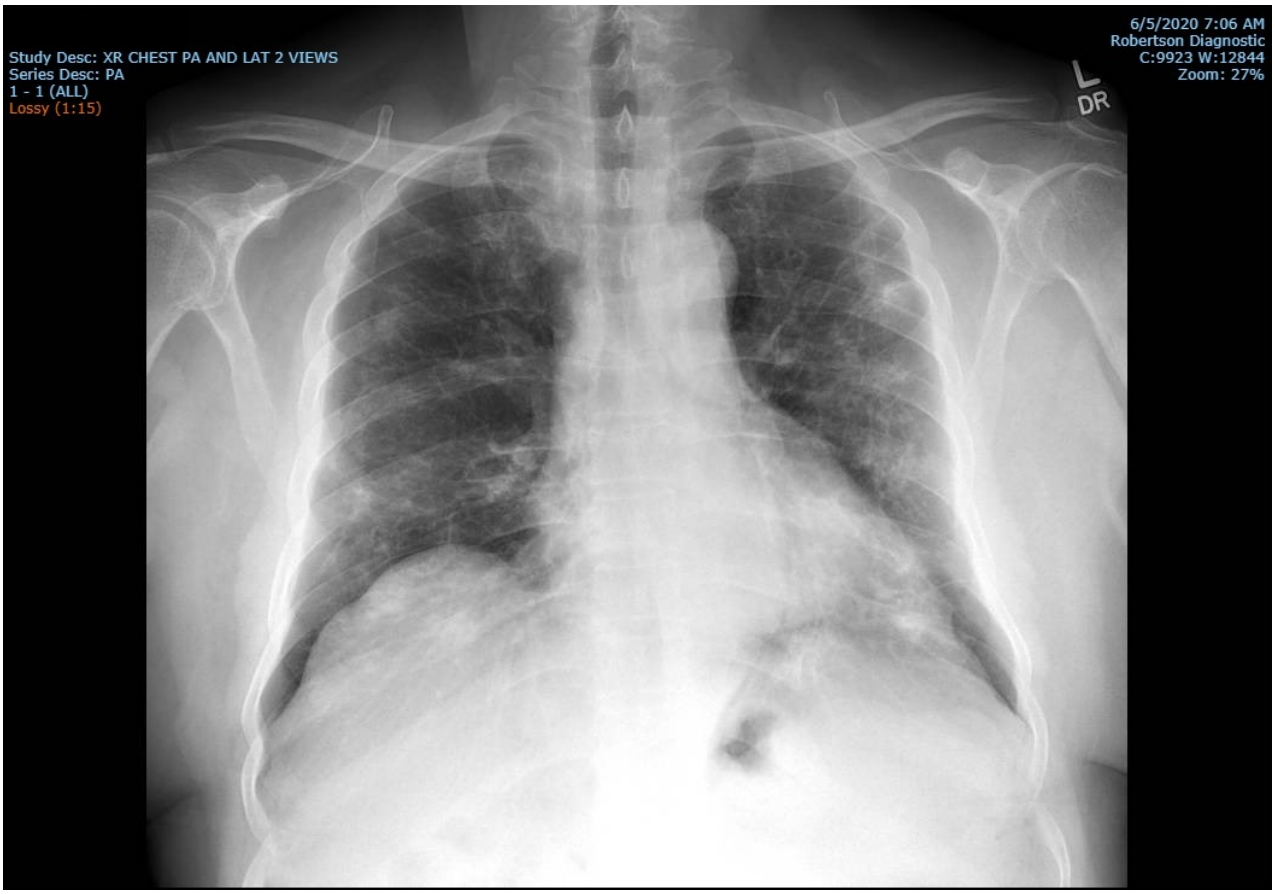

Figure 8b. Day #22 CXR: decreased parenchymal opacification present compared with day #12

Case 10: A 62-year-old SARS-CoV-2 RT-PCR positive business man was admitted to an outlying hospital on symptom day #14 for fever (104º F) dropping O2 sats (92/93%) and bilateral pneumonia. On the second day of his hospitalization, he was told there was no treatment for his condition. He requested admission to Cedars Sinai Medical Center but the "lateral" Covid-19 positive patient transfer was denied based on hospital protocol. He then left the hospital AMA.

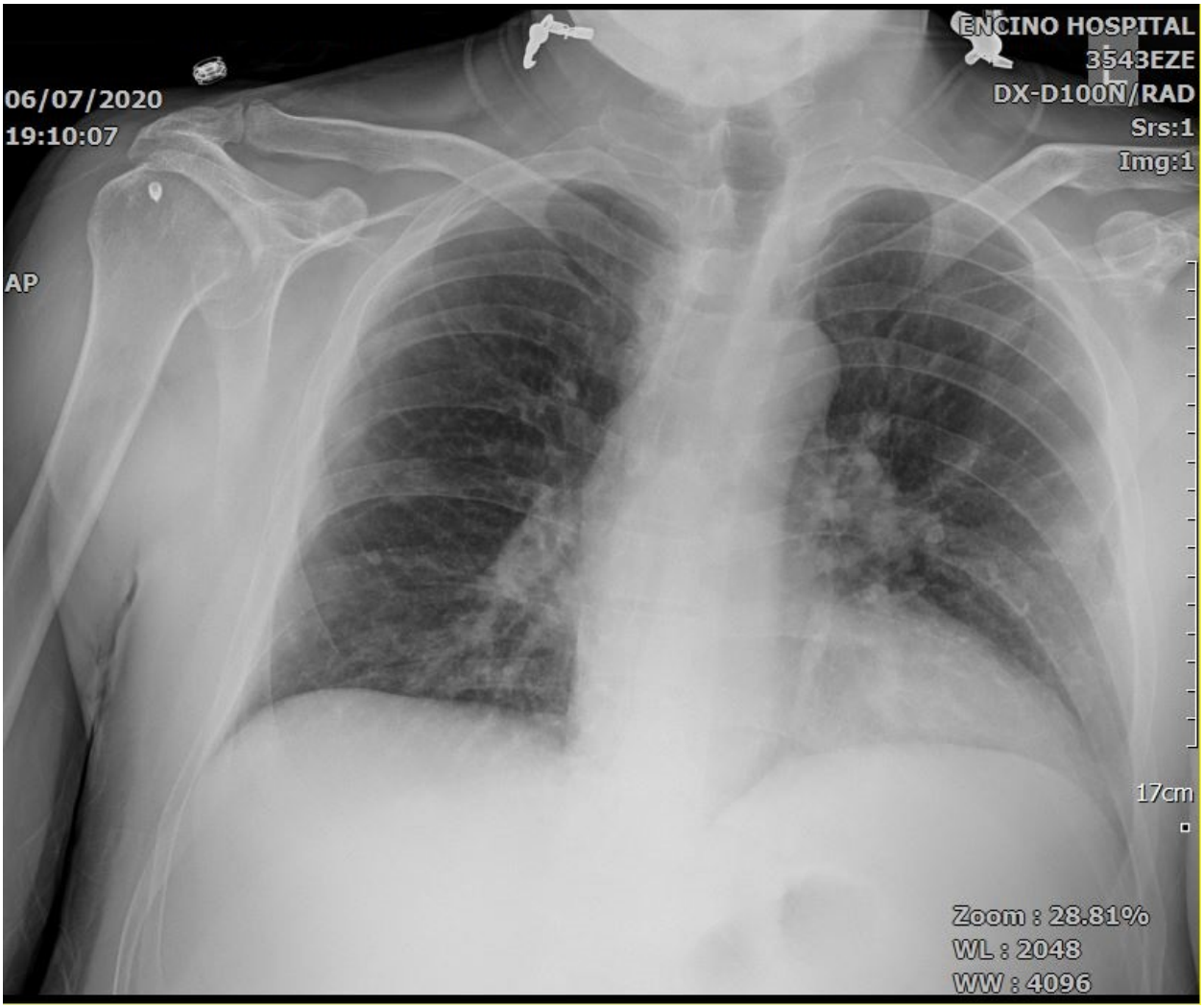

Figure 10a. Day #14 Admission CXR: scattered bilateral infiltrates predominately within the periphery.

He presented to my office with fever to 102º F, cough, extreme exhaustion and hypoxia (O2 sat 92/93%). He was begun on the NMN cocktail with a prompt response:

- Resolved 17 day persistent fever (afebrile within 48 hours)
- Improved clinical condition (17 day fever resolved in 2 days; cough and abnormal chest sensation were 75% better in 2-3 days)
- Improved oxygenation (RA O2 sat 92/93 to 96% in 3 days)
- However, the CXR taken day #19 (after 3 days of NMN cocktail) showed progression of infiltrates compared to the hospital admission CXR (taken 2 days prior to the start of NMN cocktail administration). (Figure 10a compared to 10c and 10d).

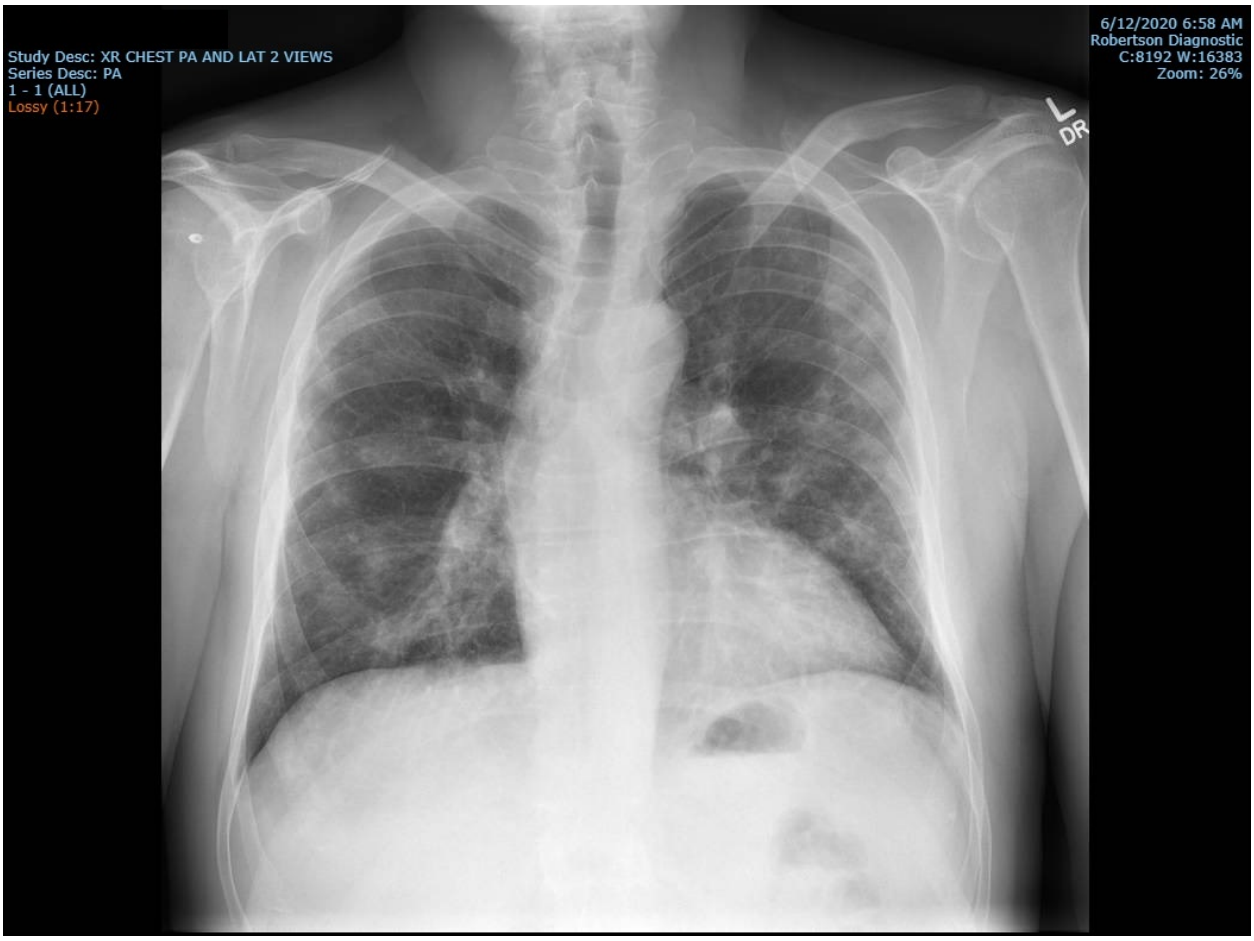

Figure 10b. Day #19 CXR: numerous bilateral ill-defined parenchymal opacities, worse since day #14 CXR

On day #26 the patient returned for a follow-up. He noted continued improvement:

- He remained afebrile and symptomatically far improved only noting some coughing and profuse night sweats
- His CRP after 9 days of treatment dropped about 50% from baseline but his IL-6 increased dramatically from 59 to 269.
- Improved oxygenation (RA O2 sat 92/93 to 98% after 9 days of treatment)
- Improved CXR (Figure 10b compared to 10c after 9 days of treatment).

Patient #10																						
Symptom Day #	1	2	4	6	7	12	13	14	15	16	17	18	19	20	21	22	23	24	26	33		
Temp (Tmax)								103.1	103.7	102	101.9	99	97.8	afeb	afeb	afeb	afeb	afeb	98.8	97		
Cough								cough					persitent cough						profuse (5 shirt changes/night)sweats		no cough	
Symptoms								loose stool					sudden incease appetite, energy						fatigue		no sweat	
O2 sat RA 5 min								93		92-93	93 (home)		96						98	99		
Covid19 Tests		(+) PCR						ABG pO2 67												(+)IgG/M Ab		
Hospital								pneumonia		Home	AMA											
CXR								bilat infilt					bilat infilt						bilat infilt	bilat infilt		
								peripheral infiltrates					worse						improved	much improved		
Absolute Lymph								700		1000			900						1100	1600		
CRP								7.5		14.9			12.2						7	1.5		
IL6										59.2			73.4						269	12.3		
ferritin								1328		1204									964	982		
Antibiotics				Hydroxychloraquine (7d)																		
Zinc sulfate Qd										220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg	220mg			
NMN/Betaine/NaCl	BID									1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr	1.67gr			

Patient #10 medical history

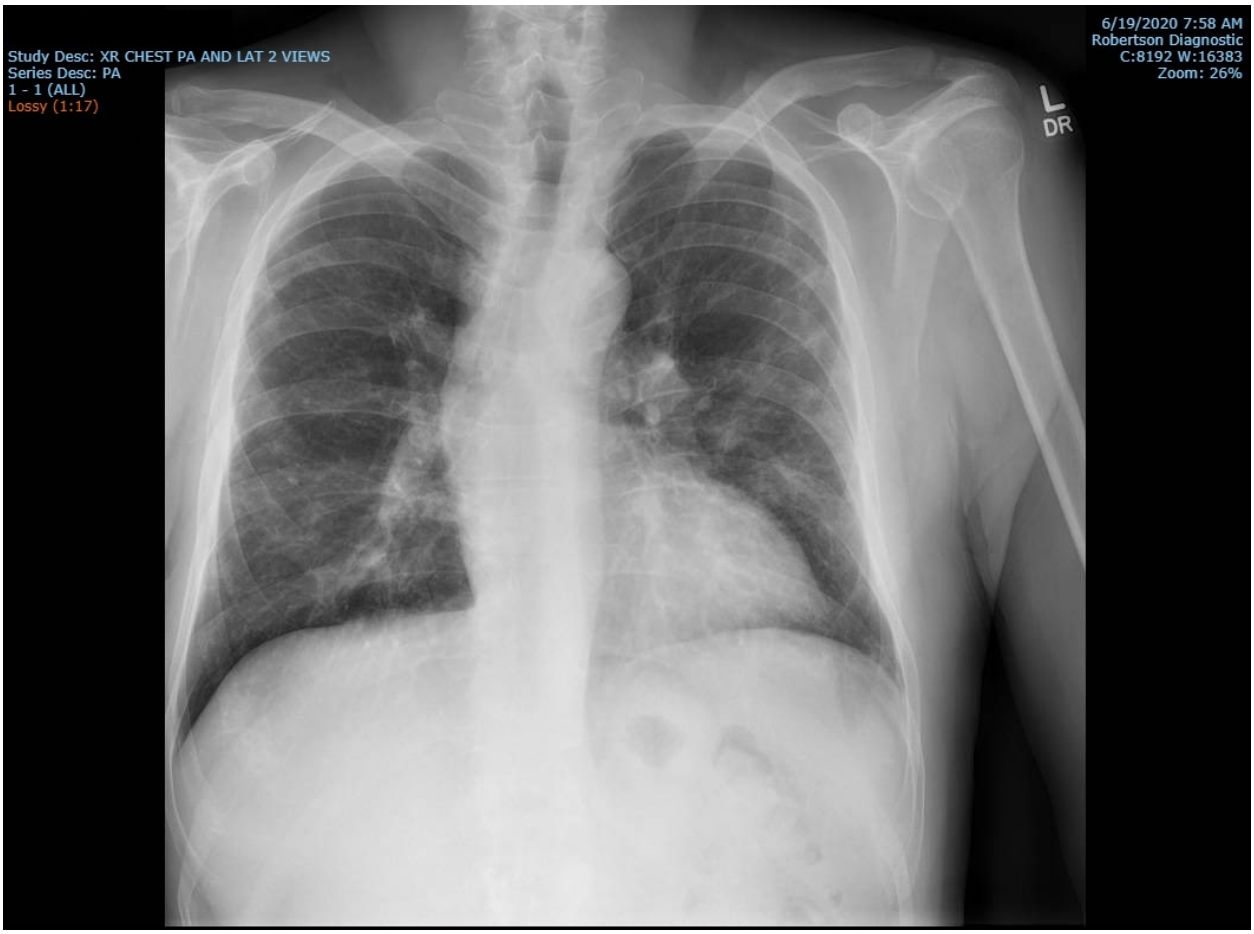

Figure 10c. Day #26 CXR: Significant decrease in bilateral parenchymal opacities compared with symptom day #19

On day #33 the patient returned for another follow-up. He was completely asymptomatic.

- Anti-inflammatory effect (CRP and IL-6 were - 90 and -79% respectively after 17d).
- Near normalization of CXR (Figure 10c compared to 10d after 9 days of treatment).

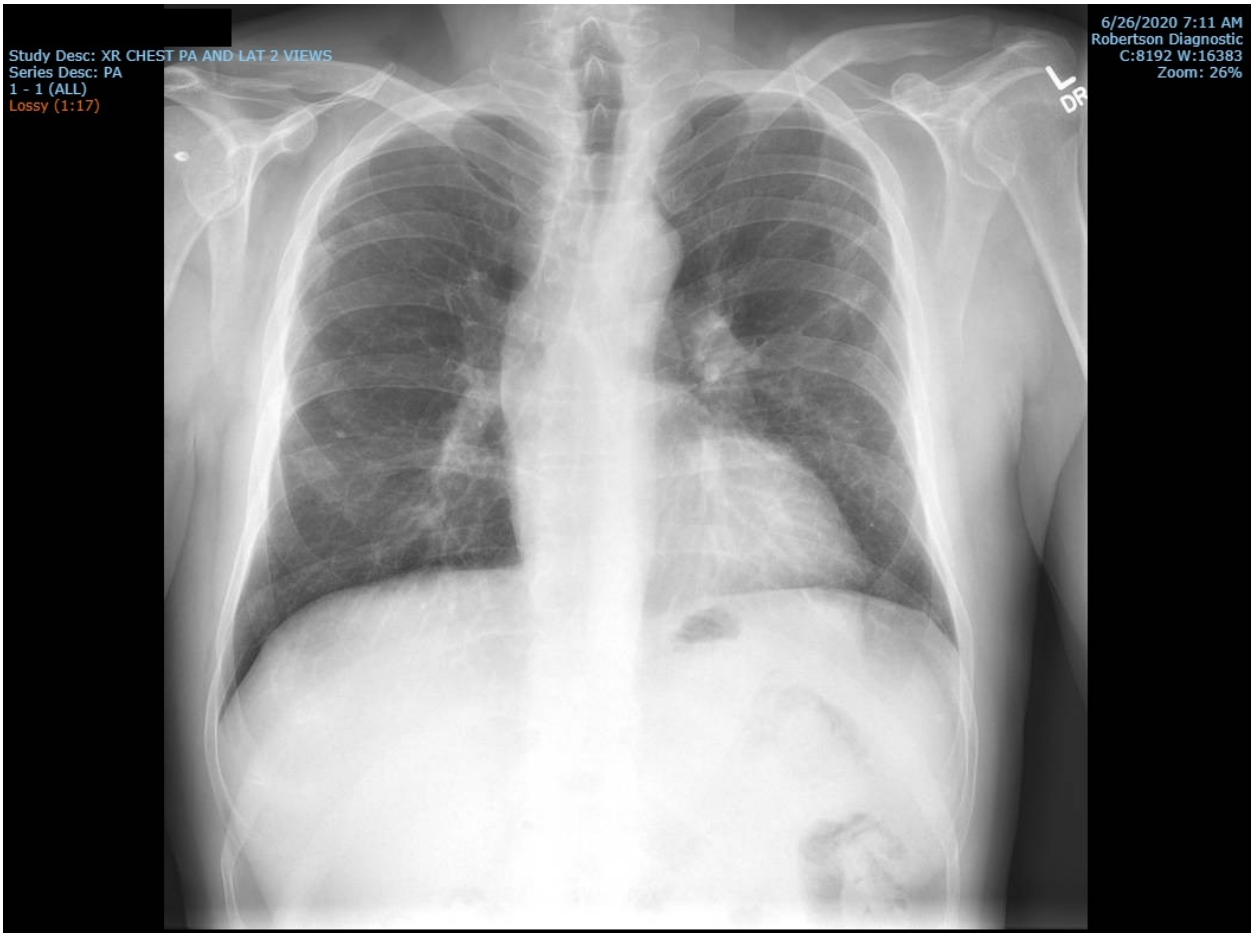

Figure 10d. Day #33 CXR: further decrease in bilateral parenchymal opacities compared with symptom day #26

Discussion: This consecutive series of nine SARS-CoV-2 positive patients - five of whom had findings consistent with ARDS or deteriorating bilateral pneumonia - show a rapid and dramatic clinical improvement associated with NMN cocktail use compared to the expected clinical course of ill elderly SARS-CoV-2 patients seen in recent observational compassionate care trials done at my local Los Angeles hospital[14][15].

NAD+ precursors boost depleted NAD+ levels and may thereby augment anti-viral defense systems as well as attenuate collateral anti-viral inflammation damage. Specifically, the poly-ADP-ribosyl polymerase (PARP) family of NAD+ dependent enzymes are directly involved in anti-viral and specifically anti-SARS-COV-2 innate immunity. However, some viruses, including SARS-CoV-2, have macro-domains to remove ADP-ribosylation from proteins apparently to disrupt cell signaling, DNA repair, gene regulation and apoptosis[16] - ample NAD+ stores are needed to combat this. The sirtuin family of NAD+-dependent lysine deacylases,

especially SIRT1, also have a broad-range of antiviral properties and are essential for successful viral recognition and control of replication.[17]

NAD+ is also critical to protect against the collateral damage of our anti-pathogen defense system. SIRT1 combats chronic inflammation[18] and with SIRT2 suppresses acute lung inflammation during sepsis[19]. Sirtuins also have pro-respiratory and anti-vascular inflammation actions[20].

However, NAD+ supplies can deplete, especially in old age when NAD+ levels drop due to increased consumption by CD38+ glycohydrolase[21]. SARS-CoV-2 infection may further drop NAD+ levels with increased transcription of the poly-ADP-ribosyl transferases, PARP9, PARP10, PARP 12 and PARP14[22]. Other contributors to heightened COVID-19 morbidity and mortality such as obesity[23][24], ARDS (oxidative stress, reduced perfusion, and endothelial dysfunction)[25] and cytokine storm[26] each further exhaust NAD+ supply.

Given the strong molecular rationale for success in treating ill elderly SARS-CoV-2 patients together with increasing evidence that lower NAD+ levels in the lung and vascular endothelium contribute to poor COVID-19 outcomes, NAD+ boosters have been suggested as first-line treatments against COVID-19[27], especially in aged patients[28].

The 9 elderly patients chronicled here were ill at the time of NMN cocktail treatment – all had persistent fevers, 5/7 had ARDS and or documented worsening hypoxia with increasing pulmonary infiltrates. The three hospitalized cases on average had grossly elevated cytokine levels (CRP ~142 and IL6 ~44) at time of treatment consistent with cytokine storm, with little if any virus (2/2). By way of comparison, in a retrospective multicenter Chinese study of 150 confirmed SARS-CoV-2 cases [68 deaths (45%) and 82 discharged (55%)] the average (range) CRP and IL-6 levels of fatal cases respectively was 125(13-230) mg/L and 12(4-31) pgr/mL vs the discharged cases 35(1-125) mg/L and 7(2-13) pgr/mL. Thus, each of the three hospitalized cases had inflammation levels pre NMN cocktail predicting fatal outcomes. CRP $\geq$ 200 (seen patient #1 and 4) is also reported to be a dire prognosticator[29]. Furthermore, cytokine storm, also seen in SARS, Ebola and dengue fever - an exaggerated pro-inflammatory response with lymphocytopenia, elevated IL-6 and CRP levels as documented in 3/9 of the cases in this report– also frequently predicts the development of life threatening pulmonary, cardiac and hematologic conditions[30].

However, even ill COVID-19 patients can have an undulating course, and the majority – even those hospitalized - recover. However, the recent article "Compassionate Use of Remdesivir for Patients with Severe Covid-19"[31] first authored by a Cedars Sinai Medical Center colleague [15], is a stark reminder that persons with clinical deterioration and ARDS requiring hospitalization with high flow nasal oxygenation (approximately 12 days after symptom onset) are gravely ill. All five patients with this presentation (patients numbered 37 to 41 on that papers Figure 2) fared poorly despite an experimental 10-day course of Remdesivir – one died, one probably died and the three documented survivors each required prolonged 25 plus day hospitalizations. Similarly, in Cedars-Sinai's recent compassionate use study of Tocilizumab[32], the six cases treated while on supplemental oxygen, one required intubation and the average hospital stay was >> 10 days (two patients were not yet discharged) as compared to the $\leq$ 5 day hospital stays post NMN cocktail documented here.

In addition to the significant inflammatory marker reduction, all 9 cases discussed here exhibited a strong temporal relationship between the administration of the NMN cocktail and fever and symptom resolution. Patient #6, a 78-year-old patient with multiple co-morbidities, who presented just five days post the onset of Covid-19 symptoms, also had his fever disappear and symptoms promptly improve after 2 days of the NMN cocktail although his symptoms relapsed several days after his abbreviated NMN cocktail course.

At this time, there is no proven outpatient Covid-19 treatment – even for individuals with high risk of poor outcomes or those with bilateral pneumonia. HCQ, AZ, Zn or HCQ alone were administered in 4/9 cases discussed here but in only one was there a transient, temporal clinical improvement. Furthermore, HCQ has shown no benefit in three recent randomized clinical trials[33,34,35]. Azithromycin, a common macrolide antibiotic with known immuno-modulatory and anti-viral properties, was administered to the first three patients. There is no suggestive evidence it helped in these cases; furthermore, in The Recovery Collaborative Group[36], Azithromax did not give any detectable advantage over control. Theoretically, HCQ may have caused eosinophilic pneumonia[37] and contributed to patient #1 and #10's rapid deterioration. However, eosinophilia was never seen on serial complete blood counts. Zinc, a critical mineral that can influence antiviral immunity, particularly in zinc-deficient individuals[38], was given to three individuals, but again only one showed a transient, temporal improvement.

Likewise, hospitalized Covid-19 patients on room air or supplemental nasal oxygen have limited options. Remdesivir has a proven benefit of modestly decreasing average hospital stay (13 to 9 days) with no survival benefit[39,40]. Dexamethasone appears effective in lowering fatality rate for hospitalized patients requiring intubation and to a lesser extent those requiring supplemental nasal oxygen but it appears to be harmful to hospitalized and non-hospitalized Covid-19 patients not requiring oxygen[41].

Tocilizumab, an IL-6 receptor inhibitor costing nearly $3,000 per dose - arrests the entire range of pro and anti-inflammatory IL-6 functions so drug timing to block only pro inflammatory IL-6 functions may be difficult. Also, reported side effects of IL-6 receptor inhibitors include hindering the body's ability to fight off the primary infection or others that often follow – and possibly increasing the risk of anaphylactic shock and lower-intestinal perforation. Uncontrolled observational studies on Tocilizumab treatment for COVID-19 looked promising[42] but Roche recently announced preliminary results of a randomized trial on COVID-19 patients with pneumonia showed no benefit[43].

Convalescent plasma and "warp speed" vaccine development are currently being studied for treatment and prophylaxis respectively, however antibodies may only be partially effective against a rapidly mutating virus[44]. Convalescent plasma was temporally associated with a temporary improvement in patient #4, however his subsequent fever, steadily rising inflammatory markers and deteriorating CXR and O2 sats – were all promptly and permanently reversed by the NMN cocktail. Even in best case scenarios, the most vulnerable individuals - the elderly with co-morbidities - often have weak or defective immune responses to vaccination and vaccine uptake is predicted to be low (58% state they would refuse or were uncertain if they would take the "warp-speed Covid-19 vaccination due to safety concerns[45]).

Despite the decreases in hospitalization and death of up to 30% that may result from appropriate treatment of patients with Remdesivir and dexamethasone, far too many people with Covid-19 are still dying each day. Additionally, a recent study showed antibody levels peak three weeks post infection and then rapidly decline – indicating long lasting immunity – natural or vaccine induced may not be easily attainable[46]. It is our joint responsibility to rapidly design, implement, and complete statistically sound studies of the most promising therapeutic agents against this disease. NMN with nicotinamide (NAM) feedback loop blockers, absorption enhancers and Nrf2 agonists is one such promising therapeutic approach.

Summary: Acutely ill elderly patients in this case study exhibited a compelling temporal relationship between NAD+ precursor cocktail administration and clinical improvement - more remarkably these cases document unusually rapid and thorough clinical turnarounds - markedly different than the expected course of acutely ill older Covid-19 patients, especially those with multiple comorbidities, worsening hypoxemia, ARDS and cytokine storm. NMN with and without boosters deserves further study in elderly patients with complicated COVID-19 as this treatment has a strong molecular rationale for success and can be safely orally administered in outpatients or hospitalized patients where dexamethasone is sometime contraindicated and Remdesivir has at best modest activity.

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