# The Evolving Face of COVID 19

COVID-19 Panel



### Objectives

- Describe the factors affecting epidemiology of COVID-19 regionally and locally.
- Discuss antiviral treatment approaches to COVID-19 and challenges to reaching the goal of Zero Harm.
- Discuss current trends related to monitoring respiratory failure and the treatment of coagulopathy in COVID-19.
- Discuss the multiple late sequelae and therapeutic interventions of COVID-19.



### Patient Presentation, Part 1

- 53-year-old female presents to the Emergency Department in spring 2020 with a 2-day history of dry cough
- Additional symptoms include fatigue and loss of appetite
- Past medical history includes hypertension and morbid obesity
- Works full-time at the post office

#### Ohio



#### Cuyahoga



#### Lake



#### coronavirus.ohio.gov



### **COVID-19 in Ohio**





#### coronavirus.ohio.gov



### When will this end?



the future trajectory of COVID-19. Nature. 2021



### Can SARS-CoV-2 be eradicated?

- Many obstacles:
- Patchy vaccine coverage due to disparities in global access to vaccines and vaccine hesitancy.
- Vaccines may not always block virus transmission (despite reducing the burden of disease).
- Future depends on dynamic interactions between changes in population immunity and ongoing viral evolution and immune escape.

Telenti A et al. After the pandemic: perspectives on the future trajectory of COVID-19. Nature. 2021



### When will this end?

- We don't know whether it will end.
- Better question: what is the future of COVID-19?
- Three possible scenarios.



### **Pandemic forever**

- No rapid control of this pandemic.
- Ongoing manifestations of severe disease combined with high levels of infection.
- Evolution of the virus.
- How to avoid that?
  - Long-term herd immunity thru very broad application of vaccines worldwide
  - Comprehensive disease surveillance by accurate and readily available diagnostic assays or devices.



Telenti A et al. After the pandemic: perspectives on the future trajectory of COVID-19. Nature. 2021

### **Epidemic seasonal disease**

- Transition similar to influenza.
- Effective therapies that prevent progression of COVID-19 disease may bring the burden of SARS-CoV-2 infection to levels that are equivalent or even lower than influenza.
- Is that okay?
  - In non-pandemic years, influenza causes 250,000-650,000 deaths globally (two thirds among people who are 65 years and older).
  - Relatively 'optimistic' view of the future of the COVID-19 pandemic.



Telenti A et al. After the pandemic: perspectives on the future trajectory of COVID-19. Nature. 2021

### **Endemic disease**

- Enough people will gain immune protection from vaccination and from natural infection.
- Childhood illness with cold season peaks, less hospitalization and death.
- Similar other human coronavirus infections (example, OC43 that arguably started as a similar pandemic in 1889).
- SARS-CoV2 appears to be more virulent than another human coronaviruses.
- Further adaptations of SARS-CoV-2 to humans may increase or decrease its intrinsic virulence.
- This requires more widespread population immunity, fewer susceptible hosts.



Telenti A et al. After the pandemic: perspectives on the future trajectory of COVID-19. Nature. 2021

### **Future of SARS-CoV-2 transmissibility**

- High rate of viral RNA recombination within SARS-CoV2, and possibly with other human or animal coronaviruses.
- The virus was reasonably expected to develop increased transmissibility, reflecting adaptations to propagation in the new human host.
- SARS-CoV-2 has shown an unprecedented capacity to evolve global variants that outcompete regional variants in extremely short time windows and before considerable selective pressure owing to pre-existing immunity.
- There is a risk of viral diversification in the currently uncontrolled or incompletely controlled pandemic in many regions of the world.



Telenti A et al. After the pandemic: perspectives on the future trajectory of COVID-19. Nature. 2021

### **Future of SARS-CoV-2 virulence**

- Virulence is not necessarily a selectable phenotypic trait that increases the fitness of the virus → change in virulence is not predictable.
- The severity of disease caused by SARS-CoV-2 is bound to decrease with increasing population immunity.
- Pre-existing immunity is likely to reduce the severity of symptoms after infection, and to prevent future severe pandemics arising from antigenically related coronaviruses that are circulating in bats and other possible animal reservoirs.
- Nevertheless, the evolution of the virus to the low level of virulence seen in common-cold coronaviruses may not occur or may take several decades to manifest.



### **Patient Presentation, Part 2**

- In the Emergency Department, she was febrile and hypoxic
- Chest x-ray was consistent with multifocal pneumonia
- Hypoxia improved with 4 L of oxygen via nasal cannula
- She was admitted to a general medical floor
- COVID-19 PCR test later returned positive

### **Antiviral Treatment Approaches for COVID-19**

- Viral replication
  - RNA-dependent RNA polymerase
  - Proteolysis
- Cell entry
  - Spike protein
  - ACE2 receptor
  - TMPRSS2
  - Endocytosis
- Neutralization



### **Current COVID-19 Therapeutics Summary**

Recommended	Not Recommended
<ul> <li>Remdesivir</li> <li>Monoclonal antibodies</li> <li>Baricitinib</li> <li>Dexamethasone</li> <li>Tocilizumab</li> </ul>	<ul> <li>Convalescent plasma</li> <li>Hydroxychloroquine/chloroquine</li> <li>Lopinavir plus ritonavir</li> <li>Ivermectin</li> <li>Famotidine</li> <li>Nitazoxanide</li> <li>Bamlanivimab monotherapy</li> </ul>

### COVID-19 Therapeutics – Deptember 200201

Agent	FDA	NIH	IDSA	WHO
Remdesivir	$\checkmark$	$\checkmark$	$\checkmark$	
Monoclonal antibodies	$\checkmark$	$\checkmark$	$\checkmark$	-
Convalescent plasma	$\checkmark$			-
Hydroxychloroquine				
Protease inhibitors	-			
Dexamethasone	-	$\checkmark$	$\checkmark$	$\checkmark$
Baricitinib (JAK inhibitor)	$\checkmark$	$\checkmark$	$\checkmark$	-
Tocilizumab (IL-6R inhibitor)	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$
Anakinra (IL-1R1 inhibitor)	-		-	-
Ivermectin				
Recommend under certain conditions	Recommend aga	ainst	Insufficient data	No recommendation

 $\checkmark$ 

### The Challenge of COVID-19 Clinical Trials

- Investigators similarly dealt with emerging data
- Adapted traditional approaches
  - Studied agents concurrently
  - Adaptive platforms
  - Merging trial phases
- Data safety monitoring board
- Communication

9 March	29. April	28 May	05. June	10. 7 297.
Slandard of Care	1		1	
Hydroxychioroquine	1	1	X	
Detamethasone	1	1	1	
Lopinavie/Ritonavie	1	1		
Azithronyein	l. I	1	1	
	Toul 24-46	1		
		Convalies	icht Plasma	+ +
		1	i	



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### **Risks and Benefits of Treatment without Evidence**

- Potential devastating consequences of disease
- Pressure to offer help as a provider



- Treatment may lead to worse outcome than no treatment
- Potential of jeopardizing patient trust



\*e.g., harms that lead to distrust, poor evaluations of care, and unwillingness to return to the health care facility

### **Strategies for Attainment of Zero Harm**

- 1. Commit to the goal of zero harm.
- 2. Become more patient-centric.
- 3. Recognize the interdependency of safety, quality, and patient-centricity.
- 4. Adopt good data and analytics.
- 5. Transform culture and leadership.
- 6. Focus on accountability and execution.



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### **Provider Responsibilities for Investigational Treatment**

- Assess the patient's individual clinical situation
  - Available alternatives
  - Potential risks versus benefits
  - Eligibility for clinical trials
- Appropriately advise the patient
  - Effectiveness not yet demonstrated
  - Potential unknown risks
  - Alternative options, including no treatment



### **Communication Strategies**

- Be honest, transparent, and clear
- Engage in shared decision-making
- Enable community participation



### **Patient Presentation, Part 3**

- Hydroxychloroquine and azithromycin were initially started
- Also treated with ceftriaxone for community-acquired bacterial pneumonia
- Patient enrolled in the remdesivir clinical trial and was randomized to receive 10 days of treatment
- Subsequently became more hypoxic and required transfer to the intensive care unit for closer monitoring















#### Patchy dense ground glass opacifications in both lung fields

#### **Extrapulmonary Manifestations**



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### **Poor Prognostic Laboratory Data**

	Value		Value
WBC	> 10,000 cells/ µL	ALT	> 40 U / L
Lymphopenia	< 1000 cells / µL	LDH	> 245 U / dL
Thrombocytopenia	< 150,000 / µL	Ferritin	> 300 µg / L
Creatinine	> 1.5 mg / dL	D-Dimer	> 1000 ng / ml
СК	> 185 U / L	IL-6	> 10 pg / mL
Hs Troponin	> 20 ng / L	Procalcitonin	> 0.5 ng / mL

#### Characteristics, Diagnosis, and Management of Covid-19 According to Disease Stage or Severity.

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis	Viral replication Inflammation				
Potential		Antiviral ther	ару		
Potential Treatment		Antiviral ther Antib	apy ody therapy	Antiinflamm	atory therapy





### **ICU Management**

Intensive Support	Immunomodulators	Anticoagulation
Oxygen therapy NIV MV – lung protection Sedation Paralysis Prone position	Corticosteroids (dexamethasone) IL-1 inhibitors (anakinra) IL-6 inhibitors (tocilizumab) Intravenous immunoglobulin JAK inhibitors (baricitinib)	Prophylaxis Therapeutic
Inhaled Epoprostenol		
Inhaled NO ECMO	Clinical Research	Palliative
Attention to other organ dysfunction	Clinical trials focusing on therapeutics	Communication End of Life Care

### ICU Management

**Intensive Support** 

**Oxygen therapy** NIV MV – lung protection Sedation **Paralysis Prone position** Inhaled Epoprostenol Inhaled NO ECMO Attention to detail

- Hemodynamics
- Renal function
- Thrombosis



Roca O, Am J Respir Crit Care Med. 2018 Dec 21

#### **Failure of Noninvasive Ventilation**

 $P_aO_2$ 

In patients with moderate-to-severe hypoxemia, the expired tidal volume above 9.5 mL/kg predicted body weight accurately predicts noninvasive ventilation failure Critical Care Medicine: February 2016 - Volume 44 - Issue 2 - p 282-290

#### **RECOVERY Trial:** Mortality in Patients on Oxygen or Mechanical Ventilation ± Dexamethasone



Better

Better

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Cleveland | Ohio

#### Systemic Corticosteroids and 28-Day All-Cause Mortality in Critically III Patients with COVID-19



\**P* = .31 for heterogeneity;  $l^2 = 15.6\%$ .









#### Therapeutic Anticoagulation with Heparin in Critically III and Non-critically III Patients with Covid-19



The REMAP-CAP, ACTIV-4a, and ATTACC Investigators\*N Engl J Med 2021;385:777-89.

	weight (kg)	Drug <u>target Heparin Assay, Lovenox is 0.3 – 0.5 IU/mL</u>
	< 100	Enoxaparin 40 mg daily
	100-150	Enoxaparin 40 mg bid
	> 150	Enoxaparin 60 mg bid
< 1000	<ul> <li>Enoxaparin shoul</li> <li>"Heparin Assay, L needed based on</li> <li>Aim: target Love         <ul> <li>Adjustd</li> </ul> </li> <li>If on CRRT or HD,             <ul> <li>use hepa</li> <li>use hepa</li> <li>use hepa</li> </ul> </li> </ul>	d be timed for 0900 and 2100 if BID ovenox" should be drawn 3.5-4 hours after the second dose, then as level and renal function <b>nox assay 0.3-0.5 IU/mL</b> oses in increments of 10-20 mg depending on level and renal function rrin 5,000 Units Q8H when weight <150 Kg rrin 7,500 Units Q8H when weight >150 Kg
D- Dimer ng/ml	Weight (kg)	Drug <u>target Lovenox or UFH levels (See Below)</u>
	< 100	Enoxaparin 40 mg bid
	100-150	Enoxaparin 80 mg bid
	> 150	Enoxaparin 120 mg bid
1000 - 3000	For patients requiring Anticoagulation" UHC © Enoxapa © "Heparin then as r • Aim: tar • Adj fun • If on CRRT or HD, by 12 Units/kg/hi • Aim: target Hepa	doses ≥80 mg, recommend using the "Enoxaparin Therapeutic are orderset for ease of ordering rin should be timed for 0900 and 2100 Assay, Lovenox" should be drawn 3.5-4 hours after the second dose, needed based on level and renal function. get Lovenox assayl 0.3-0.5 IU/mL ust doses in increments of 10–20 mg depending on level and renal ction use Low Intensity Heparin drip as per EMR (60 Units/kg IV bolus, follow "constant IV infusion). Monitor with "Heparin Assay" rin level 0.2-0.3 IU/mL
D- Dimer ng/ml	Weight (kg)	Note: Lovenox & UFH Assay have different therapeutic level

#### **Cannot Look Clinical Judgment Risk : Benefit**

#### **VTE Not Diagnosed**

#### **VTE** Diagnosed

### **Patient Presentation, Part 4**

- Completed 9 days of remdesivir
- Improved and was sent home on 2 L of oxygen on Hospital Day 12
- Continued to have fatigue at hospital follow-up 3 weeks later
- Symptoms prevented her from returning to work



### The care path of COVID-19 has been treacherous



having to navigate difficult bends and curves along the way

University Hospitals

Confidential Quality Assurance Peer Review Report Privileged Pursuant to Ohio Revised Code Sections 2305.24, .251, .251, .252, .253

### and just when things seemed to have calmed....



The evolving face of COVID-19 sneaks up behind us

Creating challenges for providers and society, forcing GPS to suggest an alternative route

## One of those challenges: the Post-acute sequelae of SARS-CoV-2 (PASC)

- PASC is the research term for the wide range of health consequences that are present more than four weeks after the acute COVID-19 illness.
- Patient advocacy groups refer to PASC as individuals having long haul manifestations or long COVID



### Long haul/Long COVID.....origin of the names



**Amy Watson** 

- Amy Watson a pre-school teacher in Portland, Oregon on March 15, 2020 became sick with COVID-19
- A month later with persistent symptoms and inspired by a picture of her wearing a trucker's when her PCR testing was performed......
- She started a support group Long Haul
   <u>Covid Fighters</u>
- Elisa Perego from Lombardy Italy in response to her prolonged illness coined the term "Long COVID"

#### Questions for you to consider regarding Long COVID (True/False)

- Long COVID generally associated only with complicated Acute COVID-19
- Risk factor generally are the same as those associated with the acute disorder
- Long COVID not a disorder of concern for younger adults, children, and those with asymptomatic infection
- Generally <10% of patients with Acute COVID will develop long haul sequelae
- Unvaccinated with long COVID may benefit from immunization
- Nearly every organ system is susceptible to the adverse effects of the disorder
- Behavioral health issues are primarily associated only with preexisting psychological disorders
- Population health concerns can potentiate long haul symptoms
- A team approach may be beneficial to the care of affected patients

### **Total Number of Acute COVID-19 cases\***



Cuyahoga County: 133,000



\*New York Times data base



### Multi-organ involvement related to long COVID













- **Difficulty thinking/concentrating** ("brain fog")
- Depression and Anxiety
- Difficulty breathing
- Coughing
- Painful joints or muscles
- Trouble sleeping
- Chest pain
- Palpitations
- Dizziness on standing
- Headache
- Fever
- Loss of smell or taste
- alopecia



### Long COVID: risk factors

- While known risk factors are associated with developing acute COVID-19 such as obesity, hypertension, COPD and smoking, definite risk factors are unknown for Long COVID
- What is known is that long COVID can occur in anyone infected with SARS-CoV-2, from young to old and even those who have asymptomatic infection
- Potentially greater risk: female > males; older children > younger children; >5 initial symptoms; disease severity



### **Prevalence of Long haul manifestations**

- Fair Health White Paper looked at claims data of nearly 2 million patients with SARS-CoV-2 infection for prevalence of post acute COVID conditions 30 days or more after acute illness
- 23.2 % had at least one post-COVID condition
- More prevalent in hospitalized patients approximately 50%, symptomatic patients non hospitalized 27.5 %; those with asymptomatic acute infection long haul symptoms present in 19%

A FAIR Health White Paper June 15, 2021 a detailed study of patients with Long-Haul COVID: an analysis of private healthcare claims One contributing factor for long COVID manifestations (among those with severe acute disease) is the Post-intensive care syndrome (PICS)

- Constellation of cognitive, psychiatric, and physical signs and symptoms newly-recognized or worsened after a critical illness
- Common symptoms include weakness, poor mobility, poor concentration and difficulty with self care
- Anxiety symptoms 34 to 38 percent of patients
- Depressive symptoms 29 to 32 percent
- **PTSD** 18 to 34 percent



### Other hypothesized causes.....

- Persistent hyper-inflammatory response
- Ongoing viral activity associated with a host reservoir
- Inadequate antibody response
- Organ damage from acute infection
- Worsening of **pre-morbid conditions**
- Physical deconditioning



# Long COVID complaints likely are potentiated by other factors resultant from the pandemic

- Adverse effects of quarantine, confinement and loneliness
- Economic hardships along with food and housing insecurities





### How many are in it for the long haul?



- Within Cuyahoga County: 133,000 cases of COVID-19
- Assume 20% have developed long
   COVID.....approximately 27K
- Assume **4 out-patient visits** for long COVID care following acute illness
- Approximately **100K visits** since the pandemic began

### **Evaluation of Long COVID: history**

- Outline the course of the acute infection, severity, Rx, etc.
- Establish a **timeline** of **long COVID symptoms** (when they began relative to acute illness) along with their **frequency** and **intensity**
- Detail co-morbid conditions which may have been exacerbated or unmasked by the infection
- Define impact on QOL, functionality, work capacity, return to school, etc.
- Record if and how **social determinants** are **impacting** the illness

### **Evaluation of Long COVID: testing**

- Remember: "One size does not fit all"; standard order sets for Long COVID are difficult to establish
- Laboratory and diagnostic testing needs to be guided by a patient's history, physical examination, clinical findings
- Generally, more conservative testing during the first 12 weeks after acute COVID-19
- However, with persistent or exacerbating manifestations a more comprehensive evaluation is needed

### Long COVID: dx assessment

system	diagnoses	Dx considerations
<b>Respiratory:</b> dyspnea, cough, wheezing, chest pain	Persistent COVID pneumonia, ILD, PE/DVT, asthma, super infection	Chest X-ray, PFTs, 6MW; consider D Dimer, CTA, HRCT
Poor general well being: fatigue, muscle pain, malaise	PTSD, chronic fatigue, myositis, collagen vascular disorder, sleep disordered breathing, anxiety, depression	CBC, Comprehensive metabolic panel; TSH, free T4 sed rate, CRP, ferritin, ANA RF, ant- CCP, anti-cardiolipin, CK PHQ9, GAD7, Ru-SATED (sleep)
<b>Nervous system:</b> memory loss, headache, dizziness, focal weakness, paresthesias, numbness, etc.	Encephalopathy, stroke, neuropathy, POTS	CBC, Comprehensive metabolic panel; TSH, sed rate, MOCA, neuropsychogical testing, MRI, autonomic testing
<b>Cardiovascular:</b> chest pain, dyspnea, palpitations, tachycardia	Myocarditis, arrhythmia, autonomic dysfunction, ischemic heart disease	Troponin, BNP, EKG, echocardiogram; CK, Cardiac MR, event monitors, tilt table testing
Behavioral Health	Anxiety, depression, psychosis, manic depression	CBC, Comprehensive metabolic panel; TSH, sed rate, PHQ9, GAD7, Ru-SATED (sleep)

### **PASC: dx assessment**

system	diagnoses	Dx considerations
Metabolic disorders:	worsening diabetes, thyroiditis, AKI, osteoporosis	comprehensive metabolic panel, TSH, free T4, U/A, renal ultrasound
Gastrointestinal:	gastroenteritis, IBS, aggravation of underlying IBD, elevated LFTs with hepatitis	Liver functions, stool cultures, US gall bladder, etc.
ENT:	Persistent loss of taste and smell; tracheal stenosis, vocal cord issues, Bell's palsy	Consider smell retraining protocol, referral to ENT as needed
MISC:	alopecia	Comprehensive metabolic panel, TSH

### Highway of Care...... UH COVID Recovery Clinic





### Multi- disciplinary team approach

#### UH COVID RECOVERY CLINIC



Manager





#### **Other specialists**

**Social services** 

Support group



#### **UH COVID RECOVERY CLINIC**

**INTEGRATED** 

Conferences to discuss disease management

Designed to aid in the investigation of PASC: clinical manifestations, pathogenesis, natural history.

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Goals: 1) provide long haul patients hope that recovery is possible: 2) guide them along a diagnostic and therapeutic care path facilitating their return to a normal life!! 3) expand our knowledge base regarding PASC helping to understand the many facets of this complex disorder





In regards to returning to normal life we want recovering patients to feel like they have won a championship....









### **GO GUARDIANS!!!**



### **Patient Presentation Conclusion**

- The patient continued to have symptoms over a year from initial diagnosis
  - Profound fatigue and sense of heaviness
  - Lack of motivation and depression
  - Headaches and body aches
  - Memory impairment and fogginess
- Diagnosed severe sleep apnea and started on CPAP
- Evaluated for bariatric surgery and referred to psychology
- Working remains limited to a few days per month
- Referred to the COVID-19 Recovery Clinic

