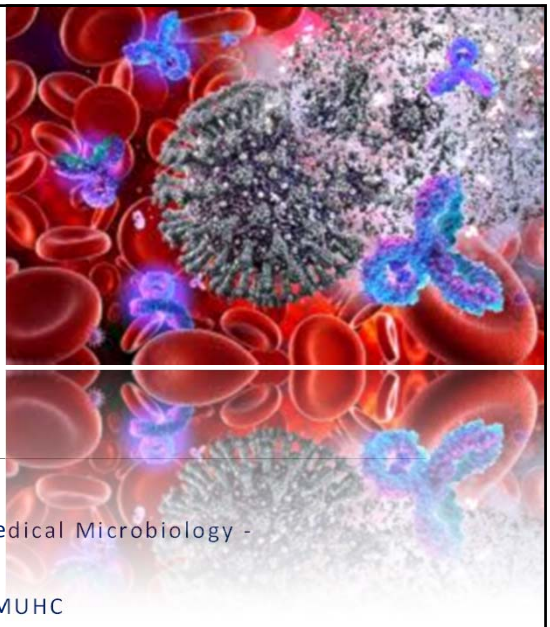
COVID-19 Therapy: Where Are We?



Drug Therapy course - May 6, 2021

Makeda Semret, MD FRCP(C)

Associate Professor of Medicine, Infectious Diseases & Medical Microbiology - McGill University

Antimicrobial Stewardship Program Lead, MUHC

Disclosures

- Clinical research on AMR/stewardship & COVID clinical trials (CONCOR-1, CATCO)
- Advisory role: Federal GoC COVID-19 Therapeutics Task Force (06/20 – 02/21)
- **No honoraria, gifts, consulting fees, research funding from industry**

MUHC ASP | Antimicrobial Stewardship Program

Objectives

- Recognize indications for treatment of COVID-19
- Choose appropriate/optimal drugs for treatment (and recognize inappropriate regimens)
- Recognize post-COVID complications: MIS-A, "long-COVID"

MUHC ASP | Antimicrobial Stewardship Program

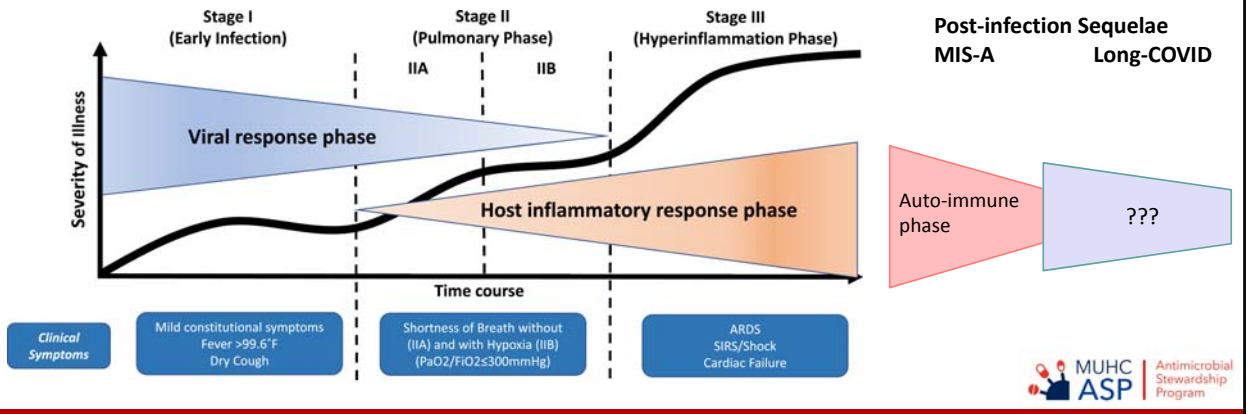
Current Context – in a nutshell

- > 140 Million cases globally - 1.2 M in Canada
- All ages at risk of infection but probability of serious COVID-19 >> with age and comorbidities
  - 12x risk of death and 6x risk of hospitalization if comorbidities vs none
  - cardiovascular disease, diabetes, chronic lung disease; obesity, cancer, kidney, immunocompromising conditions including transplant
  - Pregnancy
- VOCs: now more frequent than "original" strain → more transmission, ? Severity ??

MUHC ASP | Antimicrobial Stewardship Program

Clinical spectrum of disease

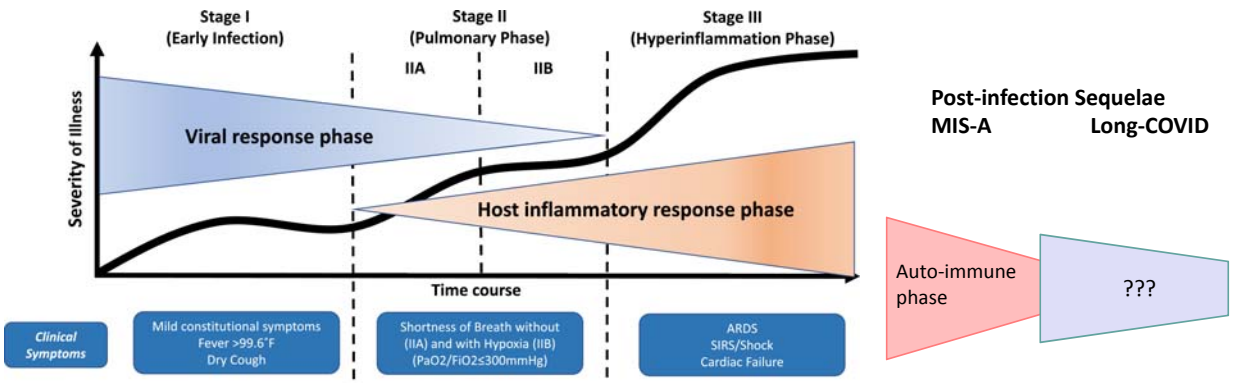
Asympto/Pre-symptomatic/Mild -- Moderate -- Severe -- Critical



MUHC ASP Antimicrobial Stewardship Program

The Journal of Heart and Lung Transplantation 2020 39405-407DOI: (10.1016/j.healun.2020.03.012)

Management considerations based on disease stage



MUHC ASP Antimicrobial Stewardship Program

The Journal of Heart and Lung Transplantation 2020 39405-407DOI: (10.1016/j.healun.2020.03.012)

A Practical Approach to Classification

- Note **day of onset of first symptoms** (not only the day of first positive test)
- Generally, can assume
  - **Day 1-10** : active viral replication phase
  - **Day 8 – 14**: immune response phase
- Decision to admit:
  - Moderate/severe/criticial
  - Mild but **high-risk** of progression to moderate or severe

MILD:
No dyspnea, normal O_2 Sat on Room air (> 92%)

MODERATE:
Dyspnea; LRTI (clin/radiological); Supp O_2 for Sat >92%

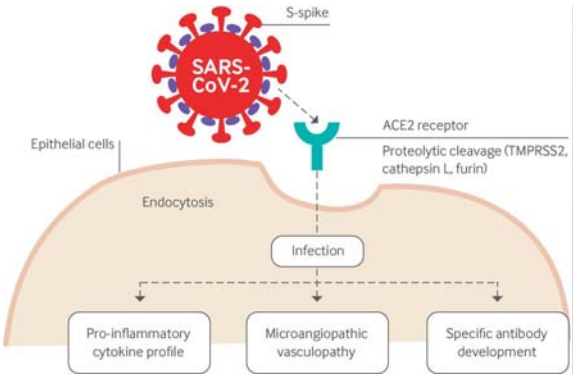
SEVERE:
Hi-flow O_2 to keep Sat > 92%; Lung infiltrates > 50%

CRITICAL:
Intubated with Resp failure +/- MOF

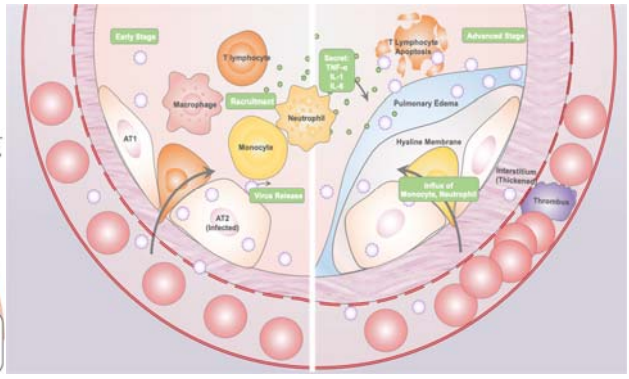
- Immunocompromised state
- Obesity (BMI > 35)
- Diabetes
- Chronic kidney disease
- Pregnancy
- Serious cardiovascular disease
- Severe chronic lung disease

MUHC ASP Antimicrobial Stewardship Program

Pathogenesis



Amy H Attaway et al. BMJ 2021;372:bmj.n436



Wang et al (2021); https://doi.org/10.1038/s41392-021-00527-1

MUHC ASP Antimicrobial Stewardship Program

Principles of treatment

- Block viral entry
- Block viral replication
- ↓ hyperimmune activation
- Reduce pro-coagulant state

➢ Antibody therapy
➢ Antiviral therapy
➢ Steroids; cytokine-inhibitors
➢ Anticoagulation

MUHC ASP | Antimicrobial Stewardship Program

Therapeutic landscape

Evidence for use (animal/human studies (RCTs)

- Remdesivir
- Dexamethasone and other corticosteroids
- Therapeutic anticoagulation (LMWH)
- Cytokine inhibitors (eg. Tocilizumab)
- Monoclonal antibodies

Tentative/mixed evidence (ongoing studies):

- Favirapivir
- molnupiravir
- Fluvoxamine

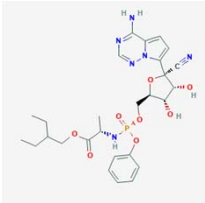
Convalescent plasma? Ivermectin?

FAILS: Long list!! (Repurposed drugs)

- *Hydroxychloroquine*
- *Lopinavir-ritonavir*
- *Chloroquine*
- *Colchicine*
- *Hydroxychloroquine + azithromycin*
- *famotidine*
- Convalescent plasma

MUHC ASP | Antimicrobial Stewardship Program

Remdesivir



- Prodrug of an ATP analog
- Initially vs Hep C and Ebola
- Activity vs RNA viruses
- Is only available IV

Several large RCTs – **mixed results**

ACTT-1: shorter median recovery time with remdesivir (10 vs 15 days), but differences in mortality not significant; clinical efficacy similar between 5 and 10 days of treatment

- Sub-analysis: largest effect in patients not severely/critically ill

WHO (Solidarity) trial: No difference vs standard of care for any outcomes

OUR RECOMMENDATION:

✓ONLY if **early in disease** (viral replication, < 10d) + **moderate severity**

✓Monitor closely for adverse events (hepatic, GI, renal, cardiac)

✓Duration x 5 days

MUHC ASP | Antimicrobial Stewardship Program

Dexamethasone

Best evidence from RCT (RECOVERY):

- Reduction in 28-day mortality for patients requiring O_2 therapy (34% less compared with no steroids)
- Higher likelihood of being discharged from hospital at 28d
- subgroup of patients without hypoxia: no evidence of benefit, actually increased mortality/harm

Pooled estimate from multiple studies:

- Reduction in mortality OR 0.72 (0.57-0.87)
- Viral clearance slower in steroid group (10-29d vs 8 – 24d in non-steroid group)
- Trend towards more antibiotic use in steroid group

OUR RECOMMENDATION:

✓Start dexamethasone 6mg (po or IV) **ONLY i**f requiring supp O_2 (moderate, severe, critical)

✓Monitory glycemia

✓If dexamethasone unavailable, equivalent doses of alternative glucocorticoids

MUHC ASP | Antimicrobial Stewardship Program

Tocilizumab

Humanized monoclonal Ab that binds IL-6 receptors

Early trials did not show a treatment effect (pre-steroids)

RECOVERY trial and REMAP-CAP
- Mortality benefit in subset with evidence of progressive disease
- Mortality 28% vs 36% in patients with rapid decompensation
- Benefit in terms of days off organ-support

Risk of serious bacterial infection; allergic reaction, liver failure

OUR RECOMMENDATION:
- ✓Tocilizumab ONLY in patients with *rapid* resp decompensation (<24h of severe), or criteria for "cytokine storm"
- ✓Avoid if known bacterial superinfection/sepsis

[8] **Proposed criteria to identify COVID-19 cytokine storm (COV**

SARS-CoV2+ AND ground glass opacities on CXR/CT + Ferritin > 250 ng/mL + CRP > 46 mg/L + at least one from each cluster	
Cluster 1	
Albumin	< 28 g/L
% lymphocytes	< 10.2% of total WBC
Absolute neutrophils	> 11.4/mm³
Cluster 2	
ALT	> 60 IU/L
AST	> 87 IU/L
D-dimers	> 4,930 ng/mL
LDH	> 416 IU/L
Troponin I high sensitivity	> 1090 ng/L
Cluster 3	
Anion gap	< 6.8 mmol/L
Chloride	> 106 mmol/L
Potassium	> 4.9 mmol/L
Ratio Urea:Creatinine (urea in mmol/L x 1000 divided by creatinine in umol/L)	> 100:1 (pre-renal AKI)

MUHC ASP | Antimicrobial Stewardship Program

Therapeutic anticoagulation

All infections prone to thrombotic complications

COVID-19: Direct and indirect effects on hemostasis
- Endothelial damage and Inflammation ➔ hypercoagulable state
- COVID-associated coagulopathy (CAC): ↑ D-dimers, ↑ PT

Prevalence of VTE in COVID-19: **14% overall**; 40% in studies using ultrasound screening

International RCTs (ATTACC, REMAP-CAP, ACTIV-4):
- o Benefit to full-dose anticoag in moderately ill (decreased need for ventilation or organ support)
- o No benefit in severe/critically ill

OUR RECOMMENDATION:
- ✓Therapeutic dose ONLY if mild/mod disease & *no contraindications* & expected stay > 3d
- ✓Continue until significant clinical improvement (or x 14d)

MUHC ASP | Antimicrobial Stewardship Program

Additional notes

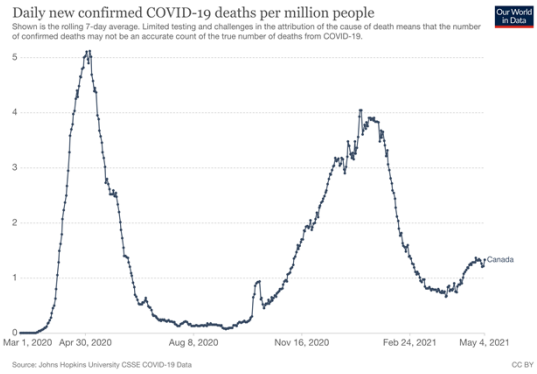
- **Monoclonal Neutralizing Antibodies to SARS-CoV2 (Bamlanivumab, combination)**
  - Bind Receptor-binding domain of virus -- BLOCK viral entry into cells and replication
  - RCT data : benefit in preventing progression to mod disease/ hospitalization
  - HC approved; but barred by provinces for logistical reasons (IV infusion)
  - **If available, would recommend ONLY early in disease (pre-symptomatic, early symptomatic and MILD) for patients at HIGH risk of progression**

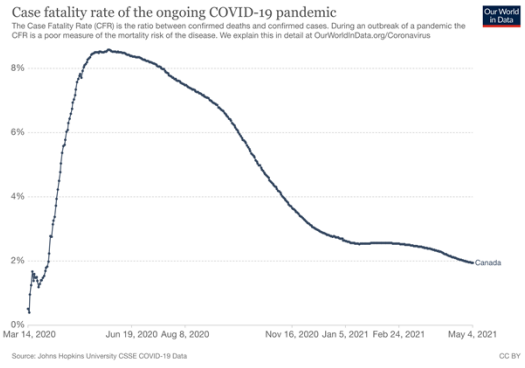
- Starting antibiotics empirically is **NOT recommended/appropriate**
  - Clinical and radiological picture fairly typical in COVID-19
  - Can get SARS-CoV 2 test result quickly
  - Overall bacterial infection rate 7% (< 3% on presentation, 15% later in disease (ICU)

- Stopping ACE-inhibitors or ARBs is NOT necessary

MUHC ASP | Antimicrobial Stewardship Program

Evolution of the outbreak





MUHC ASP | Antimicrobial Stewardship Program

Post-COVID sequelae

- **Multi-system Inflammatory Syndrome (MIS-C and MIS-A)**
  - Children >> adults
  - Fever, lab evidence of inflammation, multi-organ involvement (Cardiac, renal, GI, pulmonary)
  - Recent test + for SARS-CoV2 or exposure within 4 weeks; often SARS-CoV2 antibody AND no alternate diagnosis
  - No consensus on treatment: ASA, IVIG, steroids; +/- immunomodulators (Anakinra)
- Long COVID
  - Range of symptoms x weeks/months
  - Post-ICU syndrome with weakness
  - Fatigue, "brain fog", headache, palpitations, .. Similar to symptoms post hospitalization for other infections
  - Optimal therapy??

MUHC ASP Antimicrobial Stewardship Program

CONCLUSIONS

- Good supportive care (and oxygen) remain the mainstay of treatment for most patients
- Many compounds that were felt to be promising ended up as flops; others were unexpectedly beneficial
- *EARLY* phase therapy (neutralizing antibodies, ? antivirals) to avoid/shorten hospitalization in high-risk patients is hopefully the next step
- We've come a long way !

MUHC ASP Antimicrobial Stewardship Program

THANK YOU!

Questions?

makeda.semret@mcgill.ca

www.muhcasp.com