COVID-19: Implications for Pharmacists

Paul Reynolds, PharmD, BCCCP
Matthew Miller, PharmD, BCIDP
Gina Moore, PharmD, MBA

March 20, 2020

Skaggs School of Pharmacy and Pharmaceutical Sciences
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

COLORADO PHARMACISTS SOCIETY

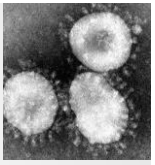
Learning Objectives

- Identify the unique clinical and epidemiological characteristics of Coronavirus (COVID-19) in the spectrum of viral clinical illnesses and previous Coronavirus (SARS, MERS) and non-Coronavirus (influenza, common cold) related illnesses
- Describe the epidemiological impact of interventions to reduce spread of disease in the setting of limited healthcare resources
- Summarize common clinical presentations of COVID-19 compared to other cold and influenza related illnesses and describe who should receiving referral for testing
- Analyze emerging literature regarding potential treatment modalities for COVID-19
- Devise potential roles for pharmacists and technicians in a variety of healthcare settings for the management of a COVID-19 pandemic
- List the steps the Colorado Pharmacists Society (CPS) is taking to address COVID-19.
- Describe how CPS is collaborating with other professional pharmacy organizations and state and federal agencies.

Before Our Talk…

- Information regarding COVID-19 is rapidly evolving
- Quality of data in a pandemic is limited (especially early)
  - Case Series
  - Case Reports
  - Important to separate preliminary information from fact
  - Experimental conditions vs real world data
  - Efficacy of antivirals vs clinical efficacy
- Pharmacist's role:
  - Trusted
  - Source of truth
  - Separate science from theory and opinion

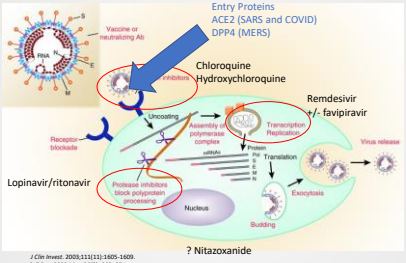
Introduction and Nomenclature



- Coronavirus as a Family of Viruses
  - Positive sense RNA viruses
  - Largest genome of RNA viruses
  - Beta-Coronaviruses most common to infect humans
    - HCoV variants – the common cold (infecting humans for 800 plus years)
    - Mutant variants – SARS-CoV, MERS, SARS-CoV-2/COVID19
- COVID-2019
  - Also known as "coronavirus" or SARS-CoV-2
  - Origination in China (patient zero likely November or December 2019)
  - 76% identical genome to SARS
  - 96% identical genome to Cave Bat CoV

Origin

Pathogens **2020**, *9*, 186; doi:10.3390/pathogens9030186



J Clin Invest. 2003;111(11):1605-1609.
Cell Res. 2020 Mar; 30(3): 269–271.

COVID-19 Myth 1: ACE/ARB Treated Patients Do Worse Because of Viral Entry ACE Protein

Answer:
Could Happen But No Data

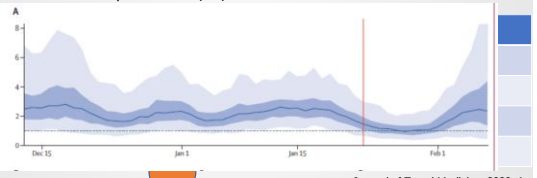
ACC/HFSA/ESC say do not discontinue to prevent COVID-19

Few differences in# hypertensive patients with mild vs severe disease

Image source amazon

Why Is COVID-19 So Clinically Relevant?

COVID-19 Has a Basic Reproduction (Ro) number of 2-3



Journal of Travel Medicine, 2020, 1–4

COVID-19 Myth 2: COVID-19 Can Live on Surfaces for Days

Answer 1: Partially False

Determined by Inoculum Size and Half Life on Object

Steel: 5.6 hours
Plastic: 6.8 hours

Very low inoculum at 72 hours but still there (same as SARS)

Answer 2: Droplets are primary mode of transmission (Aerosol Half Life – 1 hour)

Asymptomatic patients with a high viral load can transmit (2 days before symptoms)

Image source amazon
Data source: https://www.nejm.org/doi/full/10.1056/NEJMc2004973

Why Is COVID-19 So Clinically Relevant?

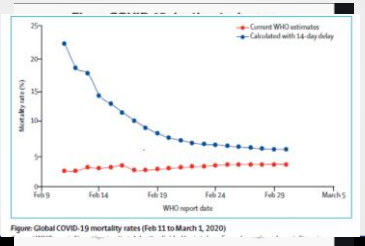


Figure: Global COVID-19 mortality rates (Feb 11 to March 1, 2020)

Source: CDC
Source: Baud et al Lancet Infectious disease 2020

UPDATE ON NEWLY DISCOVERED CORONAVIRUS

	SARS CoV	MERS CoV	SARS-CoV 2
Virion Structure	Enveloped RNA virus	Enveloped RNA virus	Enveloped RNA virus
Outbreak period	2003-2004	2012-present	Dec 2019-present
Initial site of isolation	Guangdong province, China	Saudi Arabia	Wuhan, China
No. of countries/cases	29	27	>70
No. of cases (mortality)	8,096 (9.6%)	2,494 (~34%)	~109,936 (N=3,806)(3.4%)* 6,129 critical (~14%)
No. of cases U.S.	8	2 (2014)	538 (WA, IL, CA, AZ, Mass, Wis)
Reservoir (intermediate host)	Bats (palm civet)	Bats (dromedary camels)	Bats (likely a zoonosis)
Incubation period	2-7 days (range, 2-21)	2-7 (range, 2-14 days)	2-14 days (mean 5-6)
Infectivity, rho	1.8-2.5	0.3-1.3	~3 (2.4-3.8)*
Super spreaders	Yes	Yes (common)	Yes (many examples)
Asymptomatic/mild Spread	No	Rare	Yes/Yes
Attack Rate	10.3% to 60%	4 to 20%	20-30%, 80% (early study)?
Transmission (including to HCP)	Droplet/Direct, Airborne/Indirect?	Droplet/Direct, Airborne/Indirect?	Droplet/Direct, Airborne/Indirect/Fecal
Treatment (PEP)	Supportive (none)	Supportive (none)	Supportive (drugs TBD)
Infection Prevention	Airborne, contact, face shield	Airborne, contact, face shield	Airborne, contact, face shield

*About 83% of cases are mild or asymptomatic. Mortality Rates are age Stratified:

Source: https://specialcoronapreach.com/

Differentiating Symptoms

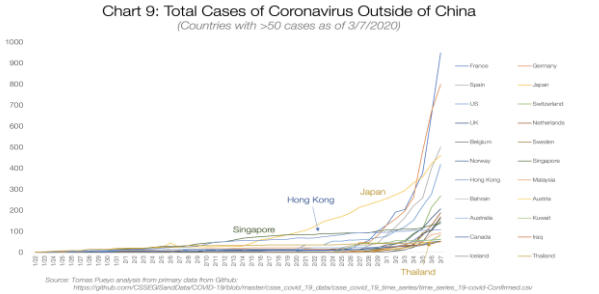
Symptom/Lab	COVID-19	Influenza	Common Cold
Fever	>80-90% – careful sometimes delayed!	>80-90%	Very Rare
Cough	70% of which majority is dry cough (30% sputum producing)	Often dry	Common – dry or wet
Myalgia/Fatigue	11-50%	Common	Rare
Immune effects	Leukopenia (30-60%) – T cell Depression	Rare	Never
Platelet effects	Thrombocytopenia (40-60%)	Rare	Never
Sneezing	No	Rare	Common
Congestion	No	Rare	Common
Sore Throat	13%	Rare	Common
Hospitalization Rate	4-16% (ICU)	0.03%	Rare
Cause of Death	Acute Respiratory Distress Syndrome (ARDS)	ARDS	Rare

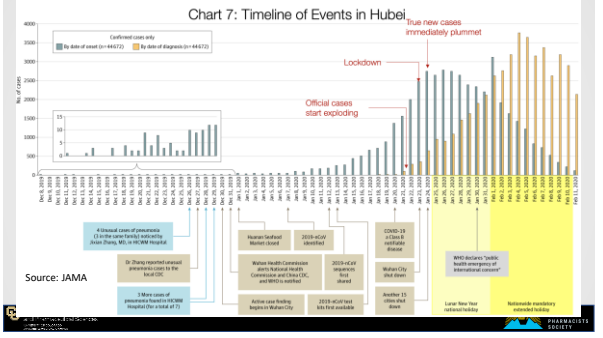
Testing for COVID-19

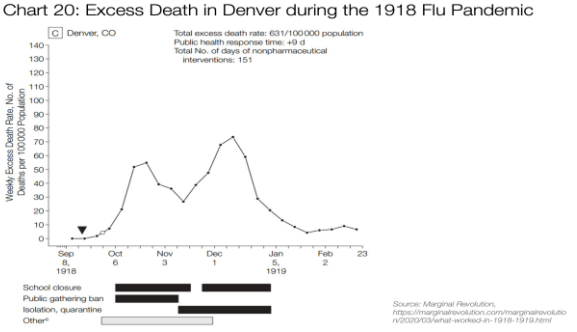
- What tests are available?
  - Standard of care: Real time rRT-PCR (Nasopharyngeal, oropharyngeal, bronchioalveolar lavage, aspirates, sputum)
  - Alternative testing (in development): IgM ELISA, Point of care testing
- Who to test?
  - At risk individuals with symptoms compatible with COVID-19
  - Hospitalized patients with symptoms compatible with COVID-19
  - Any persons (esp healthcare workers) within 14 days of close contact (from sx onset) of a confirmed COVID-19 patient
- Colorado: Mitigation strategies may go into effect

The Reason for Separation

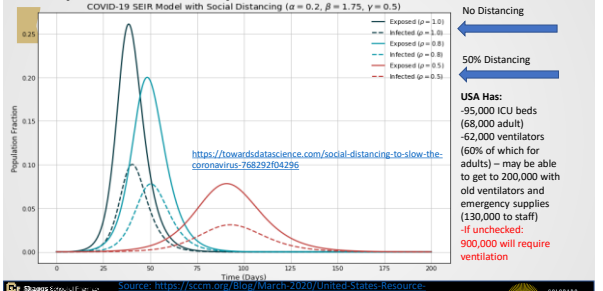
Source: Medium.com





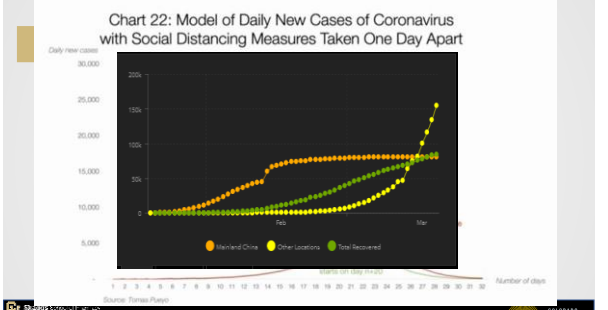


Compliance and spread



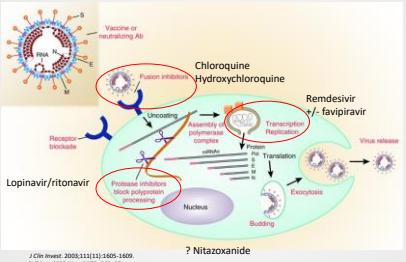
USA Has:
-95,000 ICU beds (68,000 adult)
-62,000 ventilators (60% of which for adults) – may be able to get to 200,000 with old ventilators and emergency supplies (130,000 to staff)
-If unchecked: 900,000 will require ventilation

Source: https://sccm.org/Blog/March-2020/United-States-Resource-Availability-for-COVID-19



Therapeutics for COVID-19

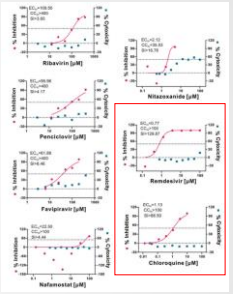
No antiviral therapy has proven effects against COVID-19, and none of the following agents have any approved indications for COVID-19



J Clin Invest. 2003;111(11):1605-1609.
Cell Res. 2020 Mar; 30(3): 269–271.

In Vitro Activity

- SARS-CoV-2 EC_{50} lowest for:
  - Remdesivir (Gilead) – investigational, broadly active against RNA viruses
  - Chloroquine – FDA approved anti-malarial agent
    - CID. 2020: Hydroxychloroquine EC_{50} = 0.72 µM vs. chloroquine EC_{50} = 5.5 µM
  - Nitazoxanide – FDA approved anti-parasitic with reported anti-viral effects
- Lopinavir/ritonavir
  - SARS-CoV-1: EC_{50} = 17 µM
    - EC_{50} down to 1 µg/mL if ribavirin added
    - HIV EC_{50} = 0.017-0.102 µM



Cell Res. 2020; 30 (3), 269-271.
Antimicrob Agents Chemother. 2014; 58(8): 4875-84.
Clin Infect Dis. 2020; Epub (PMID: 32150618)

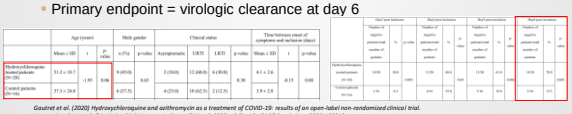
Clinical Evidence – Chloroquine/hydroxychloroquine

- In vitro data only published
  - Hydroxychloroquine 400mg PO BID x 1 day, then 200mg PO BID x 4 days
  - Chloroquine 500mg PO BID x 5 days
- No published clinical experience to date
- Reports from China (not actual data presented/published)
  - Reduces pneumonia exacerbation
  - Reduces duration of symptoms
  - Improves viral clearance
  - Well-tolerated
- Monitoring – QTc prolongation, GI side effects, retinopathy

Clin Infect Dis. 2020; Epub (PMID: 32150618)
Biosci Trends. 2020; 14(1): 72-3.

Clinical Evidence – Hydroxychloroquine

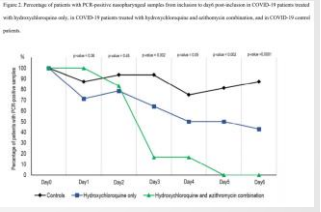
- Prospective, non-randomized, open-label study
  - Hospitalized with confirmed COVID-19
  - All patients offered hydroxychloroquine (HCQ) 200mg PO TID
    - Those refusing treatment or who met exclusion (allergic to HCQ, retinopathy, QT prolongation, G6PD deficiency) served as untreated controls
    - Antibiotics could be given for treatment/prevention of bacterial infection
  - Primary endpoint = virologic clearance at day 6



Gautret et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – DOI : 10.1016/j.ijantimicag.2020.105949

Clinical Evidence – Hydroxychloroquine

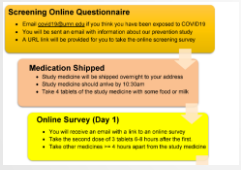
- Results excluded 6 HCQ treated patients
  - 3 ICU transfers
  - 1 died
  - 1 left hospital
  - 1 stopped HCQ for GI upset
- Limited data for clinical outcomes
- Unclear role of azithromycin

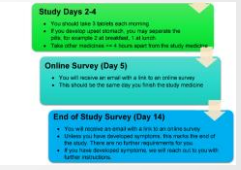


Gautret et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – DOI : 10.1016/j.ijantimicag.2020.105949

Clinical Evidence – Hydroxychloroquine

- Post-exposure prophylaxis study - HCWs:





Clinical Evidence – Lopinavir/ritonavir

- SARS-CoV-1
  - Chu et al. 2004: ARDS or death lower with lopinavir/ritonavir vs. ribavirin alone (2.4% vs. 29%)
    - Retrospective, imbalance in baseline characteristics between groups, lopinavir/ritonavir patients received concomitant ribavirin
    - Rapid viral load decline in lopinavir/ritonavir recipients from nasopharyngeal specimens
  - Chan et al. 2003: lopinavir/ritonavir plus ribavirin decreased mortality compared to ribavirin alone (2.3% vs. 11%, p < 0.05)
    - Matched, retrospective study. All patients received concomitant corticosteroids as well
    - Rescue therapy with lopinavir/ritonavir not different from matched controls
  - Park et al. 2019: lopinavir/ritonavir plus ribavirin effective as post-exposure prophylaxis against MERS-CoV

Thorax 2004;59:252-256. *Hong Kong Med J.* 2003; 9(6): 399-406
J Hosp Infect. 2019; 101(1): 42-46

Clinical Evidence

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

- Open label RCT, published 3/19/2020
  - Inclusion: adults with confirmed COVID-19 with radiographic pneumonia and hypoxia (SaO2 < 94% on RA or PaO2:FiO2 < 300
  - Exclusion: severe liver dysfunction, HIV, pregnancy, significant interactions
  - Outcomes:
    - Primary: time to clinical improvement
    - Secondary: clinical status, 28-day mortality, duration of mechanical ventilation, hospital and virologic measures

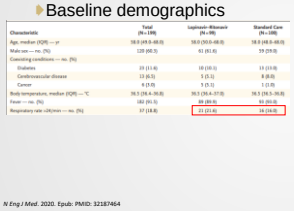
N Eng J Med. 2020. Epub: PMID: 32187464

Clinical Evidence

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

- Baseline demographics



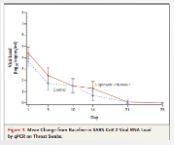
N Eng J Med. 2020. Epub: PMID: 32187464

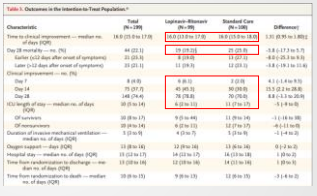
Clinical Evidence

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

- Outcomes:
  - Lower rate of serious AEs





N Eng J Med. 2020. Epub: PMID: 32187464

Clinical Evidence - Remdesivir

- Appears effective against Ebola
- Clinical studies lacking for SARS-CoV-2
- Ongoing clinical trials
  - U.S. = 3 studies (1 NIAID and 2 Gilead sponsored)
  - China = 2 studies
- Dosing – 200mg IV load, then 100mg IV daily x 5-10 days
- Safety: mostly GI and liver-related effects to date reported
  - IV contains cyclodextrin (SBECD)

https://clinicaltrials.gov/ct2/results?cond=&term=remdesivir&cntry=&state=&city=&dist=

Remdesivir

- Compassionate use available (https://rdvcu.gilead.com/)


GILEAD
Creating Possible

The following patient criteria must currently be met in order to submit a compassionate use request for remdesivir:

Key Inclusion criteria:

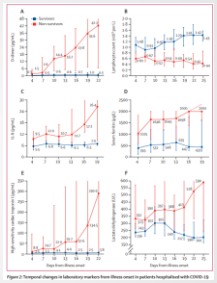
- Hospitalization
- Confirmed SARS-CoV-2 by PCR
- Invasive (ie Intubated or Tracheostomy) Mechanical Ventilation

Key Exclusion criteria:

- Evidence of Multi-organ failure
- Pressor requirement to maintain blood pressure
- ALT levels > 5 X ULN
- Cr Clearance <30 mL/min or dialysis or Continuous Veno-Venous Hemofiltration

Hyperinflammation

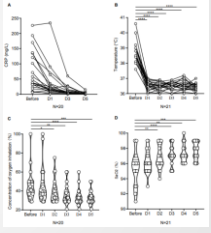
- Subset of COVID-19 progress to hyperinflammatory state
  - High, persistent fever
  - Cytopenias
  - Hyperferritinemia
  - Increased IL-6, CRP, and d-dimer
- Screening – Hscore for probability of secondary HLH
- Immunosuppression - tocilizumab



Mehta P, *et al. Lancet*. 2020; epub - DOI:https://doi.org/10.1016/S0140-6736(20)30628-0
Huang C et al. *Lancet*. 2020; 395: 497-506
Zhou F, et al. *Lancet*. 2020; epub - DOI: https://doi.org/10.1016/S0140-6736(20)30566-3

Clinical Evidence – Tocilizumab

- Observational study from China, n=21
- Standard of care + Tocilizumab 400mg IV single dose
  - n=3 had repeat dose within 12 hours
- Severe (81%) and critical disease (19%) at time of treatment
  - Severe = RR ≥ 30, SpO2 < 94% on RA, or PaO2:FiO2 ≤ 300
  - Critical = mechanically ventilated, shock, other organ failure
- All 21 survived, 91% discharged
  - Only 10% were mechanically ventilated



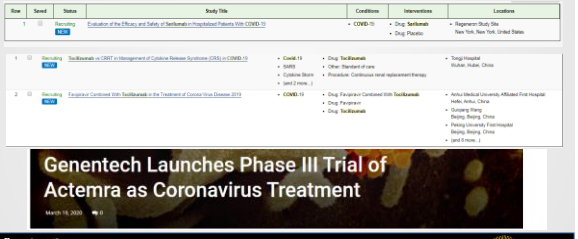
http://www.chinadrugtrials.org/user/download.htm?id=1038&filetype=pdf

Clinical Evidence - Others

- Nitazoxanide – in vitro only to date
- Interferon – in vitro and limited clinical experience from SARS-CoV-1 and MERS-CoV (combined with other agents)
- Statins – anti-inflammatory mechanism – theoretical presently and no published evidence of direct benefit for COVID-19
- IVIG – not expected to be effective, pooled sources unlikely to have any sufficient anti-SARS-CoV-2 neutralizing antibodies
- Corticosteroids – unclear role, likely beneficial during later stages of infection where inflammatory response increased

Cell Res, 2020; 30 (3), 269-271.
Antimicrob Agents Chemother. 2020; epub. PMID: 32152082

Tocilizumab and Sarilumab



Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Recruiting NEW	Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	• COVID-19	• Drug: Sarilumab • Drug: Placebo	• Regeneron Study Site New York, New York, United States
1		Recruiting NEW	Tocilizumab vs CSRT in Management of Cytokine Release Syndrome (CRS) in COVID-19	• Covid-19 • SARS • Cytokine Storm • (and 2 more...)	• Drug: Tocilizumab • Other: Standard of care • Procedure: Continuous renal replacement therapy	• Tongji Hospital Wuhan, Hubei, China
2		Recruiting NEW	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	• COVID-19	• Drug: Favipiravir Combined With Tocilizumab • Drug: Favipiravir • Drug: Tocilizumab	• Anhui Medical University Affiliated First Hospital Hefei, Anhui, China • Guoqiang Wang Beijing, Beijing, China • Peking University Third Hospital Beijing, Beijing, China • (and 6 more...)

Genentech Launches Phase III Trial of Actemra as Coronavirus Treatment

March 19, 2020

Clinical Evidence - Others

- Nitazoxanide – in vitro only to date
- Interferon – in vitro and limited clinical experience from SARS-CoV-1 and MERS-CoV (combined with other agents)
- Statins – anti-inflammatory mechanism – theoretical presently and no published evidence of direct benefit for COVID-19
- IVIG – not expected to be effective, pooled sources unlikely to have any sufficient anti-SARS-CoV-2 neutralizing antibodies
- Corticosteroids – unclear role, likely beneficial during later stages of infection where inflammatory response increased

Cell Res, 2020; 30 (3), 269-271.
Antimicrob Agents Chemother. 2020; epub. PMID: 32152082

Clinical Evidence – Vaccine


NEWS RELEASES

Monday, March 16, 2020

NIH clinical trial of investigational vaccine for COVID-19 begins

Study enrolling Seattle-based healthy adult volunteers.

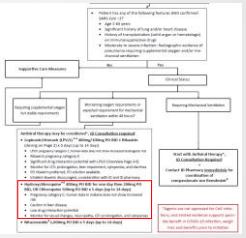

Trials to begin on Covid-19 vaccine in UK next month

Researchers hope to conduct animal tests next week and safety trials as early as next month

- Coronavirus - latest updates
- See all our coronavirus coverage

Proposed Management Algorithm

- No approved or proven treatment of COVID-19 to date
- Limited evidence may support trial of off-label agents with possible anti-viral activity (rapidly evolving, keep up to date)
- Challenges – diagnostic delays, shortages, and low quality evidence to date



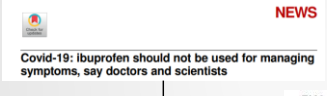
Pharmacist Involvement

- Strategies to limit healthcare exposure of patients not suffering from COVID-19
- Inventory control and resource conservation
- Treatment pathway development and resource for critical evaluation of related evidence for novel therapies to manage COVID-19
- Navigation of clinical trials/compassionate use of investigational therapies
- Problem solving around supportive care measures

EIND Process

- https://www.fda.gov/drugs/investigational-new-drug-ind-application/emergency-investigational-new-drug-eind-applications-antiviral-products
- Step 1: contact company with investigational product to obtain approval for compassionate use
- Step 2: contact FDA for approval to use investigational product
- Step 3: if FDA approves, reach back out to company and coordinate with pharmacy and local IRB

Social Media and Misinformation


NEWS

Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists


EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19

Press release 18/03/2020

EMA is aware of reports, especially on social media, which raise questions about whether non-steroidal anti-inflammatory medicines (NSAIDs) such as ibuprofen could worsen coronavirus disease (COVID-19).

There is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19. EMA is monitoring the situation closely and will review any new information that becomes available on this issue in the context of the pandemic.

What is CPS doing?

- Letter to the governor asking for emergency measures (sent March 13th)
  - Remote pharmacy practice – remove requirements for prior board approval
  - Allow 90 day supplies of chronic medications
  - Extend technician certification deadlines
  - Allow the CMO of CDPHE to allow pharmacists to provide designated services for:
    - Testing
    - Screening
    - Prescribing (standing order or CPA)

What is CPS doing?

- Community forum for COVID-19
  - Childcare options for healthcare workers
  - Clinical trial information (post-COVID exposure prophylaxis)
- Dedicated web page
- Social media posts (follow us!)

National professional organizations

- NACDS policy requests (partial list)
  - In anticipation of a COVID-19 vaccine, making sure pharmacists may access and immunize without barriers
  - Allowing pharmacists and techs to work across state lines
  - Broader prescriptive authority for mild ailments
  - Allowing remote verification of prescriptions
- NASPA
  - Regular communication regarding activities in other states

Questions and Answers