Annual Meeting
September 12, 2020
The Pharmacist’s Role in Pandemic Planning in the Emergency Department

*What to Do When You Don’t Know What to Do!*

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PGY2 Emergency Medicine Pharmacy Coordinator
University of Utah Health, Salt Lake City, UT
Disclosure

Instructions:
The speaker has no conflicts of interest to disclose.
The speaker will not be discussing any off-label uses of drugs.
Learning Objectives

At the conclusion of this activity, *pharmacists* should be able to successfully:

1. Articulate the various roles of pharmacists in an interdisciplinary team creating pandemic plans in the emergency department.
Learning Objectives

At the conclusion of this activity, pharmacy technicians should be able to successfully:

1. Explain why frequent changes in product selection, policy, and procedures during a pandemic or disaster management response occur.
What is Disaster Response?

- WHO defines a disaster as a sudden phenomenon of sufficient magnitude to overwhelm the resources of a hospital, region, or location requiring external support.

- A thoughtful fast approach in response to a disaster is critical.

- The emergency medicine approach is quite similar to Dr. Michael Ryan, Executive Director, WHO Health Emergencies Program.
How can we mitigate this situation to be less bad than it could possibly be?

Are we prepared for something bad if it happens?

Do we have the resources to respond?

How will we recover from this?
We all have emergency preparedness skills

https://now.uiowa.edu/2014/03/safety-first-children
We all have emergency preparedness skills
We all have emergency preparedness skills
Preparedness Cycle

- Preparedness
- Prevention
- Response
- Recovery
- Mitigation
How can we **mitigate** this situation to be less bad than it could possibly be?

Are we **prepared** for something bad if it happens?

Do we have the **resources** to respond?

How will we **recover** from this?
Disaster Role(s) of a Pharmacist in the ED

ASHP Guideline on Emergency Medicine Services

◦ “It is essential that Emergency Medicine Pharmacists (EMP), in conjunction with the department of pharmacy, participate in emergency preparedness planning.”

◦ “Planning and involvement should occur at a minimum at the institutional level….knowledge of local, state, and national emergency preparedness plans, programs, and support systems is paramount.”

Disaster Role(s) of a Pharmacist in the ED

• Draw on your experience of the past to do better in the future

• Katrina
• H1N1
• Ebola
• TRAINING!
Did I mention training?
Support Documents for Pharmacy Involvement

ASHP Statement on the Role of Health-System Pharmacists in Emergency Preparedness

Emergency and Disaster Preparedness and Response Planning: A Guide for Boards of Pharmacy

A Pharmacist’s Guide to Pandemic Preparedness
  ◦ APhA, ASHP, NACDS in 2007

Pharmacist as Front-Line Responders for COVID-19 Patient Care
  ◦ Joint Executive Summary by all major Rx orgs

ASHP Guidelines on Emergency Medicine Pharmacist (EMP) Services

Pharmacy Leader’s Role in Hospital Emergency Preparedness Planning


Bell C. Hospital Pharmacy: Pharmacy Leader’s Role in Hospital Emergency Preparedness Planning. 2014 (Apr); 49(4): 398-404.
Other Training for Pharmacist and Technician Involvement

Emergency Preparedness
- AHLS
- Basic Disaster Life Support
- Advanced Disaster Life Support
- National Incident Management System
- Free online training @ www.FEMA.gov

- Disaster Medical Assistance Teams
- Emergency Medication Assistance Program
Assess the Scene:

**Jan 22, 2019:** Received first communication from our ED Code Bio Coordinator

- *Mask the patient, limit contact, place in airborne precautions…*

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**Interim 2019 novel coronavirus (2019-nCoV) patient under investigation (PUI) form**

As soon as possible, notify and send completed form to: 1) your local/state health department, and 2) CDC: email (eocreport@cdc.gov, subject line: nCoV PUI Form) or fax (770-488-7107). If you have questions, contact the CDC Emergency Operations Center (EOC) at 770-488-7100.

<table>
<thead>
<tr>
<th>Today’s date</th>
<th>State patient ID</th>
<th>NNDSS local record ID/Case ID</th>
<th>State</th>
<th>County</th>
</tr>
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<tbody>
<tr>
<td>Interviewer’s name</td>
<td>Phone</td>
<td>Email</td>
<td>Physician’s name</td>
<td>Phone</td>
</tr>
<tr>
<td>Sex</td>
<td>Age</td>
<td>Residence</td>
<td>US resident</td>
<td>Non-US resident, country</td>
</tr>
</tbody>
</table>

**PUI Criteria**

- Does the patient have the following signs and symptoms (check all that apply)?
  - Fever
  - Cough
  - Sore throat
  - Shortness of breath

- In the 14 days before symptom onset, did the patient:
  - Spend time in Wuhan City, China? Y N Unknown
  - Does the patient live in Wuhan City? Y N Unknown
  - Date traveled to Wuhan City
  - Date traveled from Wuhan City
  - Date arrived in US

- Have close contact with a person who is under investigation for 2019-nCoV while that person was ill? Y N Unknown
- Have close contact with a laboratory-confirmed 2019-nCoV case while that case was ill? Y N Unknown
Assess the Scene:

January 23, 2020: Chinese government locks down Wuhan
Assess the Scene:

January 30, 2020
- WHO declares a “global health emergency”

February 4, 2020
- The “Diamond Princess” is quarantined off the coast of Yokohama, Japan
Assess the Scene:

March 3, 2020
- First official communication from management

March 6, 2020
- First patient in Utah

SALT LAKE CITY (KUTV) — Utah health officials have confirmed the first known case of COVID-19, known as the coronavirus, in Utah.

First coronavirus case confirmed in Utah

Jim Spiewak reports (KUTV)
Disaster Role(s) of an EMP: Patient Care

ED: Still open for business
- “Normal” patient care
- Resuscitation
- Medication management, safety, and optimization
- Response to critical events or procedures
  - Rapid Sequence Intubation
  - ACLS

COVID-19
- COVID-19 complicated clinical conundrums
- Chronic disease states
- The walking, but anxious well
- Happy hypoxics
- Maybe it’s COVID-19?
Disaster Role(s) of an EMP: Drug Information

- Drug cures, drugs to avoid
- Drugs to stockpile, don’t stock pile it’s bad
- Reported, perceived, actual, felt at user level shortages

- Med Twitter Ideas, both good and bad
- Literature review and dissemination
- Rumor management and follow up
Disaster Role(s) of an EMP: Regulation

- Rapid changes from the CDC, local, state, and national government
- Protecting yourself & others from health care exposure
- Emergency Medical Treatment & Labor Act (EMTALA)
Disaster Role(s) of an EMP: Operations

- ADC inventories in treatment areas
- Medication preparation at bedside/room
- Inpatient pharmacy delivery facilitation
- Safe drug return to central operations
Disaster Role(s) of an EMP: Problem solving

• Everything takes longer AND keeps changing
• Changes coming from the top down takes time
• Avoiding over use of PPE
• Communication and space issues
• Surges and inventory lag
• Disagreements in care management
• Hard to keep up with information flying around
• Non-adherence to safety practices and protocols
• Recognizing yourself as a non-redundant resource
Disaster Role(s) of a **Technician** in the ED

**Medication Procurement & Preparation Experts**
- Emergency kits
- Experts in automated dispensing cabinets
- Optimizing ADC par levels
- Shortages and formulary change management
- Best Use Date champions
- Responding to emergency requests
Disaster Role(s) of an EMP: Administration and Medication Management

Administrative
- P.A.C.E planning
- Education
- Policies, guidelines and procedures updates
- Resource management
- Protocol development
**Preparation**

- Signs of End Organ Damage / Critical Hypoxemia
  1) Severe respiratory distress
  2) Respiratory Rate >30
  3) Altered Mental status
  4) Significant increased work of breathing

- Location & Patient Selection
  - Negative Pressure Room if possible
  - If suspected Covid19, consider intubation if patient demonstrates *significant Hypoxia* despite Escalating Oxygenation Algorithm (NC @6-10L+ NRB @ 6-10L/min -> HFNC (max 30 L/Min**, 100% FiO2) or Low Pressure CPAP (max 6cm H2O in ED***)) AND
    - Lack of improvement in clinical status/blood gas after 1hr of Oxygenation AND/OR
    - Moderate-Severe respiratory distress AND/OR
    - RR>30 AND/OR Signs of End Organ Damage

- Assemble Team*
  - Minimize number of healthcare providers needed to complete procedure safely
  - In-Room (3-4): 1-2x Attending MD +/- Resident MD or APC, 1x RN, 1 Medic, 1x RT
    - If resident or APC intubating, Attending MD to run resuscitation from outside room
    - In-Room team will change with ED P.A.C.E. Surge response
  - Out-of-Room (2-3): 1x RN (in airbner PPE); 1x EMT/Runner/PPE monitor, 1x ED PharmD
  - Consider CovidAirway team if multiple critical patients or anticipated difficult anatomy

- PPE
  - Wash or sanitize hands for at least 20 seconds
  - All In-Room personnel & RN out-of-Rm must DON in order: Goggles + N95 or PAPR --> OR cap --> impermeable gown w/ thumbs through thumb holes --> Inner gloves --> Outer gloves
  - **PPE Monitor (EMT):** Supervise all donning and doffing of PPE to ensure no cross contamination

*02 Sat threshold for intubation is based on provider discretion & may vary by presentation & further data/ experience
** If using HFNC or CPAP: move to negative pressure room or use tent including during transport
***Use CPAP if no HFNC available,

* If utilizing Covid Airway team, alert early to allow time for response and PPE

** Version 4.1 updated 4/10/2020**
PRE-CHECK and PRE-BRIEF

Equipment Check

- COVID glidescope is charged & working, all blades, rigid style, & bougie in basket
- Airway Cart w/ Pre-Ox & Intubation Packs stocked & outside of room
- CritCare Cart & US are adequately stocked and located directly outside of room

Pre-Oxygenation Plan

- Position Non-aerosolizing tent over patient, place HOB at 30 deg & Determine optimal pre-oxygenation strategy:
  1) NC @ 10L/min + NRB @ 10L/min OR
  2) High-Flow Nasal Cannula w/ Surgical Mask (Max 29L/min)* OR Low-Pressure CPAP (max 6cmH2O) OR
  3) Covid Pre-Oxygenation Kit —> Convert to 2 hand seal w/ jaw thrust Apneic CPAP during apneic period
     Use MAX FLOW and MIN PEEP needed. Do not bag. Consider NP/Oral airway adjunct

Intubation Plan

Under non-aerosolizing Tent...

- Plan A: RSI with VL & preferred blade by most experienced provider. Inflate Cuff ASAP
- Plan B: Rescue Oxygenation under plastic sheet — 2nd attempt VL w/ alternate blade
  Rescue Oxygenation options:
  1) Place SGA w/ viral filter between SGA & BVM
  2) Bag w/ BVM w/ viral filter using excellent 2 hand mask seal, & minimal tidal volumes

Medication Plan

- Consider Anxiolytic Dose ketamine: 20mg IV slow push
  - May aid in patient tolerance of pre-oxygenation

  In-Room: RS (see intubation plan dosing chart)
  - Etomidate or Ketamine
  - Rocuronium or Succinylcholine

  In-Room: Sedation:
  1) Pre-prime Propofol gtt on pump
  2) Fentanyl gtt
  3) Lorazepam PRN for vent compliance

  Out-of-Room (on standby): Hemodynamic Support (available in Omnicon upon MD request)
  - Phenylephrine (100mcg/ml) Premade Push-Dose syringe
  - Epinephrine (10mcg/ml) Premade Push-Dose syringe
  - Norepinephrine gtt pre-mixed

*Reserve Ketamine for Asthma/COPD/Agitation

Non HFNC/CPAP criteria
Patient cannot be successfully oxygenated (sats >90% & without resp distress) on 6L NC + NRB

High Flow Nasal Cannula
- Set flow rate to 30 LPM
- Titrate FiO2
- Surgical mask over HFNC
- Encourage incentive spirometry and self proning
- Neg pressure Rm or HEPA Filter

CPAP provided via COVID specific set-up V60 CPAP/BIPAP machine with Viral filters in place

2) CPAP via Closed-circuit CPAP Mask w/ 1-piece viral filter
3) CPAP can be provided with No leak mask
4) Closed, Neg pressures Rm or Rm w/ HEPA Filters in place
5) All providers in PAP without precautions
6) Place on CPAP/PSV, set the PSV at 6, dial up PEEV only if patient’s saturations do not come up with 100% FiO2
7) Patient must be trained with non-aerosolizing tent
# UUED COVID-19 Intubation Plan

**V4.1 Updated 4/7/2020**

**Patient Height: ____ Weight: ____ IBW: ____ BMI: ____**

Max Personnel in Rm: 4  Recommended ETT Depth: ______

*See back of sheet for pre-calculated medication doses*  *UUE Critical Care Medicine Cards*

## Pre-Oxygenation

1. COVID Pre-Ox kit (NIPPV mask w/ viral filter & BVM with in-line ETCO2 & PEEP valve)
2. Apneic CPAP w/ excellent two-hand BVM mask seal with filter in place
3. Minimal pressure BVM with excellent two-hand facemask seal w/ viral filter & under plastic drape.

<table>
<thead>
<tr>
<th>Dose Order</th>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eltimadate</td>
<td>5-40 mg, see dosing chart</td>
<td>Half dose in shock</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1 mg/kg, see dosing chart</td>
<td>First line for asthma/COPD/Agitation</td>
</tr>
<tr>
<td></td>
<td>20 mg slow IVp for anxiolyis</td>
<td>Max dose = 200 mg</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1.2 mg/kg, see dosing chart</td>
<td>Max dose = 100 mg, IBW</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>1.5 mg/kg, see dosing chart</td>
<td>Max dose = 300 mg</td>
</tr>
<tr>
<td>Push Dose Phenytoine</td>
<td>100 mcg/mL pre-made syringe</td>
<td>IV push 1-2 ml (100 - 200 mcg)</td>
</tr>
<tr>
<td>Push Dose Epinephrine</td>
<td>10 mcg/mL pre-made syringe</td>
<td>IV push 1-2 ml (10 - 20 mcg)</td>
</tr>
<tr>
<td>Norepinephrine drip</td>
<td>0.01-1 mcg/kg/min</td>
<td>See critical care medication cards</td>
</tr>
</tbody>
</table>

## Post Intubation Sedation/Paralysis

<table>
<thead>
<tr>
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<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl drip and boluses</td>
<td>Initial bolus: 50-100 mcg FIRST Infusion: 1 mcg/kg/hr, start rate Bolus: 50-100 mcg q5 min PRN X 3</td>
<td>Use 1st for agitation/vent compliance</td>
</tr>
<tr>
<td>Propofol drip and boluses</td>
<td>Infusion: 10-60 mcg/kg/min Bolus: 0.25-0.5 mg/kg</td>
<td>Fentanyl or ketamine PRN prior to rate increase, avoid propofol boluses, if possible</td>
</tr>
<tr>
<td>Ketamine IV push OR</td>
<td>0.5-1 mcg/kg</td>
<td>May use REMAINDER from intubation vial</td>
</tr>
<tr>
<td>Midazolam IV push OR</td>
<td>4 mg IV p4hr PRN</td>
<td>Vent management or agitation</td>
</tr>
<tr>
<td>Lorazepam IV push</td>
<td>2-4 mg IVP q4hr PRN</td>
<td>Vent management or agitation</td>
</tr>
<tr>
<td>Haldol or Droperidol IVP/IM</td>
<td>Haldol: 5-10 mg Droperidol: 1.25-5 mg</td>
<td>Caution with multi Qtc prolonging drugs May repeat X 3</td>
</tr>
<tr>
<td>Vecuronium IV Push</td>
<td>0.1 mg/kg q3hr PRN vent compliance</td>
<td>Max dose = 10 mg, S/p sedation optimized</td>
</tr>
</tbody>
</table>

## Vaspressors

<table>
<thead>
<tr>
<th>Dose Order</th>
<th>Medication</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine drip</td>
<td>0.01-1 mcg/kg/min</td>
<td>See critical care medication cards</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.04 units/min</td>
<td>Do not titrate</td>
</tr>
<tr>
<td>Epinephrine drip</td>
<td>0.01-1 mcg/kg/min</td>
<td>See critical care medication cards</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>0.5-20 mcg/kg/min</td>
<td>See critical care medication cards Only AFTER norepi OR epo initiated</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Weight (lbs)</td>
<td>Etomidate (mg)</td>
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<td>40</td>
<td>88</td>
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<td>145</td>
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<tr>
<td>150</td>
<td>330</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

ED gurney = 74 inches (6'2")
Hospital bed = 82 inches (6'10")
The ED intubation and airway management protocol went through 4.1! reiterations to keep up with changes, drug stock and expert suggestions.
Tips and Tricks

- Have a working understanding of the local, state, and federal response and command systems
- Living communication tools
- Did I hear you say a drug name or “pharmacy”? 
- A “no” today does not mean “no” tomorrow
- Back up plans, don’t be afraid to be creative
- Don’t over extend yourself or your team
Tips and Tricks

◦ Have your own emergency kit, snacks, comfort items, and sleeping needs
◦ Have a robust phone # list
◦ Maintain physical and mental health
◦ Obtain your own PPE if needed
◦ Phone charger, battery bank
◦ Find a quiet place and mantras
◦ Timer for cleaning
◦ Support team
◦ Make friends with ambiguity
Which of the following roles in action should an EM pharmacist not participate in during a pandemic?

A) Creating tools for fast decision making and dosing by nursing staff?
B) Daily literature upload and dissemination
C) Patient care like drug-disease interaction and error prevention
D) Daily routine, keep the status quo
E) Collaborate with operations for ADC optimization
Test Questions

Why is yesterday’s brand new standard operating procedure (SOP) changed today already?

A) Drug formulation shortage announced overnight
B) Clinical practice for best care supports research or use of a new drug
C) Key personnel are now out on leave due to quarantine
D) Best Use Date allows for best inventory use
E) All or any of the above, because disasters aren’t predictable and we made the best SOP with the knowledge we had yesterday. Today’s a new day!


• Bell C. Hospital Pharmacy. Pharmacy Leader’s Role in Hospital Emergency Preparedness Panning. 2014 (Apr); 49(4): 398-404.
COVID-19 Medication Controversies:
-Do you have an ACE (Inhibitor) up your sleeve?
-WHO said WHAT? Some things better left NSAID

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Emergency Medicine Pharmacist
Program Director, PGY2 EM Pharmacy
University of Utah Health
Disclosure

Instructions:
No relevant relationships or conflicts of interest, financial or otherwise, to disclose

We will discuss off-label use(s) of medications
Learning Objectives

At the conclusion of this activity, **pharmacists** should be able to successfully:

1. Evaluate available literature regarding risks and/or benefits of ACE-I, ARB, NSAID use during an acute COVID-19 infection

2. Formulate a recommendation based on available literature when discussing the ACE-I/ARB/NSAID conundrum with providers and patients
Learning Objectives

At the conclusion of this activity, pharmacy technicians should be able to successfully:

1. List medications in the ACE-I, ARB, and NSAID class of medications

2. Identify patients who may have concerns regarding continued use of ACE-I, ARB, and NSAID during the COVID-19 pandemic
Road Map

Discuss controversy regarding ACEi (Angiotensin Converting Enzyme–Inhibitor) & ARB (Angiotensin Receptor Blocker) use in COVID-19 patients

Biologic mechanisms and relevant literature for various hypotheses

Current recommendations for patients taking these medications

Repeat for NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

Touch on other pertinent classes of medications
Controversy!

RAS Inhibitor Use During COVID-19

- Lancet publishes correspondence March 11th (updated March 19th): “The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACEi & ARBs... Consequently, the increased expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesise [sic] that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19.”

- Panic ensues from patients and medical providers hoping to do the right thing in this rapidly emerging situation

RAS = Renin-Angiotensin System

The Lancet Respiratory Medicine (2020) Link
Hypothesis – RAS Inhibition = Harmful

No RAS Inhibitor

SARS-CoV-2

ACE2 Receptor

RAS Inhibitor

Simplified from Nature Reviews April 2020
Hypothesis – RAS Inhibition = Beneficial

No RAS Inhibitor

SARS-CoV-2

↓

ACE

Ang I → Ang II

↑

ACE2 Receptor

Inflammation & fibrosis

RAS Inhibitor

ACEi

Ang I X Ang II

ARB X

AT1R

MasR

Ang-(1-7)

Inflammation & fibrosis

(attenuates fibrosis & inflammation)

Simplified from Nature Reviews April 2020
ACEi, ARB Use & Confounders?

Perhaps the issue in COVID-19 is not ACEi or ARB use, but potential confounders including increasing age, hypertension (or other underlying indication for ACEi or ARB treatment)

- Many studies have been completed and are ongoing attempting to answer this question
- Nothing conclusive (yet), design limitations, population confounders, when/how to adjust analyses, etc

Should we ‘play it safe’ and switch patients to another medication for HTN (e.g. amlodipine)?

- Association between RAS Inhibition and COVID-19 remains unknown
- RAS Inhibition affects much more than blood pressure (kidney protective, etc)
- Switching medications may require additional monitoring (difficult whilst physically distancing)
- IF RAS inhibition affects COVID-19, not sure in what direction and how robustly
MA ↓ Mortality – Hypertension Aug 2020

A

<table>
<thead>
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<td>Test for overall</td>
<td></td>
</tr>
</tbody>
</table>

Figure. Meta-analysis (AR) on coronavi (B) mortality in the M-H indicates Mantel-Haenszel.
Fig. 1  Subgroup analysis of death/critical events in ACEi/ARB vs ACEi/ARB. Subgroup analysis of death/critical events (OR 0.6435 to 1.034, p = 0.071) in sixteen studies with 5996 patients ACEi/ARB vs 10,103 non-ACEi/ARB patients. Total effect estimate 0.671 (0.435, 1.034)
Dx COVID-19: Continue ACEi or ARB?

- Retrospective, multi-center study including 1128 adult patients w/ hypertension diagnosed with COVID-19, where 188 using ACEI/ARB and 940 not using ACEI/ARB
- Admitted to 9 hospitals in Hubei Province, China from December 31, 2019 to February 20, 2020
- All-cause mortality was lower in the ACEI/ARB group versus the non-ACEI/ARB group (adjusted hazard ratio, 0.42 [95% CI, 0.19–0.92]; P=0.03)
- Subgroup compared use of other antihypertensive meds, ACEI/ARB associated w/ decreased mortality (adjusted hazard ratio, 0.30 [95% CI, 0.12–0.70]; P=0.01) in patients with COVID-19 and coexisting hypertension


Link to ACC Summary (April 24, 2020)
Dx COVID-19: Continue ACEi or ARB?

- Retrospective single-center study (Stony Brook Univ Hospital)

- Comorbidities, vital signs, labs, ACEi/ARB usage (prehospital & continued inpatient) plus AKI or hypotension during hospitalization

- No statistically significant differences b/w non-ACEi/ARB & ACEi/ARB users (Mortality & ICU admit)

- Patients who continued ACEi/ARB in hospital had lower ICU admission rate (12% vs 26%; $P = .001; OR = 0.347; 95% CI, .187 – .643) & mortality rate (6% vs 28%; $P = .001; OR = 0.215; 95% CI, .101 – .455) compared to patients who discontinued ACEi/ARB

- Logical conclusion continuing ACEi/ARB inpatient in hypertensive COVID-19 patients results in better outcomes

- CAVEAT! More ill patients are likely to have ACEi/ARB held inpatient (possibly preemptively in anticipation of AKI or hypotension)

Journal of Infectious Diseases July 2020

Dx COVID-19: Continue ACEi or ARB?

- Admitted to hospital (n = 614)

- Group A
  Non-ACEi/ARB (n = 279)

- Group B
  Discontinued in hospital (n = 171)

- Group C
  Continued in hospital (n = 164)

- Non-ICU
  Non-ICU (n = 126)
  105 discharged 21 death

- ICU
  18 discharged 27 death

- ICU
  18 discharged 27 death

- ICU
  18 discharged 27 death

- ICU
  139 discharged 5 death

- ICU
  15 discharged 5 death

CAVEAT! More ill patients are likely to have ACEi/ARB held inpatient (possibly preemptively in anticipation of AKI or hypotension)
“Interim” Final Word

Recommend / Strongly Encourage (and many other synonyms) continuing ACEi/ARB treatment.

Not just my opinion...

American College of Physicians, American Heart Association, American College of Cardiology, European Society of Hypertension, ESC Council on Hypertension, and many others.

American Diabetes Association didn’t have an official statement I was able to find, but publications in their society journal were congruent with the recommendation to continue treatment with an ACEi/ARB or other cardiovascular/diabetes medication that has been implicated with increased ACE2 expression.
Controversy! NSAID Use During COVID-19

- Lancet publishes letter March 11th (updated March 19th): “ACE2 can also be increased by thiazolidinediones and ibuprofen... We therefore hypothesise [sic] that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19.”

- March 14th French Minister of Health recommends against anti-inflammatory medications (e.g. ibuprofen, cortisone) and in the event of fever recommends taking acetaminophen (paracetamol) via Tweet

- March 18th WHO ‘clarifies’ stance via Tweet, “WHO does not recommend against the use of ibuprofen”
NSAID Use Caveats

This question does not have the same level of evidence as the previous therapeutic conundrum (ACEi/ARB). Much of this section is based on hypotheses, broad derivations and outright speculation. It is also more difficult to study as Over-The-Counter use makes it hard to establish usage. Not to mention individual patient dosing can vary widely, as anyone performing medication histories can attest.

NSAIDs are much broader from a chemical structure standpoint (e.g. COX 1 & COX 2 inhibition differences, varying prostaglandin effects, PK parameters) relative to other medication classes discussed in the context of COVID-19 controversy; some differences may yet be elucidated.

E.g. certain NSAIDs may be harmful while others may be equivocal or beneficial.
Why Might NSAIDs be Harmful?

- Ibuprofen upregulates ACE2, potentially increasing viral load and/or likelihood SARS-COV-2 enters cells via increased chances to bind ACE2

- In bacterial soft tissue infections, patients on NSAIDs experienced more severe infections, thought to be due to either immune-depressive effects or initial symptom suppression resulting in delayed treatment initiation

- Fever is a natural physiologic response to viral infection and reduces viral activity; antipyretics, such as NSAIDs, could reduce the body’s natural defense systems against viruses

- Centre for EBM notes, “NSAIDs do not significantly reduce total symptoms or duration of illness in Acute Respiratory Infections.” Note: this summary was not looking at COVID-19 respiratory infections specifically [March 24th 2020 Link]

- NSAIDs worsen hypertension and other disease states, which may make patients more susceptible to severe COVID-19 infections compared to their baseline risk
Why Might NSAIDs be Beneficial?

*Or at least not as harmful as initially thought*

- Ibuprofen upregulating ACE2 enzyme was found in a single study in diabetic rats; perhaps more robust evidence is needed in this area. It’s unclear how long NSAIDs would need to be taken before upregulation of ACE2 would occur in humans, if at all. Not to mention ACE2 upregulation has not been linked to worse outcomes in COVID-19 (see ACEi/ARB section)

- NSAIDs masking symptoms would be unlikely to cause problems as widespread and robust treatments of COVID-19 are currently lacking; wouldn’t be appreciably delaying treatment as there are no time-sensitive outpatient therapies to start at present*

- As the sequelae of COVID-19 severe respiratory infections are still being elucidated, perhaps the immune-depressive effects of NSAIDs may be helpful (akin to corticosteroid use)

- If antipyretic therapy is harmful to patients with COVID-19 than acetaminophen (paracetamol) would also be detrimental. I was unable to find any evidence that acetaminophen is harmful to COVID-19 patients*

- Mortality from COVID-19 may be worsened during ‘surges’ so if an NSAID is able to keep patients out of the hospital that *may* have downstream benefits

*Note this may change during the time between the slide preparation and presentation*
NSAID Literature

- Much of it derived from respiratory infections in general, not specifically COVID-19
- Naproxen as part of a medication cocktail was effective in treating Influenza A (H3N2) [Link]
- Recent systematic review of six clinical trials (included study above) recommends caution until more data are available; the authors suggest naproxen may be a good choice for future study [Link]
- LIBERATE trial is underway looking at ibuprofen as a potential treatment for COVID-19 and reduction of lung injury in acute hypoxemic respiratory failure lipid ibuprofen NCT04334629
- Case-control survey study underway: Role of Ibuprofen and Other Medicines on Severity of Coronavirus Disease 2019 (RISC) NCT04383899

It's better to have UNANSWERED QUESTIONS than UNQUESTIONED ANSWERS
What’s Your Recommendation

- Assess indication and potential benefits of NSAID treatment

- **IF** decision is made to treat with NSAIDs use the lowest effective dose for the shortest duration

- Anecdotally, many providers and patients do not fully grasp the NSAID Ceiling Effect (well shown in analgesia studies); “There are only so many COX enzymes to block”

- Assess for comorbidities and the possibility of NSAIDs exacerbating those conditions

- Continue to watch for new publications

Pro-tip: Create alert(s) in NCBI’s PubMed - must be signed in
What about other med classes?

Due to time constraints and limited data relative to ACE-I, ARB and NSAID use we will not dive deep into these classes today

• Thiazolidinediones (TZDs)
  • Harmful? (upregulates ACE2 in Rats): [Sci World J 2014](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3930274/)

• HMG-CoA Reductase Inhibitors (Statins)
  • ↓ Risk of mortality: [Link](https://www.cell.com/cell代谢science) Cell Metab Aug 2020

• Proton Pump Inhibitors (PPIs)
  • ↑ Risk of severe clinical outcomes: [Link](https://www.gutjournal.com/article/10.1136/gutjnl-2019-319122) Gut July 2020

Graphical Abstract, Cell Metab Aug 2020
Test Questions

T/F: There exists clear and convincing evidence regarding which medications should be discontinued if a patient is at all concerned about COVID19

A. True
B. False
Test Questions

MC: Which of the following medications has not been subject to controversy in patients infected with COVID19

A. Ibuprofen
B. Telmisartan
C. Docusate
D. Lisinopril
Coagulopathies in COVID

Laura Steffens, PharmD, BCCCP, MS
September 12, 2020
USHP Winter Meeting

IMPLICATIONS FOR VTE PROPHYLAXIS AND TREATMENT
Disclosure

**Relevant Financial Conflicts of Interest**
- The presenter, Laura Steffens, has no financial conflicts of interest to disclose.

**Off-Label Uses of Medications**
- The use of tPa for empiric treatment of microthrombi associated with COVID will be discussed.
Learning Objectives

**Pharmacists**
- Describe coagulopathies associated with COVID infections and apply guideline recommendations for venous thromboembolism (VTE) prophylaxis and treatment.

**Technicians**
- Distinguish between oral, intravenous (IV), and subcutaneous (SQ) medications for VTE prophylaxis and treatment.
Background

- High risk for VTE development in COVID (+) admitted to a hospital
- Similar coagulopathy pattern as seen in SARS and MERS
- Incidence of VTE 1.1-69% in COVID patients
- Higher morbidity and mortality in those who develop VTE
- Practicality of diagnosis can be challenging
Pathophysiology
Coagulation Cascade Review

Contact activation (intrinsic) pathway
- Damaged surface
  - XII
  - XIIa
  - XI
  - X
  - IX
  - IXa
  - VIII
  - VIIIa
  - Prothrombin (II)
  - Xa
  - V
  - Va
  - Active Protein C
  - Protein S
  - Protein C + Thrombomodulin

Tissue factor (extrinsic) pathway
- Trauma
  - VII
  - VIIa
  - Tissue factor
  - Trauma
  - Antithrombin
  - TFPI
  - Fibrinogen (I)
  - Fibrin (Ia)
  - Common pathway
  - Cross-linked fibrin clot
  - Xllla
  - XIII

Coagulopathy in ARDS

- Permeability of alveolar-capillary junction
- Infiltration of various inflammatory and coagulation factors
- Tissue factor exposed on damaged epithelium
- Increased production of fibrinogen
- Increased PAI-1 release (hypofibrinolytic state)
- Unrestricted inflammation and fibrin deposits
- High risk for clot development
- Concern in later stages for mass fibrin deposits
Various Thrombi Formations

**Stroke, acute coronary syndrome**
- Antiphospholipid antibodies?
- Platelet activation
- Increased fibrinogen

**Localized intravascular Coagulation**
- Activated coagulation
- Leukocyte activation
- Endothelial damage

**Venous Thromboembolism**
- Increased fibrinogen and factor VIII
- Activated coagulation
- Enhanced platelet-vessel wall interaction

---

Overall Effects

Of note, uncommon to see:

- Thrombocytopenia
- Hemolytic anemia

A Risk Factors
- Acute Illness
- Bedridden, stasis
- Genetics
- Fever
- Diarrhea
- Sepsis
- Liver Injury
- CKD
- COPD
- HF
- Malignancy

B Hemostatic Abnormalities
- Pulmonary microthrombi
- Intravascular coagulopathy
- Myocardial injury
- Increased cardiac biomarkers

C Clinical Outcomes
- Venous Thromboembolism
- Myocardial Infarction
- Disseminated Intravascular Coagulation

- Increased D-Dimer, PT
- ~neutral platelets

Inflammatory Response
Endothelial Dysfunction
Superimposed Infection

- Lymphopenia
- Inflammatory cytokines
- Increased IL6, CRP
Additional Risk Factors

- Intense inflammatory response
- Critical illness
- Traditional risk factors (immobility, venous stasis)
- Drugs interactions with investigational therapies
- Unjustified fears about medications
Progression of Disease and Coagulopathy

Disseminated intravascular coagulation

Consumptive coagulopathy

Lab characteristics
- PT  
- PTT  
- Fibrinogen  
- D-dimer  
- Red cells – schistocytes

Single center study in China (N=183)
- 71% of those who died developed DIC
- 0.6% of those who lived developed DIC

## Implications for Prevention and Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Typical Doses</th>
</tr>
</thead>
</table>
| Unfractionated Heparin (UFH)     | • Enhances action of anti-thrombin III to inactive thrombin, Factor Xa, and other clotting factors  
  • Neutralizes procoagulable factors to protect endothelial cells, maintain tight junctions, and minimize edema and leakage, particularly related to COVID  
  • Potential anti-inflammatory effects | Prophylaxis: 5000-7500 units SQ Q8-12 h  
Treatment: 80 units/kg bolus, 18 units/kg/hr IV, or other variations |
| Low Molecular Weight Heparin (LMWH) | • Same as UFH, but higher affinity for Factor Xa  
• Same postulated benefits in COVID as UFH | Prophylaxis: 40 mg daily, 30 mg BID SQ  
Treatment: 1 mg/kg BID SQ  
*Adjusted for renal function |
| Fondaparinux                     | • Binds antithrombin III to specifically inhibit Factor Xa  
• Unknown supplemental benefits in COVID at this time or if confers the benefits as UFH and LMWH | Prophylaxis: 2.5 mg daily SQ  
Treatment: 5-10 mg per day SQ (weight-based)  
*Adjusted for renal function |
## Implications for Prevention and Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Typical Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Inhibition of vitamin K activation, which is required for synthesis of clotting factors II, VII, IX, and X</td>
<td>Varies, but typical starting dose of 5 mg daily PO Adjust with INR</td>
</tr>
<tr>
<td></td>
<td><em>Unknown supplemental benefits in COVID at this time</em></td>
<td></td>
</tr>
<tr>
<td>DOACs (Rivaroxaban, Apixaban)</td>
<td>Direct inhibition of Factor Xa</td>
<td>Varies with each oral agent</td>
</tr>
<tr>
<td></td>
<td><em>Unknown supplemental benefits in COVID at this time</em></td>
<td><em>Adjusted for renal function</em></td>
</tr>
<tr>
<td>Tissue plasminogen activator (tPA)</td>
<td>Converts plasminogen to plasmin to break down fibrin</td>
<td>Typically 50-100 mg IV over various times, usually 2 hours Can be given as catheter-directed therapy</td>
</tr>
<tr>
<td></td>
<td><em>Postulated benefit during increased PAI-1 release (hypofibrinolytic state) during active COVID infection</em></td>
<td></td>
</tr>
</tbody>
</table>
Question 1

Which of the following medications do not currently have additional postulated benefits beyond prevention of VTE in COVID positive patients admitted to the hospital?

A. Enoxaparin
B. UFH
C. Rivaroxaban
D. tPA
Diagnosis and Estimation of Risk
## COVID Lab Value Trends

<table>
<thead>
<tr>
<th>Lab Value</th>
<th>Effects in COVID</th>
<th>Notes</th>
</tr>
</thead>
</table>
| D-dimer   | Elevated         | • Higher risk of ICU admission, mechanical ventilation, and/or death  
|           |                  | • Elevated in high plasmin and fibrinolytic activity (diabetes, cardiovascular disease, hypertension; challenging to attribute solely to clot |
| PT        | Elevated         |       |
| PTT       | Elevated         | • Elevation proposed due to increased factor VIII  
|           |                  | • Not as elevated relative to PT |
| Fibrinogen| Elevated         | Major roll in DIC development assessment |
| CRP       | Elevated         | Augments tissue factor exposure, further promoting coagulopathy |
| PLT       | Neutral to mild decrease | Not usually a significant finding, unless severe illness |
| IL-6      | Elevated         | Proinflammatory cytokines leading to further alveolar-capillary permeability |

PT = prothrombin time; PTT = partial thromboplastin time; CRP = C-reactive protein; PLT = platelets  
Typically less dramatic than in bacterial infections

Many studies assessing labs to predict risk of VTE development, mostly surrounding D-Dimer

High D-dimers noted in severe COVID patients admitted to the ICU

Per the American College of Cardiology:
No great data to support diagnosis of VTE based off D-Dimer alone

Diagnosis

Practicality of diagnosis can be challenging

- Infection risk
- Patient instability

**Ideally: Imaging and Labs**

- D-Dimer not specific but can have a high negative predictive value
- CTPA
- VQ Scan
- ECHO assessing new right heart strain
- Ultrasound

Assess signs and symptoms:

- DVT manifestations
- Disproportionate hypoxemia
- New right ventricular dysfunction
- *Consider empiric treatment if high concern*
Treatment
Professional Societies

- International Society on Thrombosis and Haemostasis (ITSH)
- American Society of Hematology (ASH)
- World Health Organization (WHO)
- American College of Cardiology (ACC)

Several more coming out!
## Professional Societies

### Statements on VTE Treatment in COVID patients

<table>
<thead>
<tr>
<th>ISTH</th>
<th>ASH</th>
<th>WHO</th>
<th>ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No comment</td>
<td>• Consider drug-drug interactions with selection of agents</td>
<td>No comment</td>
<td>• Enoxaparin may be favored if no contraindications acutely</td>
</tr>
<tr>
<td></td>
<td>• Prefer heparin or LMWH for hospitalized patients for shorter half life and less drug interactions</td>
<td></td>
<td>• Consider systemic fibrinolytics vs catheter-directed therapy in massive PE</td>
</tr>
<tr>
<td></td>
<td>• Consider underlying conditions, valves, etc</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Largely support pre-COVID VTE treatment guidance
### Implications for Prevention and Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pros in COVID</th>
<th>Cons in COVID</th>
</tr>
</thead>
</table>
| UFH        | • Potential role in decreasing disease progression  
             • Short half-life  
             • Minimal drug-drug interactions  
             • Ability to monitor levels | • Higher need for monitoring and nursing contact time  
             • Potentially longer duration to reach therapeutic targets |
| LMWH       | • Potential role in decreasing disease progression  
             • Minimal drug-drug interactions  
             • Ability to monitor levels | • Renally cleared |
| Fondaparinux | • Once daily dosing to minimize nursing contact time | • Renally cleared |
| Warfarin   | • Once daily dosing to minimize nursing contact time | • Drug-drug interactions with COVID therapies |
| DOACs      | • 1-2 times daily dosing to minimize nursing contact time | • Drug-drug interactions with COVID therapies |
| tPA        | • Postulated benefit during increased PAI-1 release (hypofibrinolytic state) during active COVID infection | • Really reserved for unstable PE  
             • Not recommended as empiric therapy for microthrombi only |

Useful drug-drug interaction resource: https://covid19-druginteractions.org/checker
Prophylaxis
Assessment of Severity

- **Risks Assessment Methods to Consider:**
  - PADUA scores in medically ill patients
  - Caprini scores in surgically ill patients
  - Sepsis-Induced Coagulopathy score
  - *No specific score validated in COVID patients*

This has led many institutions to develop individual risk assessments and approaches
Significant controversy surrounding dosage for VTE prophylaxis

Hospitalized patients with COVID

- Standard Dosing
- Intermediate Dosing
- Therapeutic Dosing
COVID patients are typically adult, medically ill patients

Initial and potential ongoing concern that this may not be enough

3 Dutch hospitals, 184 ICU patients with COVID

25 symptomatic VTEs

2 ICUs used lower than recommended doses for prophylaxis

Unclear implications with inappropriate dosing

Intermediate Intensity Prophylaxis

- No specific studies available currently
- Several institutions have developed individualized approaches
  - Empiric twice daily dosing
  - Elevated Anti-Xa targets

  - Recommendations are currently just expert opinion
  - Not yet well supported by the literature
Empiric Full Dose Anticoagulation

- Several hospitals have published protocols incorporating empiric full dose anticoagulation.

  Single center retrospective observational study

  Improved mortality and median survival days in mechanically ventilated patients with full anticoagulation vs not

  - No report of prophylactic dosing
  - No account for baseline characteristics
  - Did state if just prophylactic anticoagulation or none at all in the comparator group

Not well supported by the literature at this time
Empiric tPA

- In the setting of presumed microthrombi in the lungs

  - 3 case reports
  - Improvement in oxygenation and P/F
  - Response was short lived, <12 hours

Not well studied or justified currently

# Professional Societies

## Statements on VTE prophylaxis related to patients admitted with COVID-19

<table>
<thead>
<tr>
<th>ISTH</th>
<th>ASH</th>
<th>WHO</th>
<th>ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prophylactic LMWH in all hospitalized patients with no contraindications</td>
<td>• Administer in all hospitalized patients</td>
<td>• Preferred LMWH or heparin 5000 units SQ BID</td>
<td>• Risk scores for VTE prophylaxis</td>
</tr>
<tr>
<td>• Favor LMWH over UFH to decrease contact time</td>
<td>• Favor LMWH over UFH to decrease contact time</td>
<td>• Mechanical prophylaxis if contraindications</td>
<td>• Weight-based dosing needs to be further studied</td>
</tr>
<tr>
<td>• Fondaparinux in HIT</td>
<td>• Fondaparinux in HIT</td>
<td>• Unknown if intermediate-intensity or full empiric anticoagulation beneficial</td>
<td>• Unknown benefit of empiric full anticoagulation</td>
</tr>
<tr>
<td>• Mechanical prophylaxis when chemical not available or contraindicated</td>
<td>• Mechanical prophylaxis when chemical not available or contraindicated</td>
<td>• Unknown if post-discharge prophylaxis beneficial</td>
<td>• Pregnancy needs further studies for correct approach</td>
</tr>
<tr>
<td>• Unknown if intermediate-intensity or full empiric anticoagulation beneficial</td>
<td>• Unknown if intermediate-intensity or full empiric anticoagulation beneficial</td>
<td>• No known benefit of empiric therapeutic anticoagulation in setting of elevated D-Dimer</td>
<td>• Individual risk/benefit stratification for prophylactic post discharge anticoagulation ≤45 days</td>
</tr>
</tbody>
</table>

Largely support pre-COVID VTE prophylaxis guidance
## Full Dose Vs Prophylactic Dose Heparin in High Risk COVID-19 Patients

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Prospective, randomized active-comparator trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Adult high risk hospitalized patients with COVID diagnosis with O₂ requirement</td>
</tr>
</tbody>
</table>
| **Intervention** | For VTE prophylaxis:  
  • Therapeutic LMWH vs  
  • Prophylactic or intermediate dose LMWH or UFH |
| **Outcome** | Composite: venous or arterial thrombotic events, all-cause mortality |
Question 2

69 year old female presents to your ED with cough, shortness of breath, and positive COVID nasal swab 4 days prior to arrival. She is requiring high flow nasal cannula 70 L 100% with oxygen saturations ~85%. The team decides to intubate and she is admitted to the medical ICU. They are working to enroll her in clinical trials for COVID therapies. Patient reports no current home medications, but had recently moved here from Argentina. She is found to have an A1c of 14% on arrival. Some presenting data are as follows: WBC 13, D-dimer 115, CrCl ~75 mL/min (making appropriate urine), BMI 45 kg/m².

What do you recommend for DVT prophylaxis in this patient?

A. Enoxaparin 40 mg SQ daily
B. Enoxaparin 40 mg SQ BID
C. Heparin 80 units/kg bolus, followed by 18 units/kg/hr
D. Warfarin 5 mg day
Take Home Points

- COVID patients, particularly critically ill tend to be at high risk for development of VTE
- Unknown significance of D-dimer, except that *potentially* high risk for clot, and still carries good negative predictive value
- VTE diagnosis in COVID patients can be challenging
- Treatment is per usual, but mindful of drug-drug interactions and nurse contact time
- Prophylaxis definitive statements are still challenging and more data is needed
Coagulopathies in COVID

IMPLICATIONS FOR VTE PROPHYLAXIS AND TREATMENT

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September 12, 2020
USHP Winter Meeting