Resilience

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Chair of Medicine
Lahey Hospital & Medical Center
Burlington, Massachusetts
Goals

• Demonstrate defining principles of evidence-based clinical practice through a case presentation
• Apply the Evidence Cycle including PICOTT
• Focus on real-time application of evidence for individual patient care
• Kick off the conference with a focus on caring
EBM Fundamental Principles

• Not all evidence is created equal
  A hierarchy of evidence helps us differentiate information more likely to be valid or true

• Evidence alone is never enough
  Decisions are informed and guided by patient and societal values and preferences.

• Clinicians make recommendations
  Clinicians make recommendations “For” or “Against” a particular course of action and those recommendations can be “Weak” or “Strong”
Ask

Acquire

Appraise

Evidence-based medicine cycle

Apply

Hierarchy of Evidence

Patient dilemma

Act & Assess

Values & Preferences
Our Journey Begins
February 2021
COVID-19 - February 3, 2021

Massachusetts Department of Public Health | COVID-19 Dashboard
Trends: 7-day Averages Over Time

Cases

7-day average of COVID-19 confirmed cases

2,602 new +

The lowest observed value was 156.7 on 7/4/2020.

Testing

7-day weighted average percent positivity

The lowest observed value was 0.8% on 9/21/2020.

Hospitalizations

7-day average of hospitalizations

The lowest observed value was 155.3 on 8/26/2020.

Deaths

7-day average of confirmed deaths

58 new deaths

The lowest observed value was 3.7 on 9/9/2020.

For details on the definitions of each indicator please see the corresponding tab for that indicator. All data included in this dashboard are preliminary and subject to change. Data Sources: COVID-19 Data provided by the Bureau of Infectious Disease and Laboratory Sciences and the Registry of Vital Records and Statistics; Created by the Massachusetts Department of Public Health, Bureau of Infectious Disease and Laboratory Sciences, Office of Integrated Surveillance and Informatics Services.
Case Presentation:
One of 2,602

A story of resilience
The Patient: HC

*HC- written informed consent was provided*
While you listen…

• Please use Handout #1 to identify at least 2 PICOTT questions

  P: Patient, population, problem
  I: Intervention, exposure, prognostic factor
  C: Comparison (if applicable)
  O: Outcome
  T: Type of question (e.g. therapy, harm, diagnosis)
  T: Type of study design (e.g. RCT, cohort, case-control)
HC: Presentation & History

- 101 year old delightful, engaged woman

- Past history
  - High Blood Pressure
  - High Cholesterol
  - Diabetes HgbA1C around 7
  - Chronic Kidney Disease GFR 41, range 38-51
  - Congestive Heart Failure, preserved EF (60%)
  - Chronic lower leg swelling on complicated diuretic regimen and variable electrolytes (Potassium, Mag)
  - Hypothyroidism, Obstructive Sleep Apnea on CPAP
HC: Presentation & History

• Goals of Care
  • Balance fluid status (leg swelling vs. urinary frequency)
  • Walk with assistance -- Take Steps Every Day
  • Manage back pain
  • Move bowels the “right amount”
  • In case of serious illness, no heroic measures, “I am nearly 102. If it is my time, it is my time”
On her hundredth birthday…

HC’s

Tips for Living to 100

- Smile
- Grow up in a big family
- Have a positive attitude about getting older
- Walk daily
- Get excellent medical care
- Work hard
- Eat oatmeal, fish, spinach, and pickles
- Read biographies & cook books
- Be pleasant
- Keep up to date on world happenings & politics
- Have a predictable, daily routine
- Spend time at the beach
Background

Told by HC’s Daughter
Not a UTI
Portal Message Asking for Phone Call

Help!! Mom has COVID!
HC: Presentation & History

• January 28, HC started to feel “sick” with fatigue and headache
• Her daughter, BC, thought she had a urinary tract infection as UTIs had presented like this before
• BC took her mother to her local emergency department
• HC had fever to 102, was noted to have a cough and tested positive for SARS-CoV-2 (Covid-19)
HC: Presentation & History

#1-Discussion with ED Nurse
- Vitals on arrival in ED: T-102  BP/ Pulse “normal”
- O₂Sat 98% on room air
- Not short of breath and lungs are clear
- Mentation is perfect
- CXR clear, Labs are unremarkable

#2-Discussion with ED physician
- Wants to admit her for observation

#3-Discussion with hospitalist
- Wants to treat with Remdesivir for COVID-19
**Clinical Question Formation**

Interactive! Use the Chat to write in some of your PICOs…
Jamie: Please watch the chat for me…

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**PICOTTT Practice**

<table>
<thead>
<tr>
<th>Patient, Population, Problem</th>
<th>Intervention, Exposure, Prognostic Factor</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Type of Question</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
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<td>2)</td>
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<td>6)</td>
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<td>7)</td>
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</tbody>
</table>
## PICOTT Practice

<table>
<thead>
<tr>
<th>Patient, Population, Problem</th>
<th>Intervention, Exposure, Prognostic Factor</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Type of Question</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1)</strong> 101 year old COVID + patient</td>
<td>Admission?</td>
<td>Home with daughter and pulse oximeter</td>
<td>Disease Progression, QOL, Hospitalization, Mortality</td>
<td>Intervention (Treatment)</td>
<td>RCT / MA</td>
</tr>
<tr>
<td><strong>2)</strong> Comorbidities (CV, CRI)</td>
<td>CV disease, age, other comorbidities</td>
<td>people without comorbidities</td>
<td>As above</td>
<td>Prognosis</td>
<td>Prospective cohort (could be part of an RCT)</td>
</tr>
<tr>
<td><strong>3)</strong> Normal CXR and Normal Oxygen Saturation, Good Social Support</td>
<td>Followed over time</td>
<td></td>
<td>As above</td>
<td>Prognosis</td>
<td>Prospective Cohort</td>
</tr>
<tr>
<td><strong>4)</strong> 101 year old with clear goals of care and values and preferences</td>
<td>Followed over time</td>
<td></td>
<td>Unintended consequences of treatments and hospital admission</td>
<td>Prognosis</td>
<td>Prospective Cohort</td>
</tr>
<tr>
<td><strong>5)</strong> 101 year old COVID + patient</td>
<td>Remdesivir</td>
<td>Placebo</td>
<td>As above</td>
<td>Intervention (Treatment)</td>
<td>RCT / MA</td>
</tr>
<tr>
<td>6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Annotation Station:
Should we admit? Most Important Factors

1. AGE 101 years
2. Comorbidity
3. O₂Sat / CXR
Annotation Station:
Should we admit?
What is your recommendation?

Weak | For | Strong
--- | --- | ---
Weak | Against | Strong
Annotation Station: Remdesivir for COVID? Most Important Factors

1ST Choice

AGE-Comorbidity

O₂Sat / CXR

2nd Choice

Renal Function
Annotation Station:
Should we treat with Remdesivir for COVID? What is your recommendation?
Ask

Acquire

Appraise

Hierarchy of Evidence

Evidence-based medicine cycle

Apply

Values & Preferences

Act & Assess

Patient dilemma
Acquiring: Pandemic Style

- Individual Articles (frequently in pre-print)
- Societies and National Organizations
  - ID Society of America (GRADE)
  - American College of Physicians (Living Practice Points)
  - WHO Living Guideline
  - BMJ Rapid Evidence
IDSA Certainty of Evidence

Definitions

• **High:** very confident that the true effect lies close to that of the estimated effect

• **Moderate:** the true effect is probably close to the estimate of the effect, but there is a possibility that it is substantially different

• **Low:** true effect may be substantially different from the estimate of the effect

• **Very low:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.
### DEATH

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious d</td>
<td>none</td>
<td>remdesivir</td>
<td>no remdesivir</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td>2</td>
<td>randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15/1100 (1.4%)</td>
<td>20/914 (2.2%)</td>
<td>RR 0.69 (0.36 to 1.34)</td>
<td>7 fewer per 1,000 (from 14 fewer to 7 more)</td>
</tr>
</tbody>
</table>

### Time to recovery (follow up: 29 days)

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54/55 (98.2%)</td>
<td>48/50 (92.0%)</td>
<td>Rate ratio 1.22 (0.82 to 1.81)</td>
<td>34 more per 1,000 (from 46 fewer to 70 more)</td>
</tr>
</tbody>
</table>

### Clinical improvement at day 11 (assessed with: >=2-pt improvement on 7-pt scale; higher = better)

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>134/191 (70.2%)</td>
<td>121/200 (60.5%)</td>
<td>RR 1.16 (1.00 to 1.34)</td>
<td>97 more per 1,000 (from 0 fewer to 206 more)</td>
</tr>
</tbody>
</table>

### Serious adverse events

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11/246 (4.5%)</td>
<td>18/249 (7.2%)</td>
<td>RR 0.64 (0.31 to 1.31)</td>
<td>26 fewer per 1,000 (from 50 fewer to 22 more)</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate; The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited; The true effect may be substantially different from the estimate of the effect.

*Last reviewed and updated 11/22/2020*
## Overview of IDSA COVID-19 Treatment Guidelines

*Version 4.1.0 – March 5, 2021*

<table>
<thead>
<tr>
<th>Setting and severity of illness</th>
<th>Ambulatory care: mild-to-moderate disease</th>
<th>Hospitalized: mild-to-moderate disease without need for suppl. oxygen</th>
<th>Hospitalized: severe but non-critical disease (spO₂ &lt; 94% on room air)</th>
<th>Hospitalized: critical disease (e.g., in ICU needing MV, or septic shock, ECMO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-11</td>
<td>Remdesivir</td>
<td>Suggest against routine use</td>
<td>Suggest use</td>
<td>Suggest use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NA</td>
<td>R: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.</td>
<td>R: For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.</td>
</tr>
</tbody>
</table>

*IDSA*
No evidence

**Insufficient:** confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome.

**Low:** certainty of evidence is limited because true effect may be substantially different from the estimated effect.
No evidence

**Insufficient**: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome.

**Low**: certainty of evidence is limited because true effect may be substantially different from the estimated effect.
### Critical outcomes

| Mortality | Remdesivir 5-d course may reduce mortality slightly compared with remdesivir 10-d course (16) |
| Recovery | Remdesivir 5-d course may result in a modest increase in recovery compared with remdesivir 10-d course (16) |
| Hospital length of stay | No evidence |
| Serious adverse events | Remdesivir 5-d course may not reduce serious adverse effects compared with remdesivir 10-d course (16) |

### Important outcomes

| Time to recovery | Very uncertain about the effect of remdesivir 5-d course compared with remdesivir 10-d course on time to recovery (16) |
| Clinical improvement | Remdesivir 5-d course may increase clinical improvement slightly compared with remdesivir 10-d course (16) |
| Time to clinical improvement | No evidence |
| Invasive mechanical ventilation/ECMO | Remdesivir 5-d course may not reduce the need for invasive mechanical ventilation or ECMO compared with remdesivir 10-d course (16) |
| Nonserious adverse events | No evidence |
| Any adverse events | Remdesivir 5-d course may result in a modest reduction in adverse events compared with remdesivir 10-d course (16) |

**ACP**

---

**No evidence**

**Insufficient**: confidence is inadequate to assess the likelihood of benefit (benefit minus harm) of an intervention or its impact on a health outcome.

**Low**: certainty of evidence is limited because true effect may be substantially different from the estimated effect.
## Table 1. Practice Points

1. Use remdesivir* for 5 days as a treatment for patients with **moderate†** COVID-19.
2. Use remdesivir* for 5 days as a treatment for patients with **severe†** COVID-19 who do not require mechanical ventilation or extracorporeal membrane oxygenation (ECMO).
3. Consider extending the use of remdesivir* to 10 days in patients with **severe†** COVID-19 requiring mechanical ventilation or ECMO within a 5-day course.

†
WHO Living Guideline

Hospitalized patients with COVID-19 infection, regardless of disease severity

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care

Practical info
The GDG made a conditional recommendation against using remdesivir for treatment of hospitalized patients with COVID-19. If administration of remdesivir is considered, it should be noted that its use is contraindicated in those with liver (ALT >5 times normal at baseline) or renal (eGFR <30 mL/minute) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

Conditional Recommendation Against for any patient regardless of disease severity
Lack of evidence that remdesivir improved outcomes that matter to patients such as reduced morality, need for mechanical ventilation, time to clinical improvement and others.

Overall low certainty evidence on the benefits and harms of remdesivir, driven by risk of bias and imprecision limitation in the included studies also contributed to the judgement.
**Recommendation 1**

Patients with COVID-19 at any severity

We suggest no remdesivir

### Evidence profile

<table>
<thead>
<tr>
<th></th>
<th>Events per 1000 people</th>
<th>Evidence quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favours usual supportive care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>106</td>
<td>No important difference</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>105</td>
<td>No important difference</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>15</td>
<td>No important difference</td>
</tr>
<tr>
<td>Viral clearance at 7 days</td>
<td>483</td>
<td>No important difference</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>56</td>
<td>No important difference</td>
</tr>
<tr>
<td>Delirium</td>
<td>16</td>
<td>No important difference</td>
</tr>
<tr>
<td><strong>No important difference</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Favours remdesivir</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to clinical improvement</td>
<td>11.0</td>
<td>No important difference</td>
</tr>
<tr>
<td>Hospitalisation duration</td>
<td>12.8</td>
<td>No important difference</td>
</tr>
<tr>
<td>Mechanical ventilation duration</td>
<td>14.7</td>
<td>No important difference</td>
</tr>
</tbody>
</table>

https://www.bmj.com/content/370/bmj.m3379
Annotation Station: Remdesivir for COVID? Most Important Factors

Star: 1st Choice
Heart: 2nd Choice

AGE-Comorbidity  O₂Sat / CXR  Renal Function
Annotation Station:
Should we treat with Remdesivir for COVID?
What is your recommendation?

Your recommendation

Weak  For  Strong

Weak  Against  Strong
Remdesivir
What Happened?
5- Day Hospital Admission
Hospital Stay #1

• Hospitalist starts 5 days of Remdesivir
• Did extremely well from a Covid perspective
• Discharged on day 5 after completion of her Remdesivir
Discharged Home on Day 5
But Not for Long
Second Hospital Admission

February 16, 2021
Unintended Consequences

• Admitted for diuresis and rehabilitation
  • Leg swelling and immobility
  • Could not stand or transfer to the bathroom
• Discharged to Short Term Rehab
  • Isolation due to infection control procedures
  • Severely understaffed
  • Did not provide adequate OT/PT
  • Kept losing her clothes
  • Multiple bruises, skin tears from transfers
Finally Home

March 24, 2021
The Last Word: What would you say to care providers?
One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.

Francis W. Peabody, MD
JAMA March 19, 1927
Not everything that counts can be counted, and not everything that can be counted counts.

Albert Einstein
EBM Fundamental Principles

• Not all evidence is created equal

A hierarchy of evidence helps us differentiate information more likely to be valid or true

• Evidence alone is never enough

Decisions are informed and guided by patient and societal values and preferences.

• Clinicians make recommendations

Clinicians make recommendations “For” or “Against” a particular course of action and those recommendations can be “Weak” or “Strong”
Thank you BC and HC