Diagnosis and Management of Respiratory Viruses

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<table>
<thead>
<tr>
<th>Everything you need to know in one slide</th>
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<tbody>
<tr>
<td>Test patients if they are symptomatic, if they are at high risk for complications, if the test result will impact management of patient and/or infection prevention/public health decisions</td>
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<td>The virus(es) of interest depend on the host and the environment</td>
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<td>How well a test performs depends on many factors, but an NPS for a PCR-based test gives you the greatest flexibility.</td>
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<td>Only a few viruses have targeted treatment options. Dr. Cutrell will teach you about SARS CoV-2</td>
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</table>
Should the patient be tested?

- Will testing affect clinical management?
  - Antiviral/antimicrobial initiation or de-escalation
  - Additional testing

- Will testing affect others?
  - Prophylaxis of contacts
  - Infection control/public health interventions

- Is the patient at high risk for complications?
  - Adults 65 or older
    - Kids <2
  - Pregnant → 2 weeks postpartum
  - Nursing home/long-term care facilities
  - Non-Hispanic Black, Hispanic or Latino, American Indian or Alaska Native persons
  - Asthma
  - Neurologic/neurodevelopment conditions
  - Blood disorders (sickle cell disease)
  - Chronic lung disease
  - Endocrine disease (diabetes mellitus)
  - Heart disease
  - Kidney disease
  - Liver disorder
  - Metabolic disorders (inherited, mitochondrial)
  - BMI 40 or greater
  - Age <19 on long term ASA or salicylate-containing medications
Impact of testing on management

- Mixed results
  - 720 patients between 2015/2016- half rapid multiplex molecular (POCT), half not tested\(^1\)
    - No difference in mean duration of antibiotics, adverse outcomes
    - POCT group positive outcomes: 1)had single dose or brief courses; 2)received timely/appropriate influenza therapy; 3)reduced length of stay (LOS)
  - Reduction of antibiotic duration noted comparing rapid multiplex molecular assay vs standard PCR with 2 day TAT\(^2\)
    - Also used procalcitonin
    - Many high risk populations excluded
  - If influenza detected using rapid molecular testing, fewer antibiotics were started, and more high risk patients were treated with oseltamivir\(^3\)
    - No difference in LOS
  - Rapid molecular testing did not decrease Emergency Department time to disposition or antibiotic management\(^4\)
  - Patients with molecular confirmation of SARS CoV-2 receive systemic antibacterial prescriptions, despite no evidence of bacterial infection\(^5\)

- Virus confirmation does impact decisions on patient isolation protocols

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Which virus(es) should be considered?

- What virus(es) currently circulate?
  - SARS CoV-2 affects every discussion
  - CDC and state/local health departments can provide information on other respiratory viruses

- Contacts/ travel/ exposures that may impact differential diagnosis?
  - Flu is less seasonal, more year-round in tropics
  - Exposure to children or persons with other known infections can guide testing approaches

https://www.cdc.gov/flu/weekly/usmap.htm
Which virus(es) should be considered?

https://www.cdc.gov/surveillance/nrevss/index.html
SARS CoV-2

The COVID-19 community level is determined by the higher of the new admissions and inpatient beds metrics, based on the current level of new cases per 100,000 population in the past 7 days.

**COVID-19 County Check**

Find community levels and prevention steps by county.

Select a Location (all fields required)

- Texas
- Dallas County

- < Start Over

- Low

In Dallas County, Texas, community level is Low.

https://covid.cdc.gov/covid-data-tracker/#datatracker-home
UTSW SARS CoV-2 positive results

Courtesy of Dr. Ellen Araj
UTSW Other respiratory viruses

Positive Virus by Week

Courtesy of Dr. Ellen Araj
January-current other respiratory viruses

Positive Virus by Week

Number of Positive Results

January 2, 2022
January 5, 2022
January 10, 2022
January 16, 2022
January 23, 2022
January 30, 2022
February 6, 2022
February 13, 2022
February 20, 2022
February 27, 2022
March 6, 2022
March 13, 2022
March 20, 2022

Courtesy of Dr. Ellen Araj
# How to choose a test

## Turn-around-time (TAT) for test
- What is acceptable based on the clinical presentation? – outpatient vs ED vs inpatient
- Is there a speed/sensitivity trade-off?

## How many viruses do you want to look for?
- Will you “screen” with a narrow panel, and expand if this is negative? Can this be done easily?

## Method of collection
- NPS lets you look for the greatest number of viruses
- SARS CoV-2 only testing lets you use the greatest variety of collection devices/specimens

## Sensitivity and specificity of the test
- Depends on the test design and specimen collection factors

## Positive/negative predictive value of the test
- Depends on prevalence of disease

Supply chain and allocation challenges affect test availability
<table>
<thead>
<tr>
<th></th>
<th>PCR</th>
<th>Antigen</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS CoV-2</td>
<td>• Preferred modality for respiratory virus detection</td>
<td>• Not available for all viruses</td>
<td>• Not for acute diagnosis</td>
</tr>
<tr>
<td>Influenza A/B</td>
<td>• Available as single target tests, e.g.:</td>
<td>• Generally reduced analytical sensitivity compared to PCR.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SARS CoV-2</td>
<td>• Rapid TAT may acceptable “cost”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FluA/B</td>
<td>• Less likely to find residual DNA in previously infected patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Available as complexed, or highly complexed assays, e.g.:</td>
<td>• Depending on FDA approval, may be performed on NPS, NS, or NPA/NPW.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SARS CoV-2 + FluA/B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RSV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus A/B</td>
<td>• Multiple targets including all listed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>•</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronavirus NL63, HKU1, 229E, OC43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parainfluenza 1-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rhinovirus/enterovirus</td>
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</tbody>
</table>

NP- nasal swab; NPS- nasopharyngeal swab; NPA- nasopharyngeal aspirate; NPW- nasopharyngeal wash. TAT- Turn-around-time.
<table>
<thead>
<tr>
<th>Complexity</th>
<th>Product</th>
<th>Method</th>
<th>Platform/Instrument</th>
<th>Influenza Viruses Detected</th>
<th>Influenza A Virus Subtypes Differentiated</th>
<th>Other Respiratory Viruses Differentiated</th>
<th>Approved Specimens</th>
<th>Test Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>High, Moderate</td>
<td>BioFire Respiratory Panel 2.1 (RP2.1)</td>
<td>Nucleic Acid Detection</td>
<td>FILMARRAY® 2.0 and FILMARRAY® TORCH systems</td>
<td>Influenza A, Influenza B</td>
<td>A(H1), A(H1)pdm09, A(H3)</td>
<td>SARS-CoV-2, ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV</td>
<td>NPS</td>
<td>1 hour</td>
</tr>
<tr>
<td>High, Moderate, Waived</td>
<td>BioFire Respiratory Panel 2.1-EZ (RP2.1-EZ)</td>
<td>Nucleic Acid Detection</td>
<td>FILMARRAY® 2.0 EZ Configuration System</td>
<td>Influenza A, Influenza B</td>
<td>A(H1), A(H1)pdm09, A(H3)</td>
<td>SARS-CoV-2, ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV</td>
<td>NPS</td>
<td>Approximately 45 minutes</td>
</tr>
<tr>
<td>High, Moderate</td>
<td>4plex Respiratory Pathogen Panel 2</td>
<td>Nucleic Acid Detection</td>
<td>4plex System</td>
<td>Influenza A, Influenza B</td>
<td>A(H1), A(H1)pdm09, A(H3)</td>
<td>SARS-CoV-2, ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV</td>
<td>NPS</td>
<td>&lt;2 hours</td>
</tr>
<tr>
<td>High, Moderate</td>
<td>QStat-dx Respiratory SARS-CoV-2 Panel</td>
<td>Nucleic Acid Detection</td>
<td>QStat-dx Analyzer System 1.0</td>
<td>Influenza A, Influenza B</td>
<td>A(H1), A(H1)pdm09, A(H3)</td>
<td>SARS-CoV-2, ADV, Coronavirus 229E, HKU1, NL63, OC43, hMPV, RV/EV, PIV 1-4, RSV</td>
<td>NPS</td>
<td>1 hour</td>
</tr>
<tr>
<td>High, Moderate</td>
<td>Cobas SARS-CoV-2 &amp; Influenza A/B</td>
<td>Nucleic Acid Detection</td>
<td>Cobas 6800/8800 Systems</td>
<td>Influenza A, Influenza B</td>
<td>Not Differentiated</td>
<td>SARS-CoV-2</td>
<td>Healthcare provider-collected NPS and NS, and self-collected NS (collected in a healthcare setting with instruction by a healthcare provider)</td>
<td>3-8 hours</td>
</tr>
<tr>
<td>High, Moderate</td>
<td>Cobas SARS-CoV-2 &amp; Influenza A/B Nucleic Acid Test</td>
<td>Nucleic Acid Detection</td>
<td>Cobas List Systems</td>
<td>Influenza A, Influenza B</td>
<td>Not Differentiated</td>
<td>SARS-CoV-2</td>
<td>Healthcare provider-collected NPS and NS, and self-collected NS (collected in a healthcare setting with instruction by a healthcare provider)</td>
<td>20 minutes</td>
</tr>
<tr>
<td>High, Moderate</td>
<td>Xpert Xpress SARS-CoV-2/Flu/RSV</td>
<td>Nucleic Acid Detection</td>
<td>GenXpert Dx and GenXpert Infinity system</td>
<td>Influenza A, Influenza B</td>
<td>Not Differentiated</td>
<td>SARS-CoV-2, RSV</td>
<td>NPS</td>
<td>&lt;40 minutes</td>
</tr>
<tr>
<td>Waived</td>
<td>Xpert Xpress SARS-CoV-2/Flu/RSV</td>
<td>Nucleic Acid Detection</td>
<td>GenXpert Xpress System (Tablet and Hub Configurations)</td>
<td>Influenza A, Influenza B</td>
<td>Not Differentiated</td>
<td>SARS-CoV-2, RSV</td>
<td>NPS</td>
<td>&lt;40 minutes</td>
</tr>
<tr>
<td>High, Moderate, Waived</td>
<td>Sofia 2 Flu + SARS Antigen FA</td>
<td>Antigen Detection</td>
<td>Sofia FIA Analyzer</td>
<td>Influenza A, Influenza B</td>
<td>Not Differentiated</td>
<td>SARS-CoV-2</td>
<td>NPS, NS, NW/NA</td>
<td>15 minutes</td>
</tr>
<tr>
<td>High</td>
<td>Quest Diagnostics COVID-19 Flu RT-PCR</td>
<td>Nucleic acid detection</td>
<td>Roche cobas SARS-CoV-2 / Influenza A/B</td>
<td>Influenza A, Influenza B</td>
<td>Not Differentiated</td>
<td>SARS-CoV-2</td>
<td>When ordered by a healthcare provider: NS specimen is self-collected at home using the Quest Diagnostics Self-Collection Kit for COVID-19 4Flu Patient ships the self-collected specimen to Quest Diagnostics overnight via FedEx</td>
<td>4 hours</td>
</tr>
<tr>
<td>High</td>
<td>Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay*</td>
<td>Nucleic Acid Detection</td>
<td>Applied Biosystems 7500 Fast Dx Real-Time PCR Instrument</td>
<td>Influenza A, Influenza B</td>
<td>Not Differentiated</td>
<td>SARS-CoV-2</td>
<td>NPS, NPW, NPA, NS, NA, TS, sputum, TA, BAL</td>
<td>4 hours</td>
</tr>
</tbody>
</table>

How “good” is the test?

Analytical variables

- Efficiency of nucleic acid extraction
- Design of the primer/probe sequences
- Efficiency of the PCR chemistry in the assay
- Method for defining/determining Ct value
- Lower limit of detection (analytical sensitivity)
- Lack of cross-reaction with other targets (analytical specificity)

Pre-analytic Variables

- Efficiency of sample collection
  - Device used
  - Duration of collection
- Timing of collection relative to symptom onset
- Specimen storage and transport conditions
- Age of sample at time of testing
- Specimen type—
  - matrix effect
  - level of viral RNA in different specimen types

A word about Ct values:
• Not standardized across platforms
• Tests are designed to be qualitative (yes/no), not quantitative
• Should NOT be used for clinical decision-making

Importance of pretest probability

When disease prevalence is low, positive results have higher likelihood of being false positive.
Antigen tests face the same preanalytical challenges
- Most antigen tests sample the anterior nares, which may have lower viral loads at baseline
- If CLIA waived (no laboratory oversight) – quality control procedures are less stringent

For SARS CoV-2
- Antigen tests are 30-40% less sensitive compared to PCR
- Specificity is similar
- In patients with very high viral loads, this gap narrows

For influenza
- Antigen tests may be up to 50% less sensitive compared to PCR
- Many are less sensitive for Flu B
- There are newer antigen tests using instruments to standardize interpretations, that may improve the clinical performance

https://www.cdc.gov/flu/professionals/diagnosis/index.htm
CID, Volume 68, Issue 6, 15 March 2019, Pages e1–e47
# Treatment Options

<table>
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<tr>
<th>Virus</th>
<th>Treatment</th>
<th>Patient type</th>
</tr>
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<tbody>
<tr>
<td>Influenza Virus</td>
<td>Neuraminidase inhibitors; Endonuclease inhibitors</td>
<td>Treatment indicated based on disease severity, risk of progression</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus</td>
<td><em>Ribavirin ± IVIG/steroids</em></td>
<td>Multiple investigational agents</td>
</tr>
<tr>
<td>Parainfluenza Virus</td>
<td><em>Ribavirin ± IVIG/steroids?</em></td>
<td>No FDA approved regimen for adults. Treatment is off-label for transplant recipients.</td>
</tr>
<tr>
<td>Human Metapneumovirus</td>
<td><em>Ribavirin ± IVIG/steroids?</em></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td><em>Cidofovir, brincidofovir</em>, IVIG</td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Human Coronaviruses (other)</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Bitterman & Kumar, Viruses 2021. 34834953
Influenza treatment options

**Neuraminidase inhibitors:**
- Blocks the viral neuraminidase enzyme.
- Active against both influenza A and B
  - Oseltamivir: preferred agent in most cases, including hospitalized
  - Peramivir
  - Zanamivir

**Endonuclease Inhibitor**
- Targets PA subunit of viral polymerase complex; Interferes with RNA transcription, blocking virus replication.
- Active against both influenza A and B; may have better activity than oseltamivir against Flu B.
  - Baloxavir

**Indications**
- Hospitalization
- Severe/complicated/progressive illness
- At high risk for complications from influenza
45 year old male presenting with T 100.4, HR 110, cough, rhinorrhea, sore throat, fatigue.

- He has no past medical history
- Soc Hx neg
- He is s/p bilat lung transplant
- Soc Hx neg
- He has diabetes, A1c 9%
- +50 pack/year
- It is February
- FluA community prevalence is high
- It is July
- He teaches at a year-round elementary school
- It is September
- He recently traveled by plane internationally
- He is stable
- He requires intubation
Everything you need to know, again

Test patients if they are symptomatic, if they are at high risk for complications, if the test result will impact management of patient and/or infection prevention/public health decisions.

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How well a test performs depends on many factors, but an NPS for a PCR-based test gives you the greatest flexibility.

Only a few viruses have targeted treatment options.
Dr. Cutrell will teach you about SARS CoV-2.
Questions

- Thank you!