Antibiotic stewardship and the role of improved diagnosis in the management of acute respiratory tract infections

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Objectives

- Discuss antimicrobial resistance and antimicrobial prescribing patterns in the US, with a focus on acute respiratory infections
- Examine peer reviewed literature on the performance of point of care diagnostic tests for influenza, RSV, and Group A Strep
- Review the benefits of decentralized testing for respiratory pathogens
- Analyze current guidelines and recommendations for detection of respiratory pathogens
Antibiotic Prescribing for Acute Respiratory Infections—Success That's Way Off the Mark

Linder J. JAMA Int Med 2013
Antibiotic prescribing for acute respiratory tract infections (ARI) is common

Ambulatory care prescribing

85-95% antibiotics are prescribed in ambulatory settings

In 2015, enough antibiotic prescriptions dispensed in outpatient settings to give a course to 5 out of every 6 Americans \(^1\)

National Ambulatory Medical Care Survey

184,032 visits, 2010-11 \(^2\)
- 12.6% resulted in an antibiotic prescription
- ARI most common indication across all age groups
- 506 antibiotic prescriptions per 1000 population, of which only 69% considered appropriate

Antibiotic prescribing ARI often inappropriate

Outpatient prescribing from claims database of 19.2 million privately insured patients who had 15.4 million antibiotic prescriptions¹

Survey of VA outpatients with upper or lower resp infection 2009-11²
Overall 35% treated appropriately with antibiotics, 39% for those with pharyngitis

2 of 3 were not treated appropriately

Between 2000 and 2010

1.4 billion antibiotics prescribed in US

- Decreased 18% in children and adolescents
- Unchanged in adults
- Increased 30% in older adults

Sources: 1. Lee GC. BMC Medicine 2014
Impact of prescribing

Selection for resistant bacteria
Contribute to 23,000 excess deaths in US, cost of $20 billion in excess direct health care costs/year

Adverse drug reactions
Antibiotics implicated in 19.3% of all ED visits for drug-related adverse effects (mostly related to allergic reactions)
C. Diff infection (450,000 infections, 15,000 deaths/year in US)

Effects on microbiome
Growing evidence for effects on multiple diseases, obesity etc.

National Action Plan for Combating Antibiotic-Resistant Bacteria

Main Goals

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections
2. Strengthen national One Health surveillance efforts to combat resistance
3. **Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria**
4. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines
5. Improve international collaboration and capacities for antibiotic resistance prevention, surveillance, control, and antibiotic research and development

Role of diagnostics in acute respiratory tract infections

Common issues in attempts to improve diagnostic precision for ARI

✓ Clinical features similar across most respiratory tract infections; limited ability to discriminate etiology

✓ Laboratory testing can potentially improve diagnostic precision in 2 ways:
  ✓ Detection of viral or bacterial pathogens: *we will focus on Group A strep, influenza, and RSV*
  
  and/or
  ✓ Measuring the host response to infection: procalcitonin, C-reactive protein: *we won't cover these inflammatory markers in today's presentation*

✓ Tests are shifting from lab settings to clinics (increasingly to pharmacy….perhaps home?)

✓ Sophistication, accuracy and speed of point of care tests is rapidly evolving, with emergence particularly of nucleic acid assays

✓ Demonstrating impact of testing on outcomes (as well as test accuracy) is essential
Other Causes
- Viruses most common etiology
- Less commonly other bacteria: Group C and G strep, *Arcanobacterium haemolyticum*, *Mycoplasma pneumoniae*, *Fusobacterium necrophorum*, *Neisseria gonorrhoeae*, and *Chlamydia pneumoniae*
- Epstein Barr Virus (Infectious Mononucleosis) often includes symptoms of pharyngitis

Acute pharyngitis common diagnosis in primary care and ambulatory settings

- Beta-hemolytic Group A Streptococci (GAS)
- GAS in children 20-30%
- GAS in adults 5-10%

Approximately 13 million visits each year in the US

Costs related to GAS pharyngitis

$224-539 million each year

- Children miss average 1.9 days school/daycare
- 42% of adults miss 1.8 days of work
Diagnosis of GAS

Antibiotic Therapy

Emphasis on GAS because antibiotic therapy may:
- Shorten duration of illness
- Prevent the rare complications (rheumatic fever)
- Glomerulonephritis etc.
- Limit spread to others

Accurate & Efficient Diagnosis of GAS

Essential for:
- Targeted antibiotic therapy
- Symptom reduction
- Limit rare long-term complications (suppurative, non-suppurative)
- Informing infection control (prevent spread)
- Optimizing clinic efficiency and patient satisfaction

Treatments

- Penicillin remains effective but evidence of macrolide resistance 5-15% ¹
- Currently no evidence of difference in symptom resolution between penicillin vs. macrolides vs. cephalosporins ²
- Approx 9% children in one study received broader spectrum antibiotics than needed ³

Appropriate clinical symptoms assessment needed: Infection vs. colonization

Carriage of GAS is common

Systematic review of 285 studies
- overall asymptomatic carriage 7.0%
- highest in children 8.0%
- much lower in adults 2.5%
- lower in low-income countries

Other reviews show carriage rates of 25%

Importance?
- Carriers unlikely to transmit GAS to others
- Clinical Symptom Assessment in conjunction with appropriate testing modality is important
- Swabbing throats of people who don’t have symptoms may detect GAS carriage
- Little risk of developing complications
- Serology (ASO titres) can be used to differentiate infection vs colonization. Rarely used except in differential diagnosis of non-suppurative complications e.g., post-strep glomerulonephritis

What about GAS? Impact on appropriate prescribing

Evidence that diagnostic testing for GAS can reduce inappropriate antibiotics

**Rapid strep testing reduced antibiotic prescribing for children** with pharyngitis from 41% to 22% in one study in ED

**Children**

41-22%

Yet inappropriate prescribing continues, 22.5% adults with acute pharyngitis who had received negative rapid antigen testing

Accumulation of clinical features for GAS

Systematic review of 38 articles on individuals symptoms and signs, 15 articles on clinical prediction rules in children.

<table>
<thead>
<tr>
<th></th>
<th>Likelihood Ratio</th>
<th>Confidence Intervals</th>
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<tbody>
<tr>
<td>Scarlatiniform rash</td>
<td>3.91 (95%)</td>
<td>2.00-7.62</td>
</tr>
<tr>
<td>Palatal petechiae</td>
<td>2.69</td>
<td>1.92-3.77</td>
</tr>
<tr>
<td>Pharyngeal exudates</td>
<td>1.85</td>
<td>1.58-2.16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.79</td>
<td>1.58-2.16</td>
</tr>
<tr>
<td>Tender cervical nodes</td>
<td>1.72</td>
<td>1.54-1.93</td>
</tr>
</tbody>
</table>

"Symptoms and signs, either individually or combined into prediction rules, cannot be used to definitively diagnose or rule out streptococcal pharyngitis."
Diagnosis and Management of GAS Pharyngitis in the US, 2011-2015

18.8 million pharyngitis events from 11.6 million patients using claims database

Antibiotic use frequent (49.3%)
- Highest if no test (57.1%)
- High with RADT alone (53.4%)
- Lower with RADT+ culture (31.2%) or NAAT (34.5%)

Sources: Robert Luo, Joanna Sickler, Farnaz Vahidnia, Yuan-Chi Lee, Bianca Frogner and Matthew Thompson
Consequences of accuracy of rapid antigen tests

**False negatives** *(rapid antigen negative, lab test positive)*

Study of 6,504 ED patients, of whom 234 had initial negative rapid antigen and positive backup NAAT test

- 90% contactable, but half took multiple calls or letter
- Antibiotics started 7-24 hrs later

Among 15,555 adults at Cleveland clinic

- Negative rapid test + positive NAAT back up (false negatives, n=953) – 51% received antibiotics after average 2.3 days
- More concerning, 48% of those with negative rapid and negative NAAT (true negatives, n=6617) received antibiotics

**False positives** *(rapid antigen positive, lab test negative)*

- GAS may be non-viable, inhibited in culture by presence of other bacterial, non-detectable due to other bacterial species
- 61% of false positive samples were PCR positive in one study

Molecular tests

CLIA-waived NAATs now currently available from several manufacturers

Accuracy very similar to NAATs performed in lab & results in ≤15 minutes

Earlier systematic review of 6 studies

- Sensitivity 92% (95% CI 82-89)
- Specificity 94% (95% CI 91-96)

cobas Liat Strep A assay vs reference culture (with PCR for discordant results)

- Sensitivity 97.7% (95% CI 93.4-99.2%)
- Specificity 93.3% (95% CI 89.9-95.6%)

Diagnosis and antibiotic treatment of group A streptococcal pharyngitis in children in a primary care setting: impact of point-of-care polymerase chain reaction

Arundhati Rao1*, Bradley Berg2, Theresa Quezada3, Robert Fader1, Kimberly Walker1, Shaowu Tang3, Ula Cowen3, Dana Duncan3 and Joanna Sickler3

Pediatric clinic n=275, 3-18 yr
Compared rapid antigen test, point of care NAAT, culture vs. reference standard of sequencing
Clinical performance

**Table 1 Clinical performance of POC PCR, laboratory PCR, bacterial culture, and POC RADT when compared with final results by sequencing for group A Streptococcus (n = 255)**

<table>
<thead>
<tr>
<th>Final result</th>
<th>Cobas Lat POC PCR</th>
<th>Quidel QuickVue POC RADT</th>
<th>Bacterial culture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>Positive</td>
<td>105</td>
<td>1</td>
<td>106</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>144</td>
<td>149</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>145</td>
<td>255</td>
</tr>
</tbody>
</table>

- Sensitivity n/N (%; 95 CI) = 105/110 (95.5%, 89.7–98.5)
- Specificity n/N (%; 95 CI) = 144/145 (99.3%, 95.2–99.9)
- PPV n/N (%; 95 CI) = 105/106 (99.1%, 94.9–99.9)
- NPV n/N (%; 95 CI) = 144/149 (96.6%, 92.3–98.9)
- OPA n/N (%; 95 CI) = 249/255 (97.6%, 94.9–99.1)

NPV negative predictive value, OPA overall percentage agreement, PPV positive predictive value
*cobas Lat Strep A (POC) and Solana GAS NAAT (laboratory based). PCR via Clopper–Pearson (exact)
*Results based on concordant test results or bidirectional DNA sequencing when results were discordant

**Appropriate antibiotic prescribing**

**Table 2** Appropriate antibiotic prescribing in relation to group A Streptococcal testing results

<table>
<thead>
<tr>
<th>Antibiotic use</th>
<th>Final result*</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SOC (n = 152)</td>
<td>Liat (n = 103)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>No</td>
<td>90</td>
<td>72</td>
<td>2</td>
</tr>
</tbody>
</table>

Appropriate antibiotic use, % (n/N)$^c$

- 87.5% (133/152)
- 97.1% (100/103)

*Final result by bidirectional DNA sequencing; P = .0065
*RADT plus culture
*cobas Liat Strep A POC PCR assay

*Appropriate antibiotic use defined as follows: final result positive plus antibiotics = yes or final result negative plus antibiotics = no. SOC % = (61 + 72)/
(61 + 10 + 9 + 72); Liat% = (38 + 62)/(38 + 1 + 2 + 6 + 62)


Appropriate antibiotic use 87.5% in standard of care vs. 97.1% with point of care PCR
What do the GAS guidelines say?

Infectious Diseases Society of America*

- Adults: negative rapid antigen tests do **not** need lab culture confirmation (low incidence GAS, low risk complications)
- Children/Adolescents: negative rapid antigen tests should have lab culture confirmation
- ASO titres not recommended
- Testing not recommended if clinical features suggest viral etiology (rhinorrhea, cough, oral ulcers, hoarseness)
- Tests not indicated in children <3 yr
- Follow up post-treatment testing not recommended
- Testing and empiric treatment asymptomatic household contacts not recommended

Source: Shulman St et al. Clin Infect Dis 2012
Diagnosing Influenza A/B & RSV
Influenza- contribution to acute respiratory illness

- During 2010–2018, seasonal influenza epidemics associated with an estimated 4.3–23 million medical visits, 140 000–960 000 hospitalizations, and 12 000–79 000 deaths each year in the United States.

- Major reason for seeking medical care, particularly pediatric acute facilities where 11-24% flu positive in outpatient and ED settings during flu seasons.

- Disproportionately affects younger, elderly, comorbidities (e.g. asthma, COPD).

- Antibiotic prescribing (inappropriate) found in 29% in one US national study of 14,987 patients with ARI.

- Use of antiviral medications (commonly Tamiflu/oseltamivir, or Relenza/zanamivir) recommended within first 48 hours - according to IDSA recommendations.

How useful are clinical features?

- Symptoms of influenza overlap with those of other acute respiratory infections
- Symptom scores have some value in determining influenza positivity among adults presenting with influenza-like illness (ILI)
- **Flu Score** = presence of acute onset (<48hr), myalgia, chills/sweats, fever, cough
  - Positive LR of 2.7
  - Can classify about 2/3 of adults with ILI to higher risk of influenza (54%) and lower risk (7%) during influenza season
  - An imprecise diagnostic tool, but valuable for guiding need for lab test confirmation

Potential benefits of testing for influenza

Potential benefits

- Prompt initiation of antiviral therapy
- Convincing evidence that testing reduces unnecessary antibiotic use in patients positive for influenza
- Fewer additional tests needed (i.e., once have diagnosis of influenza, less need to pursue further diagnostics)
- Infection control measures – schools, workplaces, nursing homes/residential facilities, and hospitalized patients
- Epidemiological information on viral types, vaccine effectiveness, etc

Source: Egilmez E et al Rev Med Viral 2018
IDSA recommendations for outpatient (including ED) influenza testing

- **During influenza activity:**
  - Test in high-risk patients:
    - Immunocompromised persons who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (e.g., cough without fever) if result will influence clinical management.
  - Test in patients with acute onset of respiratory symptoms:
    - with or without fever, exacerbation of chronic medical conditions (e.g., asthma, COPD, heart failure) or known complications of influenza (e.g., pneumonia) if the testing result will influence clinical management.
  - Consider testing for patients:
    - not high risk for influenza complications who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (e.g., cough w/o fever) and likely to be discharged home if the results might influence antiviral treatment decisions, reduce use of unnecessary antibiotics, and/or additional diagnosis

- **During low influenza activity without any link to an influenza outbreak:**
  - Clinicians can consider testing in patients with acute onset of respiratory symptoms with or without fever, especially for immunocompromised and high-risk patients.

Source: Uyeki et al, Clin Infect Dis 2019
Diagnostic accuracy of novel and traditional tests for influenza: A systematic review and meta-analysis of 162 studies

Test sensitivity (95% Confidence Intervals). Specificity very high for all three types of tests (98.3%)

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Influenza A</th>
<th>Influenza B</th>
</tr>
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<tbody>
<tr>
<td>Rapid immunoassays (older)</td>
<td>Sensitivity 54% (49-60)</td>
<td>Sensitivity 53% (42-76)</td>
</tr>
<tr>
<td>Automated immuno chromatographic antigen detection</td>
<td>Sensitivity 80% (73-86)</td>
<td>Sensitivity 77% (65-85)</td>
</tr>
<tr>
<td>Rapid nucleic acid detection</td>
<td>Sensitivity 92% (85-96)</td>
<td>Sensitivity 95% (87-99)</td>
</tr>
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Rapid tests for influenza

Key considerations about influenza testing

- Pooled sensitivities higher in children by 12-32% - more viral shedding and for longer than adults
- Longer duration of illness – much lower sensitivity - less virus shedding
  - 6 studies from review found sensitivity dropped from 70-100% at day 1-2, down to 13-50% at day 2-4
- Poor sensitivity of older rapid antigen tests means that negative tests “can’t be trusted” (i.e. could it be a false negative test?)--- patients might not be treated with antivirals, or might unknowingly spread influenza to others
- Led the FDA in 2017 to reclassify rapid antigen tests and many were discontinued.

Impact of nucleic acid tests for influenza in clinical practice

- IDSA recommends NAATs over rapid antigen tests now for outpatient/ED settings, and for inpatients
  - IDSA describes nasopharyngeal swab as optimal specimen
- NAATs now available as point of care, rapid tests from several manufacturers
- Study in ED where triage nurses took nasopharyngeal swab samples, ran RT-PCR test themselves
  - 187 adults with influenza like illness, 52% had influenza
  - Accuracy of point of care device used by nurses (not lab staff): sensitivity 98%, specificity 99%
- Growing evidence on impact on reducing ED lengths of stay, reducing antibiotic use
- Further evidence with implementation in primary care/urgent care settings

RSV contribution to acute respiratory illness

- Yearly seasonal infection, largely affect children: bronchiolitis (RSV caused 65-70% of all cases of bronchiolitis), as well as pneumonia, otitis media. Growing evidence for role in adult and elderly population¹

- Hospitalization attributable to RSV estimated as 200,000 per year in the US: 1/2 in children 0-4, and 1/3 in seniors 65+ (compares to about 300,000 for influenza)
  - Majority of deaths in children in those with underlying immunocompromised or chronic conditions e.g asthma, CF, (but 1/5 have no known risk factors)

- Significant burden for child, parents and primary care providers in outpatient/ED settings
  - Delayed diagnosis directly associated with longer hospital stays and greater antibiotic overuse²

- Therapy:
  - Usually supportive – oxygen and feeding support.
  - Ribavirin, IV immunoglobulin have limited value in higher risk hospitalized children.
  - Palivizumab recommended as preventive measure in very high risk children during RSV season
  - Optimizing asthma therapy important in those with RSV induced asthma exacerbations

Source: Barr R et al. Ther Adv Infectious Dis 2019, Matias G et al. BMC Pub Health 2017, Lee et al., 2019
Key considerations

✓ Provides confidence of etiology of viral rather than bacterial etiology

✓ Point of care diagnostics for RSV demonstrate reductions in inappropriate antibiotics (doctors and parents feel more confident with knowing the etiology)

✓ Also reduction in use of other diagnostics – labs, chest X ray, etc (though CXR may be needed in some children/more severe illness)… and reduction of time in the ED

✓ Co-infection (RSV + bacteria) is uncommon – 1.2% in one study, so maintaining clinical suspicion always important.

✓ AAP does not recommend *routine* testing for RSV, relies on clinical suspicion and awareness of children at very high risk. Clinicians may find value for clinical management and infection control reasons/reducing nosocomial spread

Source: Barr R et al. Ther Adv Infectious Dis 2019, Matias G et al. BMC Pub Health 2017
Rapid tests for RSV: A systematic review and meta-analysis of 71 studies

Diagnostic accuracy (95% Confidence Intervals).

| Rapid immunoassays | Sensitivity 80% (76-83) | Specificity 97% (96-98) |

Accuracy differs with age

- Sensitivity varies with age
- Children 81% (78-84%)
- Adults 29% (11-48%)

Newer nucleic acid rapid tests for RSV

Accuracy of NAATs for RSV

- CDC recommends NAAT for older children and adults, while for children can use either the rapid immunoassay or NAATs
- Point of care NAATs now produced by several companies
- 12-site US study compared a point of care NAAT conducted by non-laboratory staff in CLIA-waived clinic settings, to laboratory reference NAAT test
  - 2080 nasopharyngeal swabs, 18% 5yr and under. 6.6% RSV positive
  - Sensitivity 97% (95%CI 93-99), Specificity 99.7% (95%CI 99.3-99.9)

Point of care testing for respiratory pathogens
Molecular point of care tests for respiratory tract infections

Advantages

- **No need for confirmation** of negative molecular POCTs
- **Very high sensitivity** hence preferred choice by CDC/IDSA depending on age and pathogen test
- **Clinicians more likely to trust** and act on results at point of care
- **Patient and physician satisfaction increase** if definitive results available during the patient encounter
- **Cost avoidance** by not needing to follow-up on delayed confirmatory tests, or conducting other lab tests

Disadvantages

- **Higher test cost** (though offset by no need for back up testing, impact of clinical staff/patient inconvenience)
- **Will not detect rare bacterial or viral causes** of acute respiratory infection, so clinical correlation is always required
Primary Care is changing

Traditional primary care
- ‘Bricks & Mortar’ clinics – Family Medicine, Pediatrics, Internal Medicine
- Access issues
- Higher cost, increased scrutiny of value
- Continuity, older patients, more complexity

Consumer-orientated care
- Accessible, walk-in, convenient
- Transparent menu of services & costs
- Telemedicine/virtual care
- Acute problems

Given significant burden of ARI in all settings, point of care assays (for strep, influenza, RSV) play a significant role in all
Exploring the barriers and facilitators to use of point of care tests in family medicine clinics in the United States

Victoria Hardy¹*, Matthew Thompson¹, William Alto², Gina A. Keppel¹, Jaime Hornecker³, Adriana Linares¹
Beth Robitaille³ and Laura-Mae Baldwin¹

POCT implementation is still challenging
Barriers and facilitators to use of point of care test

Clinic workflow and staffing

- Primary care clinics vary in the type of lab facility (moderate complexity, CLIA – waived)
- Staffing often a struggle
- If patient flow and waiting times for lab tests can be optimized, point of care tests have significant opportunities to improve efficiency and satisfaction
Barriers and facilitators to use of point of care test

Quality control and cost

- Reimbursement and practice viability are huge concerns
- Additional costs of newer POCTs may not always be offset by savings (reduced phone calls etc to get results, lower need for back up tests) – or, these hidden costs may not be counted
- Centralised lab oversight where possible is ideal, but some decentralised organization and management of POCT services may suit some clinics
Barriers and facilitators to use of point of care test

Perceived lower accuracy of POCTs. Not trusted. Routinely do back up tests

At times we’ve questioned accuracy in the coumadin clinic of our INRs ... and part of that, too, is discrepancy, um, from our reference lab. So, we would do a quality check and those values would come back significantly different.

If you get a negative, you’ll get a negative. If you get a positive and then that could be a false positive, or it could be a false negative.
Questions