MEDICAL LABORATORY OBSERVER MLO

Confronting the challenges of influenza-like illness

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Influenza-like illness (ILI) is a substantial clinical and economic burden on patients, healthcare providers, and the broader healthcare system. Depending on the pathogenicity of the viral strain and the effectiveness of the vaccine, there are typically between nine million and 36 million influenza cases annually in the United States, resulting in 140,000 to 710,000 hospitalizations.[1] However, influenza represents a small percentage of the hundreds of millions of upper respiratory infections (URIs) that occur annually in the U.S. alone.[2,3] This broader group of infections accounts for more healthcare provider visits than any other acute condition annually and results in almost 50 million lost days from work and school.[2,4,5] While the literature lacks reliable, contemporary data on the economic costs of URIs and more specifically ILI, it is estimated that direct and indirect costs combined likely exceed $100 billion each year.[3,6]

In addition to its high social and economic costs, ILI can lead to severe health consequences for individual patients, particularly among at-risk populations including the very young, the elderly, and the immunocompromised. Influenza alone is responsible for 12,000 to 56,000 deaths annually in the U.S.[1] And beyond the measurable mortality and morbidity of ILI, accurate, rapid diagnosis of the patient's condition also has substantial implications for key institutional quality metrics such as antimicrobial stewardship and infection control. This article will review the diagnostic challenges associated with ILI, the implications of missed or delayed diagnosis, and new diagnostic tools that may help address these challenges. Finally, areas for future research with respect to ILI diagnosis and patient management will be discussed.

Clinical presentation and differential diagnosis

ILI is a condition that presents with fever, cough, sore throat, shivering, chills, malaise, body aches, and/or nausea and is often associated with rapid onset. Frequent causes include the common cold and influenza, but ILI can be caused by more than 20 different viral and bacterial pathogens with overlapping and non-specific presentations. This complicates accurate, timely diagnosis.

More than 200 subtypes of viruses cause the common cold. While rhinoviruses represent a plurality of causative pathogens (30 percent to 50 percent of colds), other infectious agents are also implicated: coronaviruses (10 percent to 15 percent); influenza viruses (five percent to 15 percent); respiratory syncytial viruses (RSV, ~10 percent); parainfluenza viruses (PIV, ~ five percent); enteroviruses (< five percent); and human metapneumovirus (hMPV).[7] Additionally, the cause of 20 percent to 30 percent of common colds is unknown. Given the similar presentation associated with these viruses, it is not possible to establish the causative pathogen based on clinical diagnosis alone.

For instance, the differential for RSV in adults includes influenza and PIV. In infants it is even broader, including influenza, PIV, hMPV, rhinovirus, coronavirus, human bocavirus, and adenovirus. Studies have shown that RSV infection develops annually in three percent to seven percent of healthy older adults, may contribute to excess wintertime mortality previously attributed to influenza, and is a leading cause of hospitalization in young patients.[8-10]

Even the diagnosis of influenza can be confounded by the overlapping syndromes of ILI. A meta-analysis that reviewed the precision and accuracy of symptoms and signs of flu in adult patients over 60 years of age concluded that "clinical findings identify patients with influenza-like illness but are not particularly useful for confirming or excluding the diagnosis of influenza."[11]

Rapid and accurate diagnosis of the causative pathogen(s) for ILI is critical for informing patient management and selecting proper treatment, particularly in high-risk and hospitalized patients. Beyond direct patient impact, appropriate management of ILI can also help address key quality metrics such as infection control and antimicrobial stewardship.

High-risk patient populations

ILI poses a significant risk in immunosuppressed and immunocompromised patients, including hematopoietic stem cell transplant patients, solid organ transplant recipients, and patients receiving chemotherapy. Influenza, RSV, PIV, hMPV, adenovirus, and rhinovirus are associated with increased morbidity and mortality in these patient populations.[12-14] Rapid, accurate diagnosis is an important component of patient management in these populations as it helps direct appropriate antiviral and/or antibiotic therapy and can inform decisions about timing of transplant or additional therapy.[15] Current practice guidelines support testing for a wide range of suspected respiratory pathogens in these high-risk populations.[16-18]

Patients in the intensive care unit (ICU) setting are also particularly vulnerable to complications from ILI. Viral pathogens including influenza, RSV, PIV, hMPV, coronavirus, and rhinovirus and are all associated with severe pneumonia, requiring management in the ICU.[19] And while guidelines for respiratory virus testing in the ICU population

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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. **Describe the healthcare cost burden of ILI in the United States and identify the symptoms and at-risk populations.**
2. **Identify the advances in multiplex molecular testing for ILI that have improved healthcare outcomes.**
3. **Describe past studies and their outcomes as related to improved rapid multiplex testing.**
4. **Discuss future opportunities for research in rapid multiplex testing.**

are undefined, a recent study showed that fewer than half of ICU patients with hospital- or community-acquired pneumonia were tested for viral pathogens. Among the patients that were tested, overall prevalence of viral infection was 28 percent, with 63 percent of the identified pathogens being other than influenza or RSV.[20]

The pediatric population is also at higher risk of adverse outcomes from ILI, as respiratory tract infections account for increased mortality and morbidity in patients who are less than five years of age.[21] RSV and PIV are the two leading causes of hospitalization for respiratory tract illness in young children, and RSV is estimated to cause more deaths in patients less than one year of age than any infectious agent other than malaria.[9,22]

Infection control

As healthcare payment models in the United States continue to shift away from fee-for-service and toward more capitated structures, managing overall cost-of-care is becoming increasingly important for providers who carry financial risk associated with avoidable readmissions and treatment of healthcare-acquired infections. These shifting financial incentives are leading to increased emphasis on and investment in infection control practices within the hospital. The U.S. Centers for Disease Control and Prevention (CDC) guidelines related to ILI recommend infection control practices that include patient isolation, targeted triaging, cohorting, and barrier protections.[23,24]

For infection control with suspected or confirmed influenza patients, the CDC recommends adherence to standard contact and droplet precautions as well as isolation and/or cohorting.[24] RSV is highly contagious and associated with serious healthcare-acquired infections. Infection control measures, including patient isolation or cohorting, limitations on patient transport, and contact and/or droplet precautions, are recommended to limit nosocomial spread, particularly in an outbreak scenario.[25,26] Similar precautions are recommended for hospitalized patients with PIV infection, particularly if exposure to immunocompromised patients is possible.[13,23] Accurate, rapid diagnosis of the causative agent of ILI is required to appropriately inform these various infection control practices and to manage limited isolation bed space, particularly during peak respiratory virus season.

Antimicrobial stewardship

The CDC reports that annually more than two million illnesses and 23,000 deaths are caused by antimicrobial-resistant (AMR) bacteria in the United States.[27] Pervasive inappropriate use of antibiotic therapy is a major contributor to the growing public health crisis of AMR. A recent large, population-based study assessed antibiotic prescribing patterns for more than 185,000 elderly patients who presented in the outpatient setting with a confirmed nonbacterial acute upper respiratory infection. The study showed that 46 percent of patients received an antibiotic prescription, with 70 percent of those receiving broad-spectrum therapy, despite a confirmed nonbacterial infection.[28] The literature demonstrates similar results related to misuse and overuse of antibiotics in varying care settings and across diverse patient populations, sometimes resulting in adverse patient outcomes and progressive antimicrobial resistance.[29-33]

The CDC's 2013 report on Antibiotic Resistance Threats in the United States led to the creation of a National Strategy for Combating Antibiotic Resistant Bacteria (National Strategy) which noted that one-third to one-half of all antibiotics used in inpatient and outpatient settings are either unnecessary or incorrectly prescribed.[34] Inappropriate use of antimicrobial therapy not only contributes to growing AMR, but also places an unnecessary economic burden on the healthcare system, with more than $1.1 billion in annual domestic spending on unnecessary antibiotic prescriptions for respiratory infections in adults.[35]

One objective of the CDC's National Strategy is to "develop new diagnostics, including tests that rapidly distinguish between viral and bacterial pathogens and…that can be implemented in a wide range of settings."[34] The CDC report notes: *Presently, most diagnostic tests take 24 to 72 hours from specimen collection to results….Thus, treatment decisions are typically required and made before laboratory results are available. As a consequence, patients may be initially treated with antibiotics when none are needed, prescribed an inappropriate antibiotic, or treated with multiple antibiotics when a single antibiotic would have been effective….However, the technological landscape is changing at a rapid pace. The current trend is moving towards clinical presentation or point-of-need diagnostic tests suitable for use during a healthcare visit because they require only minutes.*[34]

Prevalence of ILI episodes with Detected Respiratory Viruses

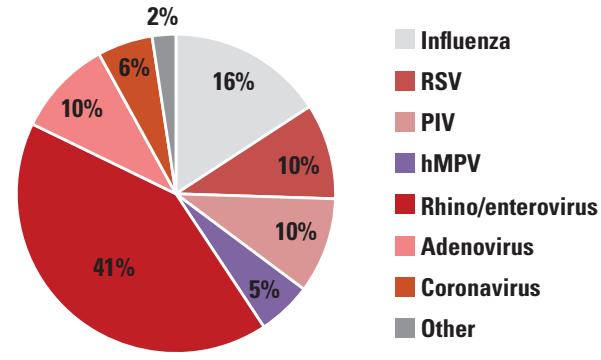

Figure 1. Respiratory viruses and influenza-like illness in a pediatric population

New diagnostic tools

Consistent with the CDC's National Strategy objective of developing new, flexible diagnostic capabilities, multiplex molecular testing is one tool that is now available to help resolve the overlapping clinical presentation of ILI and to address the need for rapid, accurate diagnosis of the causative pathogen. Previously, this type of multiplex molecular testing required advanced technical skills and equipment and was primarily restricted to the high-complexity laboratory setting. However, recent advances by multiple vendors have resulted in the commercialization of FDA-cleared, sample-to-answer platforms that significantly reduce the laboratory and staffing requirements needed to generate highly sensitive molecular results for the wide range of pathogens that are implicated in ILI. These diagnostic platforms have achieved both CLIA moderate complexity and waived status, making them accessible in a range of different care settings.

The past several years have shown rapid growth in the publication of studies reporting on the impact of sample-to-answer, multiplex molecular diagnostics for ILI. These studies have demonstrated the impact this technology can have across multiple care settings and on multiple clinical, quality, and economic outcome measures. Almost all of the studies have shown that multiplex molecular testing provides a more definitive diagnosis through a higher positivity rate while also delivering this result in a significantly shorter turnaround time, providing data in a clinically actionable timeframe.[36-39]

Study	TAT Reduction	Relative Positivity Rate (Rapid Sample-to-Answer vs. Conventional)	LoS Reduction
Rogers, et al.[36]	12.3 hours	78% vs. 60%	0.3 days***
Rappo, et al. [37]	6.0 - 12.0 hours	N/A*	N/A****
Martinez, et al. [38]	30.4 hours	24% vs. 17%	2.1 days
Xu, et al. [39]	5.4 hours	+26%**	Not reported
Brendish, et al. [40]	34.7 hours	45% vs. 15%	1.1 days

TAT = Turnaround Time; LoS = Length of Stay
* - Study only reported on patients with positive results for both influenza-positive and non-influenza-positive results
** - Relative positivity rate not reported, but author noted that in an additional 660 (26%) of 2,537 specimens, the sample-to-answer platform detected viruses that would not have been detected with conventional methods
*** - Patients with positive test results only
**** - Sample-to-answer group had trend toward shorter LoS, but result was not statistically significant due to study size. Multivariate logistic regression found that a diagnosis of influenza was associated with significantly shorter length of stay (p=0.04).

Figure 2. Summary of clinical studies on sample-to-answer, multiplex molecular testing for respiratory virus diagnosis

Rogers et al reported that the implementation of a rapid, multiplex molecular assay in a major children's hospital led to a significantly higher positive test result rate (77.9 percent vs. 59.8 percent) while also providing a 65 percent reduction in time-to-result compared to a batch, PCR assay.[36]

Martinez et al reported on their experience with a rapid, multiplex molecular assay for ICU patients compared to conventional batch testing. They reported an average 30.4 hour reduction in mean time from sample collection to reported result. This shorter time-to-result contributed substantial clinical and economic outcome improvements with a reported 10 percent increase in the relative survival rate among the rapid, multiplex testing group. These patients also experienced a three-day reduction in ICU stay, contributing to a more than $8,000-per-patient reduction in the total cost-of-care.[38]

In perhaps the most rigorously designed study completed to date on rapid, multiplex molecular testing for respiratory pathogens, Brendish et al recently reported the results of a prospective, randomized controlled trial on the use of this technology at the point of care in the emergency department (ED). Consistent with prior reports, this study showed that rapid, accurate results impacted patient management, reduced cost-of-care, and contributed to appropriate infection control precautions. For patients with a positive test result, clinicians were able to stop antibiotics earlier, rather than completing a standard five-to-seven day course. With respect to antiviral therapy, 91 percent of influenza-positive patients in the rapid, multiplex testing group received appropriate, guideline driven antiviral therapy, compared to only 65 percent in the control group. For patients who were admitted to the hospital from the ED, the rapid, multiplex testing group experienced a 1.1-day shorter overall length-of-stay (LoS), contributing to an estimated $500 net cost savings per patient. And twice as many patients in the rapid, multiplex testing group with confirmed respiratory viral infections were isolated compared to the control group.[40]

These results in the ED have been confirmed in other studies that have shown higher rates of results reported to the patient while still in the ED (51.6 percent vs. 13.4 percent),[36] lower hospital admission rates,[37] reduced time in the ED by up to 23 percent,[38] reduced time to appropriate therapy[39] and reduced overall LoS for patients subsequently admitted to the hospital.[38]

In addition to these direct clinical and patient benefits, many of the studies also show improvements in key quality metrics. Multiple studies have shown reductions in the inappropriate use of antibiotics across a wide range of care settings and patient populations, consistent with CDC guidelines and the public health goal of reducing AMR.[36-38] These studies have shown that during peak respiratory virus season, when isolation facilities are at a premium, rapid, multiplex respiratory testing can be used successfully to inform cohorting strategies.[39,40] This use of multiplex testing in support of infection control measures is consistent with clinical guidelines and best practices that recommend the "application of rapid diagnostic tests to support clinical decisions involving patient treatment, room selection, and implementation of control measures."[23]

Opportunities for future study

The development of multiplex molecular diagnostic tools for ILI continues to accelerate at a rapid pace. And while the literature supporting the adoption of this technology also continues to grow, several gaps remain to be addressed. For example, there is strong evidence to support broad use of this technology in certain patient populations, such as pediatrics, the immunocompromised, and those in intensive care, but the clinical utility of rapid multiplex testing is other patient populations that are vulnerable to complications from ILI (e.g., the elderly), is not as well established. Studies focused on establishing the impact of multiplex testing in these patient populations should be areas of future investigation. Additionally, larger prospective studies appropriately powered to assess the clinical and health economic impact of these technologies would also be beneficial. The current literature suggests that providing rapid, accurate diagnostic results for ILI translates into improved outcomes, better quality metrics, and lower overall cost-of-care, but more robust studies to validate these results would benefit the laboratory community.

For now, what we know for sure is this: ILI is a high-prevalence condition that afflicts all patient populations and results in significant clinical and economic costs. The diagnosis of ILI is challenging, given the overlapping clinical presentation and the broad differential diagnosis that includes both viral and bacterial pathogens. Implementation of guidelines-driven infection control and antimicrobial stewardship interventions are predicated on rapid, accurate diagnosis of the causative agent. This definitive diagnosis is particularly important in high-risk populations such as patients with a suppressed immune system, patients in intensive care, and infants.

Sample-to-answer, multiplex molecular testing is a technology that can help address the challenges associated with the

management of ILI. This testing has been shown to improve patient outcomes, reduce total cost-of-care, and support key quality measures such as appropriate antibiotic use and infection control. While there remain opportunities to further strengthen the evidence supporting adoption of this technology, sample-to-answer, multiplex molecular platforms are increasingly viewed as an essential tool in the diagnostic laboratory for the management of ILI. As the American Society for Microbiology (ASM) concluded in its recent white paper on the clinical utility of multiplex tests for respiratory pathogens: "There is no question that multiplex molecular panels provide superior diagnostic performance when compared to conventional methods, and there is a small, but growing, body of evidence that supports their positive impact on patient care and reduction in overall healthcare costs."[41]

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