Expert Review of Anti-infective Therapy

ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: informahealthcare.com/journals/ierz20

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To cite this article: Lori L Hudson, Christopher W Woods & Geoffrey S Ginsburg (2014) A novel diagnostic approach may reduce inappropriate antibiotic use for acute respiratory infections, Expert Review of Anti-infective Therapy, 12:3, 279-282, DOI: 10.1586/14787210.2014.881717

To link to this article: https://doi.org/10.1586/14787210.2014.881717

Published online: 06 Feb 2014.

A novel diagnostic approach may reduce inappropriate antibiotic use for acute respiratory infections

Expert Rev. Anti Infect. Ther. 12(3), 279–282 (2014)

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Respiratory infections can be due to a multitude of etiologies and are common throughout the world. Most are viral and self-limited, yet these infections are commonly treated with antibiotics thus contributing to the increase in resistance. Historically, infectious disease diagnostics have focused on identification of the microbial culprit at the site of infection but the specificity of host response as measured by the host transcriptome, now enables us to classify the etiology of infection agnostic to pathogen class. The ability to rapidly determine whether a similar set of symptoms is due to a virus, bacteria, or other agent from a common specimen (blood) will have far-reaching public health benefits, and further research is warranted to transfer this technology into the clinical setting.

The CDC recently estimated that in the USA alone, over two million people are sickened annually with antibiotic-resistant bacterial infections, resulting in at least 23,000 deaths [1]. Antibiotic-resistant infections add considerable healthcare costs resulting from prolonged and/or more expensive treatments, extended hospital stays and additional healthcare use, and result in greater disability and death compared with infections that are easily treatable with antibiotics. The inappropriate use of antibiotics is the single most important factor leading to resistance around the world and has led to the development of policies and guidelines to address this issue, with some success [2]. In addition to contributing to the emergence and increasing incidence of antibacterial resistance, antibiotics are associated with significant health risks. Common side effects associated with many antibiotics include stomach pain, nausea and diarrhea, and over 140,000 emergency room visits annually result from antibiotic-related adverse drug events mostly attributable to allergic reactions. The use of antibiotics is a major contributing factor in *Clostridium difficile* infections resulting in approximately 250,000 hospitalizations each year [3]. A substantial reduction in antibiotic prescribing and consumption must occur in order to curb these alarming statistics.

Acute respiratory tract infections (RTIs) are the most common infections in humans, and approximately 80% are attributed to viral causes, although they may be complicated by a concomitant or subsequent secondary bacterial infection. Most antibiotics prescribed in ambulatory practice are for patients with a RTI, including sinusitis, pharyngitis and bronchitis [4,5]. Determining with a high level of certainty that a patient does not have a bacterial infection, and thus, will not benefit from antibiotic therapy is a key moment in clinical decision making with far-reaching public health consequences. Respiratory viral and bacterial infections often have similar symptoms, and many patients presenting with RTI receive antibacterial therapy even if pneumonia is not suspected. Additionally, antibacterial therapy is often continued even when test results indicating a viral etiology become

Keywords: acute respiratory infection • bacterial resistance • diagnostic devices • gene expression • host-based diagnostics

 10.1586/14787210.2014.881717 ISSN 1478-7210

available to the clinician [6]. A rapid, sensitive capable of distinguishing between viral and bacterial disease could substantially reduce the indiscriminate use of antibacterial agents, reduce the development of resistant pathogens and increase judicious uses of antibiotic therapies in general.

Classical microbiology techniques (direct examination, culture and isolation) have been the mainstay of clinical laboratories for the vast majority of bacterial pathogens and many viruses causing RTI, but the time required to obtain clinically meaningful results (typically 1–3 days) reduces the usefulness of these tests in directing appropriate therapy [7]. Additional limitations include the variable sensitivity of the cultural approach, as well as the need for expensive equipment, specialized media and highly trained technicians. Molecular approaches for the diagnoses of viral etiologies have advanced this field considerably [8], and a large number of viruses and bacteria that may result in RTI can now be identified so long as the testing laboratory has access to state-of-the-art technologies. Viruses most commonly implicated in RTI are: respiratory syncytial virus (RSV); influenza A and B; parainfluenza 1, 2 and 3; and adenovirus. More recently, at least six new viruses associated with respiratory infection have been identified, including human metapneumovirus, severe acute respiratory syndrome coronavirus, human coronavirus NL63 and HKU1, parainfluenza 4 and bocavirus [9,10]. Evaluations of the sensitivity and specificity of currently available diagnostic tests for respiratory viral infections demonstrate that molecular approaches based on sequence or antigen recognition are robust, with specificities and sensitivities routinely exceeding 95%, for a number of viruses, including 2009 H1N1 influenza A [11]. As a result, these tests are now considered the reference standard for viral confirmation of infection with influenza and other respiratory viruses. However, current antiviral effectiveness decreases when it is not initiated early (within 48 h of symptom onset), and results are still often not available in time to impact treatment decisions. Newer antigen-based immunoassays such as the rapid influenza diagnostic tests can detect viral antigens in respiratory specimens and rapidly (within 15 min) display the result in a qualitative way (positive vs negative). A number of rapid tests are commercially available in the USA, principally for influenza and RSV. However, these rapid tests have reduced sensitivity, limiting their clinical utility, and negative test results should be interpreted with caution. Despite continued advances in diagnostic development, these assays all rely upon knowledge of pathogen sequence or antigens and may become less useful over time as organisms evolve and mutate and new pathogens are discovered.

The majority of clinical laboratories conducting microbiological testing have not adopted these new methods for a variety of reasons including lack of skilled technicians, capitol investment needs for equipment and cost/reimbursement issues. Also, the absence of commercially available tests for the detection of newly emergent viruses often leaves laboratories without the ability to diagnose these important infections. As the discovery of new pathogens and the mutability of known ones continue to occur at a dramatic rate, it is unlikely that pathogen-based approaches will ever fully meet the diagnostic demands faced by clinical microbiology laboratories [7]. Furthermore, even when positive pathogen identification is made, the clinical significance of that organism (e.g., colonization vs infection) must still be determined.

The Infectious Diseases Society of America has asserted that better, rapid diagnostic tests are an unmet need for RTIs [12]. Commonly used host-based biomarkers of infection include leukocyte counts, C-reactive protein, procalcitonin, IL-6 and other cytokines. Procalcitonin is perhaps the most promising of these, for example, improving the accuracy of pneumonia diagnosis when considered in the context of clinical signs and symptoms. However, low specificity makes this marker less useful in distinguishing between clinically similar respiratory infections such as pneumonia due to influenza rather than a bacterial infection or coinfection [13]. Elucidation of the broader host response to pathogens – using genomic platforms – has enabled us and others to use these biological signals to develop models for diagnosing and predicting disease in a pathogen agnostic manner, a 'paradigm-shifting' approach to disease diagnostics [14]. These genome-wide measures of a specific pathogen infection, downstream from the pattern recognition receptors expressed on immune cells, underpin the ability to develop specific host-based signatures of infection. Biological response signals detected in peripheral blood can reliably distinguish between noninfectious conditions and infection with a virus, bacteria or fungus in adult and pediatric populations, in both experimental infectious challenge settings and community-acquired infection. Recently, we demonstrated that RNA-based biomarkers developed in a human influenza challenge study could classify influenza-infected patients from healthy controls with 100% accuracy and from bacterial causes with 93% accuracy [15,16]. When an RT-PCR version of the test was evaluated in a cohort of subjects presenting to the emergency room with microbiologically confirmed respiratory or systemic infection, performance was preserved (sensitivity of 89% and specificity of 94%) [17]. These results, coupled with work in other patient populations, demonstrate that a select set of host biomarkers (e.g., RNA transcripts measured from whole blood) are capable of distinguishing with a high degree of accuracy bacterial, viral and noninfectious causes of acute respiratory illness [18].

While much of the research into new diagnostics for respiratory infections continues to focus on implementation of highly multiplexed assays that can identify diverse organisms [7,11], we contend that using unique host response profiles to inform a viral versus bacterial diagnosis have a number of advantages over pathogen-based approaches. By interrogating the peripheral host transcriptional response to infection, we are able to: overcome limitations inherent in pathogen or antigen-based methods; assay a readily accessible specimen (peripheral blood); and potentially predict disease outcomes and potential treatment response based on individualized gene expression profiles. In order for these advances to translate into clinically valuable diagnostic assays, studies in additional cohorts of patients with community acquired and experimental bacterial, viral and

clinically similar noninfectious disease are needed along with the comparison of the gene expression diagnostic to traditional diagnostics. These studies should include a broad representation of patient ethnicity and age with well-documented phenotypes, supported by confirmed microbiological etiology testing by independent laboratories and case adjudications by infectious disease specialists. Randomized trials comparing outcomes following biomarker-based antibiotic treatment and standard of care/empirical therapy are required to evaluate the clinical utility of this approach. Discussions with the US FDA and with payers will inform final strategy to bring this novel class of diagnostics into the clinic.

There is a clear need to develop more accurate methods to discriminate viral and bacterial respiratory infections in both routine clinical care and pandemic settings. Classical and pathogen-specific methods alone are unlikely to fully meet these needs, and laboratories cannot be expected to constantly adopt new equipment, reagents and expertise. Further development of a host-based test, agnostic to the specific pathogen, which can be performed from an accessible, minimally invasive specimen (blood) and which can rule out infection (as a first step) and classify viral versus bacterial infection with a high degree of certainty should be a target of research efforts. Such a test is ideal for use in low-resource areas and during pandemics, can reduce overall antibiotic use, improve the targeted use of antibiotics for bacterial pneumonia and co-infections and increase the opportunity to initiate antiviral therapies for influenza and RSV as appropriate.

Financial & competing interests disclosure

GS Ginsburg and C Woods have patents pending on host-based diagnostics for pathogen identification. They also receive funding from Novartis to develop novel biomarkers for infectious disease. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Acute respiratory tract infections caused by viruses and bacteria may be clinically indistinguishable, and diagnostic methods are often not used to make treatment decisions.
- Inappropriate use and overprescribing of antibiotics is common and has led to an alarming increase in multidrug-resistant organisms.
- Existing infectious disease diagnostics (approved and in development) are based upon a prior knowledge of the organism and thus must be tailored to detect novel pathogens.
- Improved approaches to diagnose respiratory tract infections are needed as new antibiotics in development are insufficient to overcome current resistance issues.
- The host response to infection, assayed by a multigene RNA profile in peripheral blood, represents a novel approach to guiding appropriate antibiotic therapy.

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