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MOLECULAR DIAGNOSTICS IN RESPIRATORY INFECTIONS: A CRITICAL ANALYSIS OF SYNDROMIC PANELS

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Abstract

Respiratory tract infections (RTIs) are now receiving significant attention in the field of public health due to their extensive prevalence and the alarming rates of illness and death they cause globally. The clinical spectrum varies from those showing no symptoms or experiencing moderate infection to those with severe or life-threatening illness. Swiftness is essential in diagnostics to provide timely and effective treatment of patients. The current methodology for diagnosing respiratory tract infections (RTIs) utilizes a combination of different approaches. This includes the widely accepted conventional methods, which are considered the gold standard. Among these methods, classic culture is the most often used. Additionally, novel techniques such as molecular methods are utilized, mostly for detecting viruses and atypical bacteria. Utilizing molecular approaches with syndromic panels has the potential to serve as a very effective tool for making decisions on patient care, while it is crucial to ensure optimal use of the test in various patient groups. Their use significantly decreases the time it takes to get findings and enhances the identification of medically significant infections in comparison to traditional techniques. Furthermore, when used judiciously and evaluated with caution, syndromic panels have the potential to enhance the utilization of antimicrobials and improve patient outcomes, while also optimizing the workflow in laboratories. This review provides a comprehensive summary of the primary causes, clinical manifestations, and epidemiological characteristics of respiratory tract infections (RTIs), with a specific emphasis on laboratory diagnosis and the capabilities of syndromic panels.

Keywords: respiratory tract infections, panels for syndromic diagnosis, algorithm for diagnostics, laboratory detection.

1. Introduction

Respiratory tract infections (RTIs) are now receiving significant attention in the field of public health due to their extensive prevalence and the alarming rates of illness and death reported globally [1]. Respiratory tract infections (RTIs) are disorders caused by infectious agents that affect the respiratory system [2]. The clinical range varies from no symptoms or moderate infection to severe or lethal illness, and the severity is determined by the interplay of three factors: the causative agent, the environmental circumstances, and the host [1]. These infections usually manifest as acute illnesses with a quick onset of symptoms, which may appear within hours to days following the infection. The symptoms may include fever, cough, sore throat, runny nose, trouble breathing, wheezing, and/or respiratory distress [1]. The epidemiology of respiratory tract infections (RTIs) is constantly changing due to fast sociodemographic changes and, to some extent, climatic change [3,4].

RTIs, or respiratory tract infections, are not only the most lethal infectious diseases globally, particularly among children and the elderly, but they are also the most common cause for seeking medical advice or being admitted to healthcare facilities and primary care. They are known to have a substantial influence on the rising demand for medical tests in both clinics and emergency departments, as well as on the prescription of antimicrobial drugs and hospitalizations [1,5]. Furthermore, recent epidemiological data emphasize the significant influence of respiratory tract infections (RTIs) on both the quality and life expectancy, as well as the serious danger they pose to people and worldwide public health [4].

The epidemiology research of respiratory tract infections (RTIs) must adapt to the fast-paced changes in sociodemographic and climatic dynamics. It requires regular updates to offer essential tools for health policy focused on controlling and preventing these infections. Timely and efficient laboratory identification of respiratory tract infections (RTIs) is necessary to assist and direct clinical choices towards optimal patient care, while also preventing the unnecessary use of antimicrobial drugs. The delay in identifying the causative agent of respiratory tract infections (RTIs) can result in the emergence and spread of antimicrobial-resistant pathogens. This is due to the improper use of broad-spectrum empirical therapy, leading to negative clinical outcomes, higher mortality rates, and longer hospital stays [6,7,8].

Significant technical advancements have been achieved throughout time to provide novel instruments for the identification of bacterial and viral respiratory diseases. These advancements have led to the creation of precise, rapid, and user-friendly diagnostic techniques [9]. Specifically, diagnostic facilities now have widespread access to molecular technologies. The use of molecular-based approaches enables the accurate and precise identification of bacterial and viral nucleic acids in clinical specimens and cell culture supernatants. This method eliminates the requirement for extended incubation periods typically required for bacterial or viral isolation [9]. Furthermore, molecular approaches need less specialized knowledge

compared to culture techniques and are valuable for identifying bacteria that are difficult to cultivate and viruses that do not multiply in typical cell cultures [9].

2. RTI Epidemiology

The introduction of syndromic panels in diagnostic microbiology was a significant advancement. These panels are highly effective in detecting a wide range of pathogens that could potentially cause a single clinical syndrome. This achievement addresses the requirements for accuracy and reducing the time it takes to obtain results. This review provides a comprehensive summary of the primary causes, clinical characteristics, and prevalence of respiratory tract infections (RTIs), with a specific emphasis on laboratory diagnosis and the capabilities of syndromic panels.

Respiratory tract infections (RTIs) are very lethal illnesses caused by infectious agents. They rank as the fourth most common cause of death globally, resulting in 2,603,913 recorded fatalities in 2019 [4,11]. Currently, the worldwide tally for verified COVID-19 cases stands at over 567 million, with a mortality toll exceeding 6.3 million [4,11]. Furthermore, this particular virus is known for its substantial impact on reducing life expectancy, as seen by the high rates of disability-adjusted life years (DALYs) measured annually [4,11]. The prevalence of respiratory tract infections (RTIs) varies significantly based on demographic and geographic factors, as well as age, gender, and location [4]. RTIs have a particularly large detrimental effect on the quality of life for newborns, children, and the elderly. These groups also have the greatest rates of mortality and morbidity, especially in low- and middle-income countries [4,11,12]. Both the pediatric and geriatric groups are globally recognized as the most susceptible to respiratory tract infections (RTIs) in terms of mortality and reduced life expectancy (LE).

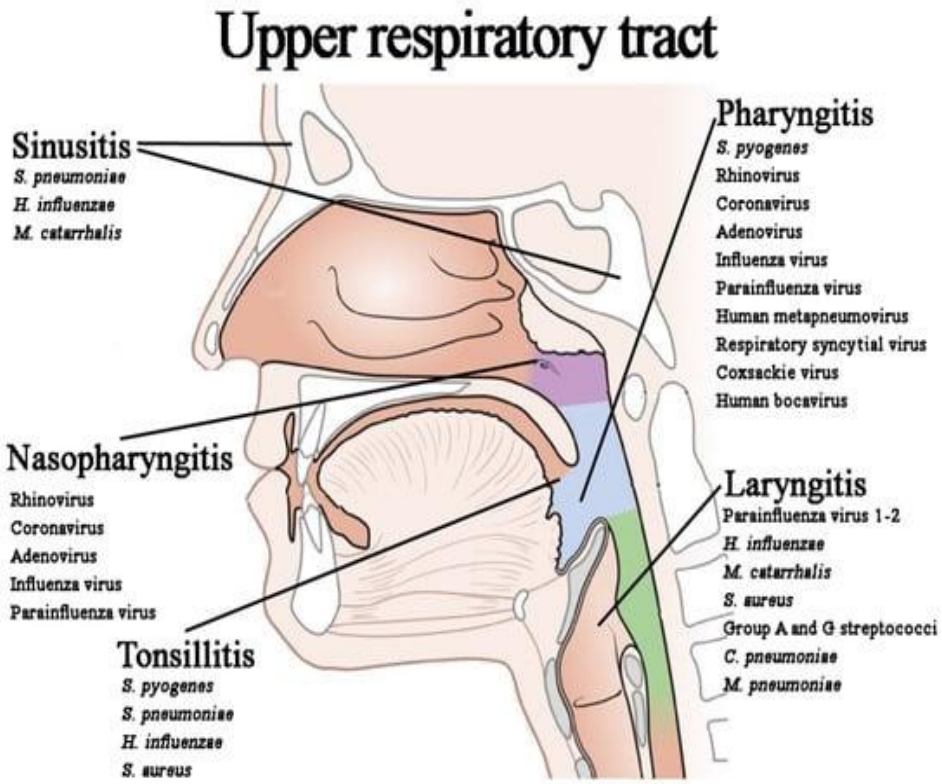
Regarding the pediatric population, the highest rates of mortality and disability-adjusted life years (DALYs) are seen in children under the age of 1 [11,12]. On the other hand, among the senior population, individuals over the age of 70 contribute to the largest number of fatalities and reduction in life expectancy (LE). The uneven distribution of demographic factors also influences the regional prevalence of RTIs, which is mostly influenced by the level of socioeconomic development. Countries and territories with low and moderate incomes are more vulnerable to respiratory tract infections (RTIs), which result in the greatest rates of death and disability-adjusted life years (DALYs). In high-income nations with high aging indices, a significant number of elderly individuals are at a heightened risk of infection and hospitalization. This leads to a rising trend in morbidity, mortality, and loss of life expectancy owing to respiratory tract infections [4,11,12].

It is important to mention that in wealthy nations, a large number of fatalities related to respiratory tract infections (RTIs) happen in aged care institutions and nursing homes. This indicates a high level of transmission of RTIs in these environments, leading to notable mortality rates and reduced life expectancy for the elderly [4]. In high-income nations, the pediatric

population is very susceptible to respiratory tract infections (RTIs) because they often attend daycare facilities and schools. These surroundings provide excellent conditions for the spread of infectious diseases of this kind.

3. The Human Respiratory Tract and the Classification of RTIs

The human respiratory system is anatomically separated into two adjacent regions: the upper tract, which comprises the tonsils, nasopharynx, oral cavity, oropharynx, and larynx, and the lower tract, including the trachea, bronchi, and lungs. RTIs are categorized as either upper respiratory infections (URIs) or lower respiratory infections (LRIs) depending on the specific part of the respiratory tract that is affected [14]. This study will not include respiratory illnesses caused by mycobacteria, since these diseases are not often included in regular laboratory



diagnostic workflows or syndromic panels (Figure 1).

Figure 1. URIs Classification with the associated most relevant causative agents.

4. Diagnostic Testing in a Laboratory Setting

Prompt and precise identification of a respiratory tract infection (RTI) is essential for effectively treating the patient with the right antiviral or antibacterial medication, implementing effective infection control measures, and minimizing the duration of hospitalization [15]. Additionally, the laboratory diagnosis must include both microbiological and virological techniques in order to provide substantial information on outbreak management, epidemiological

surveillance, antibiotic susceptibility, and strain type [16]. Although the clinical laboratory plays a crucial role, diagnosing respiratory tract infections (RTIs) caused by microorganisms or viruses remains difficult due to the intricate nature of these illnesses [17]. The differential diagnosis of respiratory pathogens is challenging due to several factors, including the quality and diversity of respiratory specimens, the difficulty in accessing certain anatomical respiratory structures, potential interferences from the oropharyngeal microbial population, the wide variety of respiratory pathogens, and the complex pathophysiology of respiratory tract infections (RTIs) [15,17].

The diagnosis of respiratory tract infections (RTIs) involves an initial assessment of the symptoms and signs related to the infection. This assessment helps determine the main clinical question that is necessary for the clinical microbiologist to establish an appropriate diagnostic process. The process begins with selecting the appropriate respiratory specimen [16]. Properly handling the respiratory specimen is essential for accurate diagnostic results. To ensure the sample is managed correctly, physicians and laboratory workers should carefully adhere to the reference guidelines [9,16].
The diagnostic process for respiratory tract infections (RTIs) traditionally involves many methods to identify the specific microbial and viral causes of these diseases. These methods include microscopic inspection, conventional culture, traditional cell cultures, antigen detection, and serology [8,15,16].

By using advanced molecular technologies, researchers are able to greatly enhance the direct detection of respiratory infections, even those that are difficult to detect and cannot be identified by standard culture methods. Furthermore, clinical microbiologists are now encountering noteworthy advancements in the realm of molecular diagnostic methods, including syndromic panels [18]. Respiratory syndromic panel-based tests enable the concurrent identification and detection of numerous infections linked to the most severe respiratory disorders [18].

It is important to have a good understanding of the benefits, limits, and time-to-results of the various diagnostic procedures available for viral and microbial identification. This knowledge is essential for accurately interpreting the results and effectively incorporating the findings into clinical care [9].

5. Multiplex panel assays

The use of increasingly sophisticated molecular diagnostic technologies has the potential to greatly improve and revolutionize microbiological diagnoses in clinical microbiology labs, resulting in quicker and more reliable results [19]. Since 2011, after the initial respiratory syndromic panel received clearance from the US Food and Drug Administration (FDA), various commercial syndromic panels with different methodologies have been introduced within a span of less than 10 years. These panels have broadened the ability to detect pathogens responsible for infections in the upper and lower respiratory tract (URT/LRT), blood (BL), gastrointestinal tract (GI), as well as acute meningitis and encephalitis (ME) [20]. Being able to detect and identify the

most common causes of infectious illnesses directly from clinical specimens is valuable for patient care, hospital infection-control policies, and epidemiologic research [21].

Respiratory panels consist of several assays that vary in the number and kind of pathogens they detect, their qualitative or semi-quantitative approach, whether they are manufactured in-house or commercially, and their procedure, with some being point-of-care diagnostic tests. They evaluate microorganisms that infect either the upper or lower respiratory tract and exhibit a broad range of clinical symptoms [22]. Nevertheless, when it comes to respiratory infections, there is no one universal specimen. Nasopharyngeal swabs, sputum, and bronchoalveolar lavage samples are not interchangeable. Each of these syndromic panels has been designed based on the kind of specimen [22]. In addition, the COVID-19 pandemic emphasized their usefulness, necessitating the modification of the tests to address the new situation [23].

6. Summary

This review examines the current technologies utilized for the laboratory diagnosis of infectious respiratory diseases. It highlights that no single method, such as molecular detection, antigen identification, or virus/bacteria isolation, is universally suitable for all diagnostic microbiology/virology laboratories in all clinical scenarios involving all types of bacteria/viruses. Clinical microbiologists and virologists face the task of selecting and utilizing the most appropriate technology for a given situation, in order to obtain the most valuable results. They should then generate clinical reports that effectively assist physicians in accurately interpreting the findings, thereby facilitating optimal patient management.

In the future, with the emergence of advanced and user-friendly molecular platforms for clinical diagnostics, the use of bacterium cultivation and virus separation in cell culture may mostly be limited to research purposes. Hence, it is advisable to conduct culture-based and non-culture-based procedures simultaneously to enhance the accuracy of distinguishing between viral and microbial infections. This approach aims to provide valuable, cost-efficient, and time-saving findings from microbial and/or viral testing. When deciding on suitable testing methods for the laboratory, lab professionals must take into account various factors such as the characteristics of the patient population (such as age, immune status, and comorbidities), the clinical symptoms, the doctor's diagnosis, the evolving patterns of diseases, and the time of year (as many viral infections are more common during certain seasons).

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