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A REVIEW ARTICLE: RESPIRATORY TRACT INFECTION AND MODERN TREATMENT METHODS

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Abstract: Respiratory tract infections (RTIs) are a target of public health development due to their widespread prevalence, irritability, and reported variations worldwide. Clinical findings range from asymptomatic or mild to morbidity or death. Diagnosis must be made quickly to ensure patient satisfaction and take prompt action. Current methods for RTI studies in clinical trials rely on a variety of techniques, including traditional gold standard methods (of which ancient cultures are often used) and the refractive process (e.g., molecular approach), which is often used to understand diseases and disorders. Although this test needs to be used appropriately in different patients, the use of molecular methods from the syndromic process has the potential to be a powerful decision-maker in the management of the patient examination. They radically shorten the time to results and increase the detection of diseases associated with conventional medicine. Additionally, team collaboration, when applied with discretion and careful interpretation, can improve antibiotic use and patient outcomes and improve laboratory work performance. This review provides an overview of the main etiological, clinical and epidemiological aspects of RTI, focusing on clinical diagnosis and the potential of syndromic groups.

Keywords: respiratory tract infections; syndromic panels ; diagnostic algorithm; time-to-results.

Introduction:

Respiratory tract infections (RTIs) are the target of public health development due to their widespread distribution and high morbidity and mortality reported worldwide [1] . RTI is defined as an infectious disease involving the respiratory system (2). The clinical spectrum ranges from asymptomatic or mild disease to severe or fatal disease, and severity is the result of the interaction of three factors: disease, environment, and host. These diseases usually present as a serious illness with symptoms such as fever, cough, sore throat, cough, rhinitis, shortness of breath, asthma and/or shortness of breath, with rapid recovery within a few hours or a few days after infection. one]. RTI epidemiology continues to evolve with socio-demographic changes and, of course, climate change *3,4).* RTIs are not only the most common cause of death worldwide, especially among children and adults, but also the most common

reason for visits to healthcare centers and facilities. It shows that the need for primary care has increased significantly. Examination, antibiotics and hospitalization are performed in clinics and emergency departments [1,5]. In addition, new epidemiological data demonstrate the serious impact of respiratory diseases on life expectancy and life expectancy, as well as threats to public and health international hygiene *4).* Epidemiological research on RTI needs to be constantly updated to keep pace with rapid changes in health and safety and to provide important tools for consumption health policy for management and prevention. Timely and rapid diagnosis of RTI is necessary to support and guide clinical decisions recommending appropriate patient management while avoiding inappropriate antibiotic use. In fact, delay in the identification of RTI diseases due to incorrect application of general treatment can lead to the emergence and spread of resistant diseases, resulting in poor outcomes, increased mortality and chronic diseases. Length of hospital stay [6-8]. Over the years, significant technological advances have been made, providing new tools for the diagnosis of diseases and respiratory diseases, resulting in improved accuracy, speed and ease of use for diagnosis [9]. Particularly molecular methods are now widely used in la boratories. This molecular-based technology provides the most sensitive and specific method for detecting diseases and viruses directly through nucleic acids in clinical samples and cultures, cell supernatants, without the need for long incubations required for bacterial or viral isolation [9]. Additionally, molecular methods require less expertise than culture and can be used to identify "hard to grow" bacteria and bacteria that do not grow in cell culture [9] . In this context, the introduction of syndromic panels opens a new era in the field of diagnostic microbiology; because these panels provide a powerful tool that can detect many diseases that together will cause a medical syndrome; This is done by meeting accuracy requirements. and reduces the time to results [9,10]. This review provides a description of the basic etiological, clinical and epidemiological aspects of RTI, focusing on clinical diagnosis and the potential of patient groups.

The Epidemiology of RTIs

RTI is the most common infectious disease and the fourth leading cause of death worldwide, with 2,603,913 deaths reported worldwide in 2019 [4,11]. Currently, more than 567 million confirmed cases and more than 6.3 million deaths have been reported worldwide for the COVID-19 virus alone [4,11]. In addition, this disease is recognized for its importance in reducing life expectancy (LE) with high annual costs in estimated disability-adjusted life years (DALYs) [4,11] . The disease burden of RTIs is uneven across populations and regions and varies by age, gender, country, and region *4) .* The negative impact of RTIs on quality of life is particularly high in infants, children, and the elderly, where reports of death and morbidity are also high compared to low- and middle-income countries [4,11,12] . Both children and the elderly have been identified as the most vulnerable populations to RTIs worldwide in terms of mortality and LE loss. While mortality and DALY rates in children are highest in children under 1 year of age [11,12], in the elderly, those over 70 years of age have the highest mortality and LE loss. This difference in population distribution is also reflected in the distribution area of RTI, which is generally affected by the growth of the economic community. Low- and middle-income countries and regions [13] are more vulnerable to RTIs, with the highest rates of mortality and disability-adjusted life years [4,11,12]In high-income countries with an aging population, many older adults are at higher risk of infection and hospitalization, resulting in increased LE morbidity, mortality, and RTI loss *4,* 11, 12]. Note that in high-income countries, most deaths from respiratory diseases occur in nursing homes and nursing homes; this suggests that the prevalence of RTI is high in such regions and higher mortality and LE loss are reported in the elderly. Very high *4).* Similarly, children in high-income countries are at high risk for respiratory infections because they attend nurseries and schools, which are ideal environments for the spread of this epidemic.

Respiratory tract infections

Upper respiratory tract infections: cold, sinusitis, epiglottitis and laryngitis [13-24]

Causes: Most upper respiratory tract infections are caused by bacteria. Epiglottitis and laryngotracheitis are exceptions, and severe cases may be caused by Haemophilus influenzae type b. Pharyngitis is usually caused by Streptococcus pyogenes.

Pathogenesis: Bacteria enter the respiratory tract by inhaling droplets and penetrating the mucosa. Epithelial cells may be destroyed with redness, edema, bleeding, and sometimes exudation.

Symptoms: The first symptoms of flu are usually runny nose, nasal congestion and sneezing without fever.

Fever may occur with other upper respiratory tract infections. Children with epiglottitis may experience symptoms such as difficulty breathing, slurred speech, choking, and stridor. Children with laryngotracheitis (croup) may also develop shortness of breath, stridor, and cyanosis.

Microbiological Diagnosis: Flu can often be diagnosed in the clinic. It is used to treat bacterial infections and infections from throat swabs, pharyngitis, epiglottitis and laryngotracheitis. In case of epiglottitis, blood culture is also performed.

Prevention and Treatment: Infections can be treated effectively. Streptococcal pharyngitis and epiglottitis caused by Haemophilus influenzae can be treated with antibiotics. Haemophilus influenzae type B vaccine is commercially available and has become an important part of childhood vaccination.

Lower respiratory tract diseases: bronchitis, bronchiolitis and pneumonia. [13-24a

Cause: Lower respiratory tract diseases are caused by bacteria or viruses. Most bronchitis and bronchiolitis are caused by bacteria. The most common pathogen in community pneumonia is Streptococcus pneumoniae. SARS is caused by bacteria and bacteria such as Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella, Coxiella burnetii. The causes of nosocomial pneumonia and pneumonia in immunocompromised patients are diverse, with gram-negative bacteria and staphylococci being the main pathogens. Pathogenesis: Bacteria enter the distal airways via inhalation, inhalation, or hematogenous spread. Bacteria accumulate in or on the epithelium, causing inflammation, mucus production, and impairment of mucociliary function ; Other lung functions are also affected. In severe bronchiolitis, inflammation and necrosis of the epithelium can obstruct the small airways, leading to airway obstruction.

Symptoms: Symptoms such as cough, fever, chest pain, shortness of breath and phlegm. People with pneumonia may also experience non-respiratory symptoms such as confusion, headache, myalgia, abdominal pain, nausea, vomiting, and diarrhea.

Microbiological diagnosis:

Bacteria, viruses and bacteria are the pathogens of sputum. Culture of nasal irrigation fluids is usually sufficient in infants with bronchiolitis. Fluorescent staining techniques can be used in Legionnaires' disease. Blood culture and/or serological methods are used for bacteria, rickettsiae, fungi and many other diseases. Enzyme-linked immunoassay methods can be used to identify microbial antigens and antibodies. Detection of nucleotide fragments of microbial antigens by DNA probes or polymerase chain reaction can

provide rapid diagnosis.

Prevention and Treatment: Most infections are treated symptomatically. Bacterial pneumonia can be treated with antibiotics. High risk groups are recommended to receive polysaccharide vaccines against 23 Streptococcus pneumoniae serotypes

Nutrition, infection and immunity

The role of nutrients in supporting the immune system is diverse and should be healthy and balanced if there is an appropriate immune system. is to be developed. nutrients must be provided in response [25]. The immune system protects the body from infectious agents and consists of innate responses (the body's first line of defense) and adaptive responses that suppress the immune system [26]. It is known that there is a relationship between nutrition, infection and immunity, and changes in one affect the other [27]. Micronutrients (vitamins and minerals) play many roles in influencing and supporting various levels of the immune system [26]. Then, the deficiency of one or more micronutrients affects the body and the immune system, causing the immune system to weaken and the number of infections to increase. Many nutrients are thought to be important for immunity, including vitamins A, B2, B6, B9 (folate), B12, C, D, E,as well as iron, zinc, selenium, copper red and magnesium. Vitamins A, C, D, E and zinc are important for the structure and function of the external body and the mucosal barrier against invading bacteria [28]. Cellular processes of innate and adaptive defense, such as cell differentiation and proliferation, phagocytosis, respiration, killing activity, cytokine production, and antibody production, all depend on essential vitamins A, D, C, E, B6, and B12 and folic acid. , iron, zinc, copper, selenium and magnesium [28]. This small review focuses on vitamin D because there is increasing evidence supporting the role of vitamin D in preventing ARTI. Vitamin D improves immune epithelial integrity by enhancing cell adhesion [29]. It has also been shown to induce the production of antimicrobial peptides that can directly kill bacteria [30]. Vitamin D receptors are expressed on many immune cells, including B cells, T cells, and present antibodies [31—33]. Additionally, some immune cells, including macrophages and dendritic cells, can produce a form of vitamin D, 1,25-dihydroxyvitamin D3 *34).* Both of these observations suggest that vitamin D is important in the immune system. In fact, vitamin D deficiency weakens the local immune system and antigen-specific antibodies in the body and is associated with greater damage [35]. Vitamin D metabolites have also been shown to influence the expression and release of antibodies and cytokines[36], and vitamin D promotes the production of antimicrobial peptides such as antibiotics *t34,* 37]. There is now evidence that 1,25-dihydroxyvitamin D3 affects endothelial membrane stability and causes many physiological and immune changes *t34).* Low levels of 1,25-dihydroxyvitamin D3 are associated with the risk of several immune-related diseases, including respiratory infections and COVID-19 *t34).* Vitamin D has also been shown to be involved in the expression of pulmonary angiotensin-converting enzyme 2 and has the potential to reduce COVID-19 lung stress [38]. Other studies suggest that vitamin D may act on inflammatory factors

such as progesterone-induced blocking factors and the cytokine IL-6, which appears to be elevated in COVID-19 [39].

Vitamin D and RTIs

Further research has investigated the role of vitamin D in the development of ARTIs. Table 1 summarizes the evidence from the meta-analysis and Table 2 summarizes the evidence from clinical trials published in the last 5 years, focusing on adults, although some meta-analyses included a broader age range. Two meta-analyses focused on clinical studies *t42, 43)* and four meta-analyses focused on evidence from randomized trials [40, 41, *43).* Compilation of these observations demonstrated an interaction between serum 25-hydroxyvitamin D levels and the risk and severity of ARTI and risk of community-acquired pneumonia (30). Meta-analyses represent a higher level of evidence because they can establish relationships. The largest meta-analysis, which included data from 45 randomized controlled trials (n = 73,384 participants), concluded that a daily intake of 400—1,000 IU (10—25 pg) of vitamin D was best effective in preventing ARTI [40] . Similar findings have been reported in previous meta-analyses: vitamin D supplementation was associated with a reduction in ARTI, particularly in those with baseline 25-hydroxyvitamin D deficiency [41]. An analysis of vitamin D supplementation (15 randomized controlled trials, n = 7053) found a 6% reduction in the risk of RTI treatment, but this was not statistically significant and the difference between studies was very high (I 2 = 57%) *[44).* Evidence from individual randomized controlled trials shows similar findings. Five studies show that vitamin D supplementation reduces the incidence [45,48,50] , duration and severity *49) ,* and symptoms *(34)* of RTIs. In asthma patients, Ramos Martinez et al. Vitamin D has been shown to reduce RTI, which is associated with higher levels of sputum IL-10, IFN-y, and cathelicidin LL-37 [48] . Vitamin D doses used in different studies ranged from 10 IU (0.25 pg/day) [48] to 4,000 IU (100 pg/day) [50]. Similarly, the duration of RCTs ranges from as little as *4* weeks [47] to more than 12 months in healthy controls [50]. Regarding the pathological nature of the disease, only four studies clearly indicate whether it is a disease *t44,* 48, 51] or an infection [45]. Additional studies have focused on the location, timing, and/or severity of RTIs, but their source has not been elucidated or diagnosed

Novel Treatment new fluoroquinolone agents such as delafloxacin, enoxacin and zabofloxacin, have been identified as effective against existing fluoroquinolone-resistant pathogens. These new Fluoroquinolone agents target both topoisomerase IV and DNA gyrase with stronger affinities, resulting in the inhibition of bacterial DNA replication (Kollef and Betthauser, 2019), reducing mutant selection and toxic side effects, and resulting superior potent activity against the most common community-acquired pneumonia (CAP) pathogens (Pfaller et al., 2017c). Delafloxacin is effective against Gram-positive bacteria, including methicillin-sensitive Staphylococcus aureus (MSSA), methicillin-resistant Staphylococcus aureus (MRSA), Moraxella

catarrhalis (M. catarrhalis), and S. pneumoniae. While enoxacin is effective against Gram-positive bacteria, including multidrug-resistant S. pneumoniae, MRSA, ertapenem-nonsusceptible Enterobacteriaceae, Legionella, Chlamydophila, and Mycoplasma. Antibacterial activity of zabofloxacin against MSSA and MRSA is similar to gemifloxacin, but 2—16 times stronger than that of moxifloxacin and ciprofloxacin (Park et al., 2006). Nemonoxacin RCT (NCT01529476) of a phase 3 was conducted in resistant isolates of S. pneumoniae. Solithromycin influences the formation and function of POS ribosomal subunit, causing the frame-shift mutation during translation (Still et al., 2011). Due to the lack of a cladinose moiety, it does not induce erm(B)- Lefamulin Lefamulinis a potent semi-synthetic antibacterial agent belonging to a novel class known as the pleuromutilins. Lefamulin's in vitro antibacterial profile includes the most important bacterial pathogens causing LRTIs. The antibacterial spectrum comprises S. pneumoniae, H. influenzae, M. Catarrhalis, the atypical respiratory pathogens, MRSA, §-hemolytic streptococci, and Enterococcus faecium (Waites et al., 2017a; Veve and Wagner, 2018). Moreover, as demonstrated in cross-resistance studies, lefamulin remains active against clinical isolates resistant to the following Antibiotics: macrolides, lincosamides, streptogramin B, oxazolidinones, tetracyclines, §- lactams, Quinolones, trimethoprim-sulfamethoxazole, mupirocin, and vancomycin (Mendes et al., 2019; Paukner et al., 2019) Streptogramins Pristinamycin Pristinamycin is a streptococcal-type antibiotic produced by Streptomyces faecalis. It inhibits protein synthesis by binding to the bacterial ribosome POS subunit (Nespoulous et al., 2018).. Pristinamycin has strong antibacterial activity against MRSA, MSSA, H. influenzae, and S. pneumonia (Cooper et al., 2014). pristinamycin has a synergistic Antibacterial effect with vancomycin (Reid et al., 2010)mediated resistance (5Rd et al., 2015). It is less susceptible to mef(A) -mediated efflux than other macrolides as a result of its increased ribosomal binding and greater intrinsic activity (Darpo et al., 2017a). Cephalosporin Cephalosporins, including ceftobiprole and Ceftaroline, are the "new-generation" that is effective against MRSA, MSSA, penicillin-resistant S. pneumoniae, Escherichia coli, and Pseudomonas aeruginosa (Green et al., 2014). Pleuromutilin

Conclusion:

Currently, UK vitamin D guidelines are set at 10 micrograms per day from October to March to maintain healthy bones, teeth, and muscles (39). However, given the new meta-analytic evidence and the number of clinical studies, combined with the global COVID-19 pandemic, this view seems necessary to be revised. It is good to pay for respiratory health and re-evaluate supplementation. Regarding antibiotic use, further clinical studies are needed to evaluate the effects of vitamin D and the occurrence, symptoms, and severity of ARTIs. A Cochrane review evaluated evidence from seven studies using vitamin D as an antiviral drug to treat pneumonia, but the results were inconclusive (42). In Sweden, vitamin D3 supplementation [1,500-1,600 IU (37.5-40 pg) per day for 12 months] has been shown to reduce antibiotic use from 20 to 15 days per person *(43).* similarly, future research should clarify the

history of pathological RTI. Different doses of vitamin D may be required for infection and disease, but there is not yet enough evidence to make a decision on this issue.

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