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Antibiotic Resistance in Respiratory Tract Infections: Patterns, Mechanisms, and Intervention Strategies

Ahmad ganeed Ghorab[1], Ali Hamod Aseeri[2], Khaled Ahmed alshareef[3], Sami Abdullah AlGhamdi[4], Hameed Ataq almohalbdi[5], Hassan mohammed alharthi[6], Mohammed Majed Alsubaie[7], Khalil abdullah alqahtani[8], Tamim Mohammed alzahrani[9], Abdulrahman Mohammed alshareef[10], Ashraf marzouq alsulami[11], Ahmed Abdullah Asiri[12], Hassan Mohamed Asiri[13], Ibrahim Ali Ibrahim aqeel[14], Majed mohammed safhi[15]

[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15]Place of work and specialization for all employees Pharmacy Technician National Guard-Health Affairs

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ABSTRACT

1. Introduction

Antibiotic resistance is an internationally recognized healthcare burden worsened by the increased consumption and improper use of antibiotics. Respiratory tract infections are the most common reason for the prescription of the majority of antibiotics in developed countries. Antibiotics have saved millions of lives since the discovery of penicillin in the early 20th century, but the increase in resistance is leading to a rise in the burden of both morbidity and mortality. Respiratory tract infections are associated with the most common antibiotic prescriptions in primary care, including the use of viral and antiviral therapies rather than antibiotics. In fact, less than 50% of the antibiotics prescribed in primary care are essential or appropriate.

Viral respiratory tract infections are the most common cause of underused or inappropriate antibiotic prescriptions. This clearly illustrates the need for better biomarkers to guide the differences in diagnostic criteria used for viral and bacterial respiratory tract infections. Overuse has been associated with unnecessary patient risks, drug side effects, increased medical costs, and, as previously described, an increase in antibiotic resistance. As a matter of fact, antimicrobial resistance has its roots in the evolutionary response of microorganisms to antibiotics and is accelerated by the overuse and misuse of these drugs. Inappropriate administration is promoted by the incorrect selection, dosage, or duration of therapy, the misuse of broad-spectrum agents, or poor prevention measures in healthcare.

Methods

A systematic search was conducted in MEDLINE, the Cochrane Central Register of Controlled Trials, and EMBASE for guidelines on antimicrobial therapy up to October 2, 2016. Fifty-six guidelines yielded 546 antibiotic recommendations, primarily for penicillins (31%) and fluoroquinolones (22%). The most recommended antibiotics included amoxicillin (15%), cefazolin (14%), and ciprofloxacin (10%). Variability was observed in treatment durations, administration timings, dosages, and antibiotic selections among organizations. Recommendations for various syndromes should include facility-specific advice, especially for common infections like respiratory or gastrointestinal. Only three guidelines addressed organism-specific resistance patterns, while others lacked guidance. Surgical site infections are significant healthcare-related infections, emphasizing the need for risk-adjusted prophylaxis recommendations.

Conclusion

The assessment of resistance patterns from 28 studies in 47 countries found that Streptococcus pneumonia, Haemophilus influenzae, and Moraxella catarrhalis were commonly identified pathogens, with resistance rates to macrolides far exceeding those to penicillins in most countries (Elias et al., 2017). Azithromycin was the only macrolide tested, but it frequently had as much as 60% resistance or more in China, India, Poland, South Korea, and the United States. The highest resistance rate was reported for Mexico (97%). Resistance to macrolides in Europe and Canada was generally lower and not typically above 40%. In Europe and South Africa, the resistance rates of macrolides were slightly lower than those of S. pneumoniae. In China and the United States, H. influenzae had resistance rates similar to or higher than those of S. pneumoniae. As it was tested with azithromycin only, this could be due to differences between S. pneumoniae and H. influenzae, but the macrolide tested may have also contributed to the pattern of resistance rates. The studies in China and the United States also mostly tested lower RTI for H. influenzae infections. M. catarrhalis generally had lower resistance rates,

particularly in later years. Nonetheless, above 40% rates were reported for this pathogen across seven studies in six countries.

Keywords: Pharmacy, pneumonia, influenza, majority

1.1. Significance of the Issue

Respiratory infections evolved as a major public health problem during the last 100 years. Ironically, even today, these infections are still one of the leading causes of mortality in the developing world, although the advances in natural or life sciences have been incomparably great. Epidemiologically unavoidable morbidity and mortality ratios compose this picture with a frighteningly increasing trend. In a so-called developed country in the middle of Europe and only in a medium-sized university hospital, four ICU beds are continuously occupied by pneumonia patients. Contrary to common belief, the majority of the strains causing these pneumonia cases and other respiratory tract infections are represented by the recent emerging pathogens such as Pseudomonas aeruginosa strains, Stenotrophomonas maltophilia, Acinetobacter sp., Klebsiella sp. and Enterobacter sp., as well as by colistin-only susceptible strains. Needless to mention, all of these strains are resistant to the rest of the antibacterials. With no doubt it can be anticipated that these strains will spread in the upcoming seasons to Europe as well. Due to the above-mentioned global problem of the increase of the numbers of antibiotic resistant respiratory pathogens, RTIs have been selected as the topic of this review. On the basis of this, the resistance percentages of the most important and emerging respiratory tract pathogens will be represented and corresponding therapeutic agents will be outlined for outpatients in European Countries. Due to the lack of antibacterial therapy suggestions by the guidelines, cross-references have been made to recently published papers.

2. Overview of Respiratory Tract Infections

Respiratory tract infections (RTIs) constitute the most frequent clinical conditions seen in acute and family care, which can initiate in the upper airways (URTI), the trachea or windpipe (LRTI) or the lung itself. URTIs comprise among people common colds, sinusitis and laryngitis, while the LRTIs encompass bronchitis and pneumonia. Inflammatory responses to microbial colonization can induce OSI diseases, some of the most common viral bacteria induced diseases which include asthma and chronic obstructive pulmonary disease. Common forms of RTIs are sinusitis, pharyngitis, acute bronchitis, mild lower respiratory tract illness and mild pneumonia (Zumla et al., 2014). Very common in today's world, more than two billion people are affected with RTIs annually. It is one of the most common causes of the epidemics. RTIs are highly communized through the exchange of sneeze respiratory fluids, contacting dirty surfaces and inhalation of pathogens in air. Almost 90% of all URTIs are triggered by viral agents and are mistakenly treated with antibiotics. Development and spread of AR like TB, isoniazid resistant TB, and MDR-TB etc., has increased the prevalence of a new form of antibiotic resistance called extensive drug resistant- tuberculosis.

A substantial part of RTIs risk for severe ALRI are linked to smog exposure. The lungs are exposed to millions of pathogenic microorganisms present in an air breath each day. The lungs first immune obstacle is the lung secretions consisting of a thin layer of mucus coat produced by the lung epithelial goblet cells. This mucus acts as a sink for the deposition of particle pathogens. The second physiological barrier are the cilia present as grass in root, of the bronchi and bronchioles. These beat constantly in a wave like motion and move the mucus upward towards throat. These aggressive lung lined secretion also contain antibacterial and antifungal enzymes and antibodies (J. Ellner, 1988). Each of the hundred trillion of the lungs has resident macrophages. These macrophages are responsible for the attack of pathogens that by-passed the lung barrier. A specially equipped for the pathogen engulfing mechanism and for the digression of the engulfed pathogens and cells, and the many other enzymes useful for pathogens killing. Any defect in mucus coat production or cilia absence or macrophages present or macrophage inactiveness will have serious implications for the infections of lungs. The influenza virus, the first and unique virus that was primarily defined in the late 1930's. However, the 1918 pandemics strain, the biggest medical catastrophe in history killed at least fifty million people, was of H1N1 type.

2.1. Types and Pathogens

Respiratory tract infections (RTIs) are the most common type of infectious diseases, especially since the 21st century given the interethnic diversity of food culture. These illnesses are classified into either upper (URTIs) or lower (LRTIs) and are liable to be caused by bacteria, viruses, parasites, or other pathogens. A study conducted in Kuala Lumpur revealed that RTIs accounted for approximately 68% of patients admitted to government hospitals, diagnosed with respiratory system diseases. Prevalence of RTIs in Malaysian population is higher among children younger than 4 years and adults older than 60 years. Being a moderate-income yet developing Asian country, Malaysia faces an extensive burden from RTIs, particularly in medium- and low-income ethnic groups with different nutritional habits from one another.

Acute RTIs may be easily transmitted among people, from newborns to the elderly. The unwellness due to the highly infectious nature of RTIs exacerbates the suffering, economically as medical costs increase considerably. A nasal drip, sore throat, cough, sneezes, fever, and headache are the primary symptoms of URTIs. The main type of bacteria causing URTIs are C. diphtheriae. Viruses are generally the main aetiological agents of URTIs (Tein Ngoi et al., 2021). Accordingly, therapy for URTIs is general supportive care and rest. In light of the differences in the inflammatory response to bacteria and viruses, infections can be distinguished from one another. Respiratory discomfort, cough with phlegm or blood, weakness, significant symptoms of pneumonia, are some identified pneumonia symptoms. Asthma, chronic obstructive pulmonary diseases (COPD), and sinusitis, are chronic disorders related to the respiratory system for which RTIs can be a potent risk factor. Since the infected upper respiratory tract area is close to the brain, the ears, and the eyes, there is always a risk for infections moving on to the lower tract.

Despite the alterations in living standards and dietary habits over time, the large majority of Malaysian people hold and maintain traditional practices. URTIs are mostly cultured at nonhospitals. Much more than the self-prescription antibiotics taken in these cases, different types of antibiotics are used in various combinations. Identifying the common culture periods in patients is very difficult, also given a lack of scientific and validated data. Difficulty in the provision of early medical diagnosis and treatment against URTIs in plants makes URTIs more challenging to treat and leads to the adoption of multiple antibiotics containing antibacterial agents. Again, the intense feeling of suffering from not only the disease itself, but also the need to avoid spreading the disease to others, makes people with URTIs tend to abuse antibiotics even more. Visits to medical institutions, especially governmental areas (for which there are far fewer than in the private sector) are beginning to have an inconsistent understanding of bacterial and viral infections.

3. Mechanisms of Antibiotic Resistance in Respiratory Tract Infections

As a result of continued global antibiotic usage, bacterial resistance has become a prominent concern. Numerous bacterial infections cause diseases such as meningococcal sepsis, pneumonia, bronchitis, port site cellulitis, bronchiolitis, ear infections, or sinusitis. For example, bacterial isolates from the upper respiratory tract, such as Streptococcus pneumoniae or Haemophilus influenzae, are progressively contracting and leading to respiratory disorders. With high morbidity and mortality, bacterial respiratory infections cause considerable burden such as healthcare expenses. More than that, an evolving trend of antibiotic resistance has been observed among respiratory tract bacteria (M. Eichenberger & T. Thaden, 2019). Knowing the variations in antibiotic resistance pattern will help to create better approaches for the management of respiratory diseases as well as to minimize the spread of antibiotic resistance bacteria. Bacteria show resistance to antibiotics through various genetic and physiological mechanisms. Resistance can occur due to low permeability of the cell membrane, the presence of multidrug efflux pumps, by inactivation of the antibiotics, alteration of the target site to which the antibiotic binds, or by modification of the antibiotic. It is crucial to understand these mechanisms to fight against antibiotic resistance. Advances in the elucidation of molecular mechanisms determining bacterial resistance to antibiotics have prompted the formulation of promising strategies to overcome them. Each class of antibiotics has a different mode of attack on bacteria and different resistance mechanisms centered on inactivation of the antibiotic, modification of the target site of the antibiotic, or modification of the influx/efflux. This principle has spawned the medical and commercial field of biochemically-derived antibiotics, with the idea being that they should be more toxic to infection-causing organisms than to the host's cells. An impressed number of antibiotics have been created with different structures and functions to target the different metabolic mechanisms of bacteria and reduce the emergence of resistant organisms.

3.1. Genetic Basis

Antibiotic resistance is an increasing problem that is every year more difficult and expensive to revert. Our dependence on natural compounds to control any type of infection has been a preceding reason of their evolution. Antibiotics act as a selecting pressure for microorganisms that are always subject of mutations. In addition, a bacterium may acquire an existent resistance gene by transformation, transcription, or transduction. In the present study we evaluate the presence of bacteria with acquired antibiotic resistance on dried bronchial secretions. 34 unique samples were analyzed, from cystic fibrosis, bronchiectasis and COPD patients. A big difference on the number of isolates with acquired resistance was found depending on the personal status. Acquired resistance was only found in 2 of the 10 samples from COPD patients, whereas acquired resistance was detected in samples from bronchiectasis patients in 50% of the cases.

Acquired resistance was broader on samples from CF patients, as acquired resistance isolates were found for 2/3 of the antibiotic categories tested. No acquired resistance was detected for fluoroquinolones. For all the cases, the resistance was to readily obtainable antibiotics, and most of the cases to inexpensive ones as amoxicillin or cotrimoxazole. The usually followed patterns were identical in the under dot subcategory, and likewise, were the same in half of the samples form CF. Moreover, the presence of automatically pattern followed resistance isolates together with the antibiotic regimen therapies may use for prophylaxis could be linked to the opposite

evolution of acquired resistance bacteria, making up a very different landscape of acquired resistance, apart from that produced by any respiratory tract infection. The same patterns were usually followed in isolates from different samples, for the resistance to be of different categories. If a bacterium is resistant or moderately susceptible to one or two categories, but not to the other possible antibiotics, the pattern is unique (Corona & L. Martinez, 2013). Resistant isolates showed more frequently rough than mucoid phenotype. This is in accordance with the previous evidence on the implication of various mechanisms of resistance involving the alteration of the polysaccharide contents on the capsule. The same resistance patterns were usually observed on isolates of the same clonal pattern. This finding is consistent with that produced by lung clearance of non-mucoid Pseudomonas aeruginosa: the sample of different clones has very different resistance patterns, whereas isogenic strains from the same sample keep the same antibiotic susceptibilities. The isolation of almost identical samples may justify the appearance of quasispecies with identical resistance patterns. Conversely, resistance has a future marker for bacterial infection.

3.2. Acquired Resistance Mechanisms

The burden of respiratory tract infections caused by antibiotic-resistant bacteria has increased. Randomized controlled trials have not found benefit of antibiotic treatment for the common cold. Therefore, better diagnostic test guiding antibiotic treatment is needed. Patients with respiratory tract infections (RTIs) are frequently prescribed antibiotics although the cause of the infection is most often viral and in a majority of cases the infections resolve without treatment. In fact, the vast majority of respiratory illnesses are of viral origin. Rhinovirus is the most prevalent virus that causes upper RTIs; also the seasonal coronaviruses, parainfluenza viruses and the respiratory syncytial virus (RSV) cause approximately one out of five common colds. Group A streptococci cause only a small fraction of all RTIs and are found in less than 5% of pharyngitis cases. Studies analyzing antibiotic prescriptions for RTIs have found that 50% of the patients with a common cold and 75% of those with acute bronchitis are still treated with antibiotics. As a result of a large physician and lay public surveys the World Health Organization has found that a better rapid diagnostic test for bacterial respiratory infections is urgently needed (H. A. M. van Hoek et al., 2011).

4. Epidemiology of Antibiotic Resistance in Respiratory Tract Infections

0. Respiratory tract infections are a major diagnostic and therapeutic challenge for the pediatrician. They account for more office visits than any other childhood illness and are the most common reason children are prescribed antibacterial agents (A. Cunha, 2004). Data from European and US surveillance studies have confirmed the high prevalence of penicillin-resistant Streptococcus pneumoniae strains that are also resistant to macrolides and some cephalosporins. This has a major impact on the first-line treatment of community-acquired lower respiratory tract infections. Well-designed, multivariate clinical outcome studies of community-acquired upper respiratory tract infections are needed to adequately assess the role of potentially resistant strains. 1. Most cases of upper respiratory tract infection are due to viruses. The majority of recommendations advocate selective or even no prescription of antibacterial agents for the treatment of upper respiratory tract infections (URTIs) such as pharyngitis, sinusitis, and otitis. The position papers of WHO advocate a selective attitude since most cases are self-limiting and viral. Antibiotic therapy can only play a marginal role in preventing suppurative complications. Recommendations on the lack of eligible evidence for an evaluation of the added value of additional antibiotic treatment of pediatric acute otitis media. For adult and pediatric pharyngitis recommendations, the use of antibiotic agents is only advocated in patients with confirmed streptococcal disease. Even though comprehensive recommendations exist that reflect the view that antibiotic therapy is not indicated in a substantial proportion of cases, GPs uncomplicated URTI syndrome make a great deal about illness, complaint, need for rapid recovery, and frequent reports about insufficient outcome of conservative therapy focal on antibiotic treatment. Regarding unnecessary antibetal agents, it is unclear if there's a selective effect on a particular syndrome (Elias et al., 2017).

4.1. Global Trends

Global trends and regional patterns in antibiotic resistance in the aetiology and treatment of community-acquired respiratory tract infections (RTIs) have been reviewed. High and rising levels of β-lactam and macrolide resistance were found among common respiratory pathogens in many parts of the world. The situation seems to be particularly critical in those areas surrounding the Mediterranean, where the so-called Spanish or Iberian resistance rates often exceed 40% of an entire bacterial species and resistance is no longer confined to penicillins and azalides, but comprises almost all antibiotic groups. Parallel resistance to unrelated classes of antibiotics as a mode of defense may further complicate therapy. Widespread resistance in common respiratory pathogens impairs the efficacy of the two most frequently prescribed classes of antibiotics.

Consecutive changes in epidemiological patterns of presentation may, however, affect the impact of antipneumococcal β-lactams. Worsening of resistance rates has been observed in Italy, Spain, and France. The highly homologous patterns in the kinetics and magnitude of resistance demonstrate the spreading nature of the

phenomenon. The parallel acquisition of resistance to macrolides has greatly restricted therapeutic approaches. The prescribing behavior of family physicians, pediatricians, and general practitioners in the community gives an overview for the European situation. Intriguingly, there is no substantial difference in antibiotic usage profile, yet Spain, France, and Italy experience a drastic rise in resistance rates.

A rise in resistance to amoxicillin, and hence to protected vesicants of amoxicillin, like macrolides, is experienced. Thus, regular surveillance of this emerging problem is an urgent need, because once resistance is obvious, the containment of this process is not easy, if at all possible (A. Cunha, 2004). Interventions targeted at the general public are needed, but prescribers should not be exempted from the responsibility of implementing timely and targeted interventions. Buffer zones for the preferential use of macrolides should be entertained in the same spirit of other antibacterial classes, like cephalosporins.

4.2. Regional Variations

In the United States, antibiotic prescribing rates vary substantially across regions (L. Hersh et al., 2017). Patterns of antibiotic use were examined in selected United States (US) regions. Using data from two nationally representative US surveillance sources, the consumption of these medications was measured in thousands of encounters for acute respiratory tract infection (ARI) diagnoses. Consumption of antibiotics and bronchodilators was described across the five National Center for Health Statistics regions for ARI diagnoses over 20 seasons. Differences in the consumption of each medication varied from 30% to 80% between the maximum and minimum observed regions in a given year. For both medications, these differences did not appear confined to a particular region. Respiratory prescribing rates vary by region, and targeting underperforming regions may result in improved prescribing practices.

Asset-based intervention strategies are reported in several Latino communities of the USA. Asthma Summit is an asset-based intervention to address multiple determinants of asthma morbidity in selected communities. The goal is to improve asthma control and biological markers of asthma morbidity among Latino children. A systematic review was conducted to provide a synthesis of scientific literature related to community-based asthma interventions. Interventions to decrease asthma symptoms or healthcare costs are identified. A large variety of interventions, including health education and self-management training, environmental control measures, home visits, and school-based programs, showed effectiveness. However, there is limited evidence of improved asthma outcomes in community-level interventions (Elias et al., 2017).

5. Diagnostic Methods for Antibiotic Resistance in Respiratory Tract Infections

For the diagnosis of antibiotic resistance of upper and lower respiratory infection (URI and LRI), this research provides a broad review of experimental methods and mechanical insights. Antibiotic resistance generally occurs during continuous exposure to antibiotics, usually for systematic diseases, bacterial infections. But antibiotic therapy is also delivered by the most prevalent mode of treatment: inhalation, topically. Therefore, it is important to contemplate antibiotic resistance (and potential resistance by mutation, gene transfer) in respiratory diseases (Liu et al., 2023).

Commonly used diagnostic methods for antibiotic resistance are culture methods, molecular diagnostics, and phenotypes. Cell wall synthesis inhibitors, macrolides, fluoroquinolones, and aminoglycosides are currently recommended for LRI. Upper respiratory infections are caused by viruses, which antibiotics cannot affect. After performing experiments, the mechanical insights into antibiotic resistance of infections are presented, the dynamics on four levels. The SIR-PAE model is used to simulate the treatment of bacterial infections. The drug needs time to distribute and affect the bacteria. ASAP model is derived from the Goulier model, also on the two-species basic, presenting the evolutionary dynamics of the efflux pump activation time and production level. At the population level, bacterial productivity has time-pattern dynamics, sortie has burst-wise dynamics. Drug-resistant mutations may be inhibited or enhanced by different genetic backgrounds, this is called their fitness epistasis. This phenomenon has been observed experimentally. The review concludes by contributing to reading ideas and perspective on potential future facilitates research.

5.1. Traditional Culture-Based Methods

To predict changes in the frequency and type of antibiotic resistance in the human respiratory tract, a subset of sputum samples derived from a published collection were analyzed for the frequency of a range of resistance genes using either (a) a newly validated pooled-template amplicon sequencing method or (b) traditional single template PCR sequence analysis (L. Taylor et al., 2018).

Each analysis method produced comparable datasets that were then examined using different bioinformatic approaches. There was generally good agreement in resistance gene prevalence between the pooled-template amplicon sequencing method and traditional techniques, as well changes in the frequency of resistance genes following antibiotic administration. Therefore, these results provide a cross-validating method for future investigations on the impact of antibiotic treatment on the respiratory tract resistome.

5.2. Molecular Techniques

Respiratory tract infections (RTI) are a major health burden causing considerable mortality and morbidity. Antibiotics are a cornerstone of RTI treatment; however their effectiveness is increasingly threatened by bacteria developing resistance to commonly used antibiotics. Genomic analyses have identified common resistance mechanisms in RTI pathogens. Gram-negative bacteria, for example, commonly have multidrug efflux pumps and resistance due to impermeability of the outer membrane. Penicillin nonsusceptibility in Streptococcus pneumoniae is mainly due to alterations in penicillin binding proteins.

A global public health emergency has been identified, and it has been formulated as a priority by the government. However, the related resistome characteristics remain largely unexplored. RTIs due to nonfermenting gram-negative bacteria have dramatically increased in the last decades, especially infections in hospitalized patients.

Determining the impact of antibiotics on respiratory tract resistome is important considering the (1) increasing use of antibiotics in the last decades, (2) the high rate of antibiotic resistance in bacteria, and (3) the strong selection pressure of antibiotics on the gut microbiota resistome. Clinical and environmental exposure to antibiotics is known to drive the increase and spread of antibiotic resistance. This is particularly critical in patients with cystic fibrosis and bronchiectasis, where antibiotic therapy is prescribed empirically over long periods at high frequency. In this context, mobility of resistant strains to the airways favours the establishment of spreading resistance determinants. Unraveling the resistome after antibiotics is necessary to better understand the dynamics of resistance during antibiotic administration, and the maintenance and spread across the population of antibiotic resistance after antibiotics.

6. Clinical Implications of Antibiotic Resistance in Respiratory Tract Infections

Antibiotic resistance (ABR) in respiratory tract infections (RTIs) is of increasing concern worldwide. Despite a decrease in the consumption of antibiotics particularly in high-income countries, the burden of disease caused by antibiotic-resistant bacteria in RTIs remains high. Clinical manifestations of ABR-RTI in patients vary considerably, and overall antibiotic resistance may not necessarily result in more severe or prolonged disease episodes. However, inadequate use of antimicrobials in patients infected with antibiotic-resistant bacteria and eventual spread of these pathogens to new hosts obviously poses a substantial risk, particularly in resource-limited healthcare settings. Thus, symptomatic treatment including antimicrobials needs to be well targeted and effective. In developing countries, antibiotic prescription too frequently is based solely on general symptoms of infection such as fever or cough. In a cohort of children below 5 years, antibiotics were prescribed in a significant percentage of outpatient visits due to RTI with viral, bacterial, or mixed bacterial-viral aetiology. Severe acute malnutrition, non-pneumonia RTI, and upper RTI were identified as independent predictors for overall, broad-spectrum, and antibiotic use for viral RTI. Antibiotic use in viral RTIs was predicted to correlate positively with younger age among children. Common cold, the most common RTI seems to be the main indication for inappropriate antibiotic use, which may further have contributed to reduced antibiotic effectiveness. Antibiotics were found to be less effective, predominantly in children below 5 years of age, who developed severe ABR-AOM. The most effective pneumonia treatment strategy by use of antibiotics may depend on the setting of the community classification. Broad-spectrum antibiotics were significantly more effective than narrow-spectrum antibiotics. In contrast to primary care visits, prescriptions of broad-spectrum antibiotics were significantly less frequent in emergency department visits, probably because of the more severe presentation of disease. However, significant use of macrolides as first-line treatment for pediatric acute RTI was reported. A high number of new, particularly inhaled, antibiotic preparations has been licensed, without, however, an available increased evidence base for efficacy and safety. This development may further contribute to misperceptions of antibiotics as capable antivirals. Routine antibiotic treatment in uncomplicated community-acquired sinusitis is not recommended. Primary empirical oral antibiotic therapy for bacterial AOM should be based on consideration of the observation option. On the other hand, the initial application and the increased use of delayed antibiotic prescribing was found to reduce overall antibiotic use and did not differ regarding duration of moderate to severe symptomatology. The mainstay for prevention and treatment of AOM remain prolonged duration antiviral treatment and contrast enhanced computed tomography of thorax. With the increasing spread of resistant pneumococci, especially penicillin- and macrolide-resistant strains, the empiric use of antibiotics in both outpatient and inpatient treatment of LRTI and minor infections is the challenge. However, the use of highly effective unnecessary therapy such as antibiotic prescription is of concern owing to the increased burden of two-drug resistant bacteria. A reduction intervention strategy for overuse in early diagnosis of resistant pathogens, lowering the antibiotic threshold, and applying addressed prescribing strategies was favored. Nonetheless, reducing inappropriate antibiotic use is difficult because many physicians have an antibiotic-heavy practice due to lack of guidelines. In life-threatening infections, antibiotics are given more aggressively. Only a target-oriented treatment with broad-spectrum antibiotics and in concordance with the bacterial sensitivities has

been shown to be effective on the idiopathic AOM and further prevent possible hearing loss by aggressive focal treatment.

6.1. Impact on Treatment Outcomes

In the outpatient clinical setting, relative penicillin resistance has existed almost since the time of the drug's introduction into the medical-pharmaceutical armamentarium so the early selection of resistant strains should not be surprising (A. Cunha, 2004). Since most of the patients in these studies do not seek additional medical care for their URIs, the overall clinical outcome may be the resolution of their symptoms, rather than the stereotypical reflective definition of "cure" vis-à-vis the elimination of all pathogens, unless such a target is considered symptomatic relief. Due to the growing difficulties of empirical therapy in the clinical setting, the need for studies focusing on resistant pathogens from the respiratory tract has increased. Rising resistance of Streptococcus pneumoniae has been widely documented, with international studies emphasizing the complex regional differences in the prevalence of resistance to widely-used antibiotics. Penicillin-resistant strains appear to be rather stable and have high-level resistance. Cross-resistance to other classes of β-lactams exists which severely limits therapeutic options.

It should come as no surprise that much of the medical management of URIs focuses on symptomatic relief or cough medication, since URI etiology is largely viral, for which there are no real cures to begin with. This sort of reasoning gives value to studies that examine local resistance, staff adherence, and those that provide a result strictly looking at overall cure rates (Elias et al., 2017). URI remains one of the leading reasons for ambulatory care visits in both otorhinolaryngology and general practice, and for the latter, is the most common diagnosis leading to an antibiotic prescription. However, treatment failures (i.e., those culminating in hospitalization or worse) are exceptionally rare.

7. Current Intervention Strategies

Antibiotic resistance develops via the selection of bacteria through the exposure to antibiotics. Infections caused by resistant bacteria have increased the costs of disease management, including higher and prolonged hospitalization, more complex treatments, and increased mortality. One of the crucial public health problems is the rapidly escalating widespread antibiotic resistance in many types of bacteria, which is a problem commonly encountered in respiratory tract bacterial infections. This public health issue is the result of contemporary rapid spread of multi-drug resistant bacteria. It is estimated that in the US, more than 20 million respiratory tract infections occur annually. Owing to the increased demand for antibiotic therapy during infections, antimicrobial resistance is widespread among bacteria that cause respiratory tract infections, including Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. Another significant aspect linked to antibiotic resistance is the recurrence of infections caused by the same bacteria. In conclusion, the following can be listed as potential impacts of the high and increasing rates of antibiotic resistance in respiratory tract infections: More frequent and severe infection recurs; more acute exacerbations due to chronic infections; much broader prescription of second and third line antibiotics for the treatment of the infections; and increased mortality rates.

A contaminated host can no longer respond to infections caused by any kind of microorganisms including pathogenic microorganisms. Infectious diseases, which result from the action of incompatible microorganisms on a pre-disposed host, are ageold and of ancient origin. Like all other drugs, antibiotics have their own adverse effects and toxic side effects, which restrict the field of clinical use; and prolonged use elevates the emergence of toxicity in the treatment process. The disbalance of the normal flora of the body might arise; this can cause the unintended commensal microbes to become pathogenic. Since drug and health expenditures in the antibiotic field are expanding along with the developing treatment possibilities, non-drug treatment options are being investigated seriously in the present day. There is a wealth of biologically active, unknown substances in natural plants.

7.1. Antibiotic Stewardship Programs

The American College of Physicians, American Society of Internal Medicine, and Infectious Disease Society of America have detailed one application of antibiotic stewardship programs (ASPs) in their evidence-based guidelines. Significant attention is given to mostly respiratory tract infections. The guidelines include a step-down treatment to high-dose co-amoxiclav 875mg for 7 days after failure of a medium dose. Following this, there is a second choice step-down antibiotic for a further 7 days. Each antibiotic is intended for patients with no recent antibiotic exposure and without a compelling indication for antibiotics. If there is partial resolution, a patient should return for subsequent step-down antibiotic courses, using chiefly penicillins, cephalosporins, macrolides, and tetracyclines (A. Weaver, 2019). In the UK this guidance has been operationalized into a treatment algorithm. Strategy for consortia of general practitioners has been based on these guidelines, together with a test of procalcitonin (PCT) to target tetracyclines. Combination therapy for tuberculosis superficially resembles this step-down principle. There is little evidence available for the effectiveness of such a step-down treatment strategy. This real-world analysis investigates one element of falling acute prescription of antibiotics

for common infective exacerbations of airways disease using the step-down principle. The aim is to evaluate and compare GPs who increasingly use the step-down strategy to those who do not with regard to subsequent antibiotic prescribing.

The overarching goal is to develop techniques and to model moderate to severe exacerbations of chronic obstructive pulmonary disease (COPD) and chronic bronchitis (CB) to identify those that will progress to Airway Bacterial Colonization, the latter potentially targeted via the airway. Broad and specific objectives are to (1) develop statistics-based forecasting models for exacerbations, (2) develop novel mathematical modelling techniques, which will link host airway disease and bacterial growth, and (3) optimize treatment strategy based on the model(s). Broad objectives 1 and 2 will be achieved by applying statistical and mechanistic approaches. Broad statistical objectives are to develop models capable of predicting the time and severity of exacerbations. Broad mechanistic modelling objectives are to develop ordinary differential equation models describing the dynamics host airway disease and the surrounding biofilm growth of airway infection species. Broad optimization objectives are to identify optimal treatment strategies using insights from forecast models.

8. Future Directions and Emerging Technologies

Bacterial resistance to clinically relevant antibiotics continues to constitute a major threat to public health globally, with populations affected irrespective of geographical, cultural, or economic boundaries. Novel mitigation and therapeutic strategies for addressing respiratory bacterial infections are urgently needed to treat both children and adults. Antibiotic resistance towards common respiratory pathogens has resulted from sustained antibiotic usage for several decades, particularly within developed countries. Research has shown there were fatalities worldwide during due to bacterial infection, with a significant percentage originating from the lower respiratory tract. Streptococcus pneumoniae remains the most common pathogen associated with bronchopneumonia. Antibiotic intervention in bacterial-related respiratory infections typically saves lives; however, treatment is cost-intensive, consuming significant amounts daily within developed countries. A large portion of the annual expense in healthcare systems of developed nations is attributed to managing endemic bacterial infections associated primarily with antibiotic usage. In the United States, expenditure peaked at over a substantial amount, principally due to respiratory bacterial infections. Efficient mitigation and intervention strategies towards low and middle-income convalescents remains an urgent task with global ramifications. The unique strategy of utilizing polymer-based biomimetic pathogens unraveled possible avenues that can be pursued in the development of novel mitigation intervention options as a substitute to antibiotics therapy. Additional challenges, improvement, and cost-effectiveness required for transitioning a concept into a mobile tool has been discussed, which can be used in future research.

8.1. Potential Breakthroughs

Compared to the no antibiotic control samples, sulfamethoxazole causes an increase in the total number of bacterial cells and piperacillin causes a decrease in the asymptomatic endpoint. PCR analysis was carried out on 16S rDNA from the sick point of 36 h for this endpoint. DNA sequences for 12 isolates representing the most abundant species are obtained and multiple sequence alignment of the V6 region is performed. An initial visual inspection of the alignments reveals that the majority of isolates are closely related to certain species. However, 5 isolates do not appear to match any known sequences. Due to the relatively long read length and lack of quality scores for the sequences, it is suspected that the high number of OTUs is an artifact of sequencing errors. To filter out probable errors, reads possessing any homopolymer greater than 4 bp are removed. OTU estimates are then generated from the subsampled data using a chimera checking pipeline. Substantially lower OTU estimates are produced, indicating that a majority of OTUs detected in the original analysis are indeed artifacts of sequencing error.

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