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"INFLUEZA AND BACTERIAL CO-INFECTION A SYSTEMATIC REVIEW

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ANIL GAUTAM

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S.NO	PARTICULARS	PAGE. NO
1	INTRODUCTION	12-30
2.	REVIEW OF LITRATURE	31-45
3.	AIMS AND OBJECTIVE	46-47
4.	MATERIAL AND METHOD	48-50
5.	OBASERVATION AND RESULT	51-58
6.	DISCUSSION	59-60
7.	CONCLUSION	61
8.	REFERENCE	62-85

INTRODUCTION

INTRODUCTION

The influenza virus is a member of the Orthomyxoviridae family and contains ribonucleic acid (RNA) as its nucleic acid. The influenza A and B viruses are the most common viruses that cause respiratory disease in humans (1,2).

Previous studies suggested temporal relationship between influenza and co-infection indeed retrospective analysis of lung biopsies of patients who died from influenza in the pandemic of 1918 suggested bacterial super infection of the lung(5,6). Despite the fact that influenza B viruses are almost entirely found in humans, influenza A viruses (IAVS) circulate within the population as a yearly recurring epidemic illness and emerge from a large zoonotic reservoir (3,4).

Human influenza virus infections primarily replicate epithelium, but other cell types, including many immune cells, can be infected by the end and will initiate viral protein production (7).

Previously, researchers investigated the prevalence of specific bacterial species in influenza cases, focusing on the presence of methicillin-resistant (staphylococcus aurous) [MRSA] (8,13).

However, preliminary studies of the H7N9 influenza virus describe few details of patients with bacterial co-infection and the reasonable selection of antibiotic therapy for the most common pathogen as well as an accurate diagnosis marker before obtaining a positive culture for this potentially fatal disease (14).

Bacterial co-infection is a major cause of morbidity and mortality in influenza patients (15). Regardless of whether the infection is seasonal or caused by a novel virus, the two most common

co-infecting organisms are Streptococcus pneumonia and Staphylococcus aureus (16). However, no

case reports of influenza and Pseudomonas aeruginosa co-infection were found in the literature.

A 39-year-old woman with dyspnea and a one-week history of fever, cough, and malaise presented to the emergency department. Her initial temperature was 36.5 degrees Celsius, her heart rate was 111 beats per minute, her blood pressure was 80/54 mmHg, and her respiratory rate was 20 breaths per minute, with an oxygen saturation of 93 percent while breathing oxygen at 4 L/min. The white-cell count was 810/mm3, with 63.8 percent neutrophils, 23.1 percent lymphocytes, and 11.8 percent monocytes. The rapid influenza antigen test came back negative. In both lungs, a chest radiograph revealed patchy infiltrates. Intravenous piperacillin/tazobactam 4500 mg every 8 hours and oral oseltamivir 150 mg twice daily were given.

Patch densities and ground-glass opacity were seen on computed tomography of the chest. Due to the rapid deterioration of the respiratory condition and refractory shock, an emergency endotracheal intubation with mechanical ventilation and extracorporeal membrane oxygenation was performed. Gram staining of bronchial alveolar lavage revealed gram-negative bacilli with a lack of phagocytes. Despite receiving highly intensive care, the patient died 23 hours after arriving. The Taiwan Center for Disease Control found influenza A (H1N1) pdm09 in a polymerase chain reaction analysis of a nasopharyngeal swab (17). P. aeruginosa was found in blood and sputum cultures two days after the patient died.

P. aeruginosa(18) isolates' antimicrobial susceptibility was determined using the Phoenix

Automated Microbiology System (Becton Dickinson, Sparks, MD, USA).

Laboratory Standards Institute recommendations. P. aeruginosa isolated from the bloodstream was susceptible to imipenem (minimum inhibitory concentration Z 2 mg/mL), meropenem (_1 mg/mL), aztreonam (8 mg/mL), amikacin (_8 mg/mL), ceftazidime (2 mg/mL), cefepime (_2 mg/mL), ciprofloxacin (_0.5 mg/mL), gent A severe and prolonged influenza epidemic was observed in Taiwan in 2015-2016; as of June 30, 2016, there were 2018 confirmed severe complicated influenza cases, including 163 deaths, the majority of which occurred in individuals.

An influenza and bacterial co-infection mouse model study discovered that type I interferon-associated suppression of type 17 immunity and antimicrobial peptide production during influenza increased host susceptibility to P. aeruginosa co-infection. However, no definitive relationship has been established. Even though oseltamivir and empirical antibiotics were administered early, our patient died. One study found that after using peramivir, patients with complicated influenza had a 62 percent chance of survival (19). Peramivir may be an option for treating acute influenza infection. Because P. aeruginosa is a pathogen that can co-infect with influenza A(H1N1)pdm09, clinicians should keep this in mind when treating patients who have influenza-associated pneumonia and severe leukopenia.

A timely antiviral agent and antibiotic use could save a life. The 1918 influenza (H1N1) pandemic killed over 50 million people worldwide (Johnson and Mueller, 2002; Morens et al., 2008). The majority of deaths were caused by bacterial co-infection rather than direct virus effects.

Similarly, during the 2009 influenza pandemic, bacterial co-infection was positively correlated with

IAV-caused mortality, and nearly 30 percent of critically ill influenza patients had bacterial co-infection.

In patients in intensive care units, bacteria such as Streptococcus pneumoniae (S.P), group A streptococcus (GAS), Staphylococcus aureus, and Haemophilus influenzae (H.I) aggravate their

illness (Estenssoro et al., 2010; Farias et al., 2010; Rice et al., 2012). Antibiotic use may reduce influenza-related deaths by limiting bacterial co-infections.

However, as bacterial antibiotic resistance rises, IAV-caused bacterial co-infection will inevitably become one of the leading causes of severe pneumonia and bacterial-related invasive diseases (20). Understanding the underlying mechanisms of IAV-bacterial co-infection is therefore critical for the development of new drugs against IAV-bacterial co-infection. GAS is an opportunistic pathogenic streptococci that usually causes chronic diseases like pharyngitis, but can also cause severe, invasive infections like bacteremia, necrotic fascilltis, and pneumonia.

The first step in GAS infection is adhesion to host tissue, which is mediated by cell adhesion molecules such as fibronectin, integrins, and cluster of differentiation 46 (CD46) (21).

Influenza causes widespread annual epidemics infecting up to 20% of the population and resulting in significant morbidity and mortality(23).1 Co-infecting bacterial pathogens are a major cause of that morbidity and mortality and are associated with both pandemic and seasonal influenza virus illness.24 2 Lung tissue samples from the 1918 influenza However, the key host factors that contribute to IAV-induced bacterial co-infection remain unknown. Cyclophilin A (CypA; encoded

by PPIA) is a highly conserved peptidyl-prolyl cis/trans isomerase (PPIase) (Fischer et al., 1989). CypA is the primary intracellular receptor of the immunosuppressive drug cyclosporine A (CsA), which is commonly used in transplantation medicine to inhibit T cell function by binding to CypA. (22).

According to the pandemic, the majority of the estimated 20-60 million deaths were caused by bacterial infections rather than by direct effects of the pandemic virus 25.

In seasonal epidemics, influenza bacterial co-infection is linked to an increase in hospitalizations,4,5 more severe symptoms,6, and an increase in mortality (26). Viral damage to the respiratory tract's epithelial lining is thought to facilitate the establishment of bacterial infections. Given the significant symptom overlap between influenza and bacterial infections, it can be difficult to identify influenza patients who have bacterial co-infections clinically (27). The identification of coinfected patients and the pathogen that infects them allows clinicians to begin appropriate antibiotic therapy and improve patient outcomes (28). Prior research has looked at the prevalence of specific bacterial species in influenza cases (29,30). Despite the presence of methicillin-resistant S(31,32) aureus (MRSA),15-18 the frequency of overall co-infection in influenza patients remains unknown (33,34). We conducted a systematic review to determine (35,36). to determine the frequency of bacterial co-infections in patients with laboratory confirmed influenza and the most common common co-infecting bacterial species(37,38)

Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality

worldwide (39,40). It accounts for over 4.5 million outpatient and emergency room visits in the United States each year, resulting in 24.8 admissions per 10,000 adults per year, with higher rates in the elderly (41,42). A review of 98 studies on the prevalence of CAP among adults in Europe discovered that its prevalence varied by country, age, and gender. A population-based (43)cohort study of 11 241 patients aged 65 years conducted in Spain found an incidence of 14 cases per 1000 person-years (44).

The prognosis of CAP patients varies greatly as well (45,46). It is worth noting that in-hospital 30-(ICU)(47). Other than age, comorbidities, frailty, cardiovascular complications, inflammatory response, and aetiology are all associated with mortality(48) (49,50) Streptococcus pneumoniae is still the most commonly identified bacteria in CAP patients, despite the fact that the overall incidence of pneumococcal pneumonia appears to be decreasing in some institutions, and, interestingly, respiratory viruses are becoming more common (51,52). Traditional microbiological analysis identifies no pathogens in up to 62 percent of cases.

Day mortality ranges from 4% to 18%, rising to 50% in patients admitted to the intensive care unit of instances. The detection of viral and bacterial co-infection (VBC) in CAP has increased with the development of multiple molecular detection tests (53,54). A prospective study of 49 adults admitted to ICUs with CAP found that 39 percent of those treated with viral polymerase chain reaction (PCR) techniques had VBC. The role of VBC, on the other hand, is debatable because the presence of bacteria in the airway can lead to viral replication and vice versa. Furthermore, up to 38% of healthy people who tested positive for influenza viruses in their nasal epithelium do not

develop disease (55,56).

Given the limitations of previous research, the role of VBC in immunocompetent adults hospitalised in a non-ICU setting with CAP remains unknown (57). As a result, the current study aims to identify risk factors, clinical features, and outcomes of VBC-CAP in adults admitted to conventional wards who do not have severe immune compromise (58).

Respiratory viruses, such as influenza virus, are known to cause severe disease and to be linked to pneumonia, particularly in the very young and elderly populations, as well as in people with serious medical comorbidities. Furthermore, respiratory virus infection frequently increases susceptibility

to secondary bacterial infections. The mechanisms underlying this viral/bacterial synergy have remained elusive, and have previously been linked to virus-induced lung tissue damage (59,60).

A dysfunctional host antibacterial immune response during influenza infection, however, has been implicated as the major contributor to secondary bacterial susceptibility using recently developed animal models (61) In this paper, we will look at recent scientific advances that have provided new insights into this major clinical problem.

Bacterial pneumonia is a common complication of influenza infection (62). Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pyogenes are the most common bacteria involved in secondary infections (63). Such co-infections may be especially troublesome during influenza pandemics (64). Indeed, examinations of published autopsy case reports revealed that.90% of deaths.

The 1918 influenza pandemic was most likely caused by secondary pneumococcal pneumonia (65). One could argue that because antibiotics were not available in 1918, secondary bacterial infections would not be a serious problem today.

Despite the availability of antibiotics, the majority of deaths in the 1957-58 "Asian influenza" pandemic were due to secondary bacterial pneumonia. According to one study, 75% of confirmed fatal cases of influenza in the 1957-58 pandemic had bacteriological and histological evidence of bacterial pneumonia, most likely caused by S The remaining fatal cases appeared to be primarily the result of influenza viral pneumonia. Furthermore, during the 2009 H1N1 (swine flu) pandemic,.50% of those who died had histologic and microbiologic evidence of bacterial

pneumonia (66). Surprisingly, according to one report, 43 percent of the children who died from the H1N1 virus in the United States from April to June

Staphylococcus aureus or Staphylococcus pneumoniae In August 2009, there were laboratory-confirmed bacterial co-infections in all six children with culture or pathology results and no recognised, high-risk medical conditions.

Given the difficulty and uncertainty in detecting and cultivating bacteria from the lungs of deceased patients, the number of co-infected patients in all of these studies could be significantly higher (67,68 Co-infections are also a recurring problem with seasonal influenza (69). In the United States, approximately 90,000 people die each year from bacterial infections, and methicillin-resistant S.

MRSA (Methicillin-resistant Staphylococcus aureus) has emerged as a growing problem for both hospital- and community-acquired pneumonia. Furthermore, new MRSA variants continue to emerge as pulmonary pathogens. and have been linked to community outbreaks as well as postinfluenza pneumonia (72). Bacterial co-infections are thought to have caused.over the last 20 years (70). MRSA, in fact, kills more people than HIV (71).

The mouse infection model is widely used in the study of influenza infection. In both humans and mice, influenza virus titers in the lung peak 3-5 days after infection, and the virus then begins to be cleared, with infection nearly resolved by days 10-12. (73). Murine Several groups have also established models of viral/bacterial co-infection, and these models appear to accurately mimic clinical observations regarding the high susceptibility to secondary bacterial infection folloswing influenza,(74), with greatly increased disease severity and fatality rates.

The most commonly used viral strain for murine co-infection studies is mouseadapted H1N1 A/PR/8/34, but nonadapted H1N1 CAL/04/09 has also been used (75). The greatest susceptibility is used in different mouse studies, and these differences are primarily related to whether the individual focus is on understanding influenza-induced susceptibility to secondary

bacterial infection or the resulting poor disease outcome. Many studies, for example have used a

high level of bacterial challenge doses, particularly when studying influenza and S.(76)aureus co-infection, which leads to extensive neutrophil recruitment and exacerbation of inflammation, a

clinical feature that can eventually result in bacterial pneumonia and a poor outcome.

Similarly, some studies have concentrated on the late stages of bacterial infection (24 hours or later after secondary infection), when there is an influx of neutrophils into the lung and intense inflammatory responses as a result of bacterial outgrowth (77 Thus, researchers who use high doses of challenge bacteria and/or study the later stages of infection are more likely to study neutrophil function, either their antibacterial activities or the accompanying inflammatory lung damage.

Alternatively, our experiments show that a normal mouse can effectively clear up to 105 pneumococci very quickly (within 4-12 h); higher challenge doses necessitate neutrophil recruitment for survival. They used this system to investigate phagocytic function very early after bacterial infection, avoiding the(78).) The confounding issue of whether the observed pathology is the result of a failure to control the initial bacterial infection or an overwhelming inflammatory response following the infection.

They propose that using the smallest viral and bacterial doses required to observe pathogen synergy, in a situation that most closely resembles the natural clinical scenario, is ideal for studying the mechanism of influenza-induced susceptibility to secondary bacterial infection (79).

Since 1918, the mechanisms underlying influenza virus-bacterial infection synergy have remained a mystery (80). Following influenza infection, it is clear that susceptibility to various encapsulated bacteria increases, implying a general defect (81).

It preferentially replicates in epithelial cells, causing direct damage to the airway epithelium. Historically, the widely accepted mechanism for microbial synergy has been that virus-induced epithelial barrier damage provides more attachment sites for bacteria, resulting in invasive disease (82).

In both humans and mice, influenza-induced lung tissue damage is greatest on day 6 after infection,(83,84), which generally correlates with the time of greatest susceptibility to bacteria. Virus strains that cause minimal epithelial cell damage, on the other hand, enhance subsequent bacterial infection in mice (85,86).

During murine viral infection, influenza neuraminidase and platelet-activating factor receptor expression may increase bacterial adherence (87). Although mice lacking the platelet-activating factor receptor or mice treated with a competitive receptor antagonist had no effect on survival rates after bacterial infection (88). Furthermore, genetic deletions that alter viral neuraminidase expression have no effect on mice susceptibility to secondary bacterial pneumonia. Finally, there was no correlation between human mortality and virus attack rates in 1918, implying that factors other than viral-induced lung damage were at work (89).

Influenza-induced suppression of antibacterial innate immunity. The idea that influenza infection impairs innate bacterial clearance in the lung is gaining traction in the field (90). The majority of cells in the normal airway are alveolar macrophages, which serve as the first line of defence against respiratory infection (91 Influenza-induced suppression of antibacterial innate immunity The idea that influenza infection impairs innate bacterial clearance in the lung is gaining traction in the field

(90). The majority of cells in the normal airway are alveolar macrophages, which act as the first line of defence against respiratory infection (91).

Alveolar macrophages obtained from uninfected mice killed 90% of Staphylococcus epidermidis, whereas macrophages obtained from influenza-infected animals killed only 68-73 percent. Jakab and others (93). Reported defective phagolysosome formation by virus-infected mouse alveolar macrophages but no defect in phagocytosis, whereas Nugent and Pesanti discovered no defect in either uptake or killing (94). The disparities in the results from these different laboratories could be due to a variety of factors, including differences in the number of days since the initial virus infection and/or secondary bacterial challenge, variations in virus and bacteria doses, and variations in virus and bacterial strain combinations studied (95).

More recently, it has been discovered that alveolar macrophage-mediated clearance of S(96). pneumoniae that occurs within 4-6 h of intranasal bacterial challenge is significantly inhibited by prior influenza virus infection, with maximal inhibition occurring on days 7-8 following viral infection (97). Surprisingly, this is when affector T cells have migrated into the The peak of IFN-g expression in the pulmonary tract occurs when the lung airways begin to recover from viral infection. Indeed, whereas bacterial clearance is suppressed(98) in wildtype mice after influenza infection, it is nearly absent in virus-infected IFN-g2/2 mice and in wildtype mice treated with neutralising anti-IFN-g mAb after influenza infection.

It should be noted that in normal mice infected only with pneumococci, increased IFN-g expression can enhance TNF-a expression, leading to increased neutrophil recruitment (99). TNF-a production is reduced in animals previously infected with influenza virus, even in the presence of IFN-g (100).

This is probably related to the discovery that influenza infection causes Desensitization of TLR4-mediated signalling Although pneumolysin produced by pneumococci is a TLR4 ligand, there is no

evidence that TLR4 is required for immunity to S(101) aureus. Furthermore, this TLR signalling defect is relatively long-lasting and can be seen months after viral infection.

Infected hosts have been reported to be partially responsible for the increased susceptibility to secondary bacterial infection, most likely due to an effect on neutrophil function., However, only a minor reduction in susceptibility to secondary bacterial infection is observed in IL102/2 mice. Furthermore, IL-102/2 mice recover from influenza infection faster than wild-type animals due to earlier induction of adaptive immunity. (106)

Shahangian et al. discovered that mice lacking the IFNa/b receptor were partially resistant to secondary infection with S.(107), pneumoniae following influenza, and that this effect was correlated with neutrophil chemoattractant production. A similar function for IFN-a and IFN-b was reported in a mouse model of upper respiratory tract pneumococcal colonisation The discovery that IL-17, IL-22, and IL-23 were decreased following co-infection with influenza virus and (108), S. aureus, and that this decrease was dependent on type 1 IFN, indicated an important role for the Th17 pathway in this effect (109,110) Furthermore, intentional overexpression of IL-23 during influenza resulted in significantly improved bacterial clearance (111).

Multiple studies have shown that impaired antibacterial immunity contributes primarily to lethal influenza and bacterial co-infection,(112,113), and that inhibited innate antibacterial immunity is

associated with dysregulated pulmonary cytokine responses following influenza infection.

(114,115) Alternatively, these immune regulators, such as type I IFN, IL-10, and IL-17, frequently have opposing effects on protective antiviral immune responses. (116) Failure to maintain appropriate antiviral or antibacterial immune responses can have a negative impact on the outcome of co-infection (117,118 Recent co-infection research has primarily focused on the mechanism underlying influenza-induced susceptibility to secondary bacterial infection. (119) However, broad

pulmonary inflammatory infiltration is a key clinical feature of bacterial pneumonia. Overwhelming bacterial infection may explain widespread lung pathology in the later stages of infection. However, excessive inflammation was discovered to be independent of pulmonary bacterial infection.) burden Furthermore, viral virulent factors like PB1-F2 can directly mediate the immunopathogenesis of influenza and pneumococcal co-infection. (120) Nonetheless, excessive inflammatory responses following secondary bacterial infection pose another challenge for clinical management of disease and are most likely the cause of increased disease severity and mortality despite treatment. (121)

PATHOGENESIS OF INFUENZA VIRUS

Transmission It spreads through infected aerosols produced by coughs and sneezes, and only rarely through contacts or fomites. Small-particle aerosols (10 m) are more efficient at transmission. Target cell entry: Viral HA binds to specific sialic acid receptors on the host cell surface, allowing viral entry. Ciliated columnar epithelial cells are the most commonly infected, but it can also infect

alveolar cells, mucous gland cells, and alveolar macrophages Local replication: irus replicates in infected cells, and infectious daughter virions spread to adjacent cells, involving a large number of respiratory epithelial cells over several hours. Spread: Viruses rarely spread to the lower respiratory tract or cross the bloodstream to involve extrapulmonary sites. Localized harm: Infection with

influenza virus causes cellular destruction and desquamation of the respiratory tract's superficial mucosa. Edema and mononuclear cell infiltrations occur at the local site, resulting in cytokine influx, which accounts for local symptoms. Local damage makes secondary bacterial invasion more likely.

CLINICAL MANIFESTATION OF INFLUENZA VIRUS

Incubation Period

It takes between 18 and 72 hours, depending on the size of the inoculum and the host's immune status. Simple Influenza (Flu Syndrome) The majority of people are either asymptomatic or develop minor upper respiratory symptoms such as chills, headache, and dry cough, which are followed by high-grade fever, myalgia, and anorexia. It is a self-limiting condition that is indistinguishable from infections caused by other upper respiratory tract pathogens.

Complications

Pneumonia: Secondary bacterial pneumonia is the most common complication in patients infected with the influenza virus. Staphylococci, pneumococci, and Haemophilus influenzae are common agents. Primary influenza pneumonia is uncommon, but it can lead to more serious complications. Other pulmonary complications include worsening chronic obstructive pulmonary disease. 40%).

Exacerbation of chronic bronchitis and asthma. Reye's syndrome: It is fatty liver degeneration with acute encephalopathy that occurs in children and adolescents (2 to 16 years old) after taking aspirin or salicylates. Though the cause is unknown, this condition is frequently seen following influenza B, varicellazoster, and, in rare cases, influenza A viral infections. The mortality rate is high (10)

EPIDEMIOLOGY OF INFLUENZA VIRUS

Influenza outbreaks occur almost every year around the world, but the severity and extent of spread vary greatly. Influenza epidemics are estimated to cause 3-5 million cases of severe illness and 2.5-5 lakh deaths worldwide each year, with significant economic consequences. Seasonality: Influenza outbreaks are common during the winter. The most common seasonal flu strain varies by season and location (e.g. H3N2 in Pondicherry in 2018). The nature of antigenic variation in influenza types determines the epidemiological pattern (as described earlier). HlNl 2009 flu was caused by the genetic reassortment of four strains (one human strain, two swine strains, and one avian strain), which occurred in pigs. Despite the fact that the word 'swine flu' to describe HlNl 2009 flu, but this is not the correct terminology as it is a reassortant of four strains.

Clinical Features

Uncomplicated influenza: Most of the cases present with mild upper respiratory tract illness and diarrhea Complicated/ severe influenza can occur very rarely in high-risk groups, is characterized by features such as secondary bacterial pneumonia, dehydration, CNS involvement, and multiorgan failure. Categorization of Seasonal Influenza A/H1 N 1 Ministry of Health and Family Welfare,
The government of India has issued a guideline for classifying seasonal influenza A/HlNl cases. This guideline assists in making decisions about performing laboratory tests, initiating antiviral treatment, and placing the patient on home isolation or hospitalisation when screening patients with influenza-like illness. GISRS: Global influenza surveillance has been conducted. through the World Health Organization's Global Influenza Surveillance and Response System (GISRS) (WHO). It

monitors the evolution of influenza viruses globally and serves as a global warning system for the emergence of pandemic influenza viruses.

Sialic acid receptors found on host cell surfaces are specific for HA antigens of influenza virus, which determines the different host specificities of influenza virus • A 2-6 sialic acid receptors are specific for human influenza strains and are abundant on human upper respiratory tract epithelium but not on lower respiratory tract epithelium. This explains why most human Flu strains cause mild upper respiratory tract infections but not pneumonia. 2-3 sialic acid receptors are specific for avian influenza strains and are abundant on the intestinal epithelium of birds. They are found in very small numbers on the upper respiratory tract and on some other parts of the body in humans.
lower tract epithelial cells This explains why avian flu strains cannot easily infect humans and require close contact. However, once infected, they can infect the lower respiratory tract and cause pneumonia.

PREVENTION AND CONTROL

General Preventive Measures Droplet precautions should be taken: Strict hand hygiene Isolation room: Patients should be kept in isolation rooms or cohorting to be followed. Coughing and sneezing containment:
Cough etiquette and respiratory hygiene Use of personal protective equipment (PPE) such as gloves and masks for both staff and patients. Work restrictions: The CDC recommends that people with influenza-like illness stay at home for at least 24 hours after they are fever-free (100°F) without the use of fever-reducing medications.

Live Attenuated Influenza Vaccine (LAIV)

This vaccine is created through reassortment of currently circulating influenza A and B virus strains with a cold-adapted attenuated master strain that can grow at temperatures ranging from 25 to 33

degrees Celsius. Such live attenuated strains can grow in the upper respiratory tract (at 33°C) but not in the lower respiratory tract (at 37°C); thus, they may cause mild flu-like symptoms but never infect the lower respiratory tract, and thus never cause serious adverse effects. It is a trivalent vaccine that is intranasally administered spray It can be given to all healthy people aged 2 to 49 years old (except during pregnancy), but not to highrisk groups. However, due to efficacy concerns, LAIV is not recommended for use in any population in 2017-18. Injectable vaccines are the most commonly used vaccines in immunisation programmes. Types: There are three types of injectable vaccines. l. Inactivated Influenza Vaccine (IIV), e.g. Fluzone: It is made by growing the vaccine strains in the allantoic cavity of embryonated chick eggs, then harvesting, purifying, and they are inactivated with formalin or beta propiolactone and then standardised based on hemagglutinin antigen content (15 g of HA/dose).

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

Yang et al (2018) conducted a retrospective analysis of 83 patients with H7N9 illness from April 2013 to February 2014. Analysis was done on the severity of patients with bacterial co-infection and early detection markers in H7N9. The most common pathogen, they discovered, was Staphylococcus aureus. [123]

In a review by Peteranderl et al In 2016, they provided an overview of the state-of-the-art knowledge regarding the molecular basis of influenza contamination, illnesses development, key players in pathogenesis leading to severe illnesses and lung failure, as well as available and anticipated prevention and treatment methods for influenza virus contamination. To lower the occurrence of secondary infections with higher morbidities, it will also be important to understand the processes behind the elevated vulnerability to bacterial expansion associated with influenza infection. Future treatments for ARDS are anticipated to be based on the promising findings of ongoing research on stem cell-based therapies, including training these cells to be damage- or pathogen-specific prior to application to optimise their unique modes of action in various forms of acute lung injury. [124]

In a pathophysiology and epidemiology report by Kalil and Thomas (2019In this study, it was found that acute pneumonia affected 30–40% of hospitalised patients with influenza in the laboratory. Anyone over 65, Caucasian, a nursing home resident, with a chronic lung or coronary heart condition, a history of smoking, and a weakened immune system is significantly more prone to acquire pneumonia.

Although a secondary bacterial infection—most frequently caused by Staphylococcus aureus and Streptococcus pneumoniae—can also coexist with or be a symptom of influenza and contribute to its primary ability to cause severe pneumonia, this is less common. A high risk of bacterial sepsis and ARDS is associated with influenza. [125]

In study Catia Cilloliz et al ilIn patients hospitalised with influenza A H1N1 pneumonia, bacterial co-infection was common (33 percent). Higher platelet count at entrance and underlying COPD were the most important indicators of bacterial co-infection. Bacterial co-infection was linked to a higher PSI risk class but did not impact death in these patients. In this work, two Spanish hospitals with expertise in the study of respiratory illnesses report all consecutive patients admitted with influenza A H1N1 pneumonia throughout the whole 2009–2010 pandemic period. In contrast to earlier trials,12e14 we included both critically and non-critically many patients. Our data show that COPD and an elevated platelet count were the strongest predictors of bacterial co-infection occurring often in influenza A H1N1 pneumonia. Bacterial co-infection did not affect these patients' mortality while being linked to greater severe scores upon admission. [126]

In study by Meifang Yang, Hainv Gao, et alPatients with bacterial co-infection and H7N9 infection had a more serious state. In individuals with influenza A (H7N9), elevated PCT is an effective diagnostic for the detection of bacterial co-infection. PCT concentrations above 0.81 g/L strongly imply bacterial co-infection in H7N9 influenza patients. Our recommendation is that individuals with PCT levels more than 0.81 g/L and bacterial co-infection symptoms receive empiric antibiotic therapy. In addition, local epidemiological traits, drug resistance patterns, S. aureus, and MRSA should be taken into account while selecting an empiric antibiotic therapy. To

determine the occurrence, more large sample size prospective and intervention research on bacterial co-infection are required. [127]

In study by Nirav S. Shah.et.al In the aetiology of severe influenza infection, this study emphasises the significance of bacterial co-infection. Prevention strategies to combat co-infection include guaranteeing high influenza vaccination rates, vaccination against S. pneumoniae and H. influenzae, optimum antiviral timing, and early and appropriate antibiotic therapy targeting MRSA and Pseudomonas. It's crucial to use MRSA-specific therapy, especially when treating patients with community-acquired pneumonia. It is crucial to comprehend the intricate and synergistic interactions between influenza and bacteria in order to reduce mortality in upcoming seasonal and pandemic influenza seasons. [128]

In study by Xiaoyuan Bai et.al IAV can promote bacterial co-infection in a previously unknown way, according to this study's results. IAV infection resulted in an upregulation of CypA, which prevented the ubiquitin-mediated proteasome degradation of FAK. CypA then facilitated GAS co-infection by increasing the expression of integrin a5 and actin rearrangement via the FAK/Akt signalling pathway. The clinical phenomenon that the use of CsA in the context of transplantation does not increase, and may actually decrease, the incidence of infection in comparison to that during standard immunosuppressive therapy may also be explained by CypA deficiency or CsA treatment significantly inhibiting GAS infection or IAV-GAS co-infection (Kim and Perfect, 1989). These findings present a possible treatment approach and increase our understanding of the biological roles of CypA in bacterial infection and virus-bacterial co-infection.

In study by Yingzhi liu et al, In this retrospective cohort study, which included 19,361 adult

patients hospitalised for respiratory infections, 5.6% had a viral-bacterial co-infection that was validated by a lab test. These individuals had considerably higher 30-day mortality rates than those who had bacterial infection alone, viral infection alone, or clinically suspected co-infection. In this sample of patients, the prevalence of viral-bacterial co infection was lower than previously reported

(2 77 percent). Heterogeneity study population kind of viral respiratory disease is probably to blame for this .detection methods case definition, community-acquired or nosocomial co-infection, seasonal variation and pandemics. Subgroup analysis of ICU patients showed that although the 30-day mortality of the co-infection group was significantly higher than those with viral infection alone, there was no difference to bacterial infection alone group. This may be limited by the small sample size in the bacterial infection alone group. mortality in patients with clinically suspected viral bacterial co-infection was similar to those with viral infection alone and lower than those with laboratory-confirmed co-infection.

Another notable finding of this study is that H. influenzae (226/1087, 20.8%), P. aeruginosa (180/1087, 16.8%), and S. pneumonia (123/1087, 11.3%) were the three most common bacterial pathogens in patients with laboratory-confirmed viral-bacterial co-infection Given that all co-infection in this cohort was presumably community-acquired (samples collected within 48 h of hospital admission),P. aeruginosa as a more prevalent co-pathogen is surprising. P. aeruginosahad been a rare cause of community-acquired respiratory infection (0.8%_1.9%) . However, recent studies reported an increasing rate of P. aeruginosa co-infection with influenza . Inour cohort, among the patients who detected with P. aeruginosa,15.0% (27/180) and 44.4% (80/180) were diagnosed with congestive heart failure and chronic pulmonary disease, respectively. In patients with chronic disease, frequent institutionalized care and recent hospitalization are risk factors for

community-acquired P. aeruginosa infection . This may explain the higher prevalence of this pathogen in our cohort.

In study by Masafumi Seki et.al Patients who had both bacteria and the influenza virus in their systems had more severe cases of pneumonia than those who only had bacteria. The frequent

rise in secondary bacterial infections and subsequent development of severe pneumonia may be significantly influenced by underlying chronic lung disorders. Possible causes of such severe pneumonia include the influenza virus and the human immune system. More research is required to pinpoint the pathophysiology of lung pathology and to determine the best forms of treatment and prevention.

In study by Dennis E, Metzger and Keer Sun, The findings presented above suggest that an induced adaptive immune response against viral infection (an intracellular pathogen) compromises innate immune defences against bacterial infection (an extracellular pathogen). This would explain why secondary bacterial infections in the clinic happen just when the patient is starting to heal and the virus is starting to be eliminated from their lungs. Although some researchers discover a considerable drop in the overall number of alveolar macrophages in influenza-infected lungs, other studies have not seen a significant fall in numbers but have instead discovered a changed phenotype. Along with this, the phagocytic lung cell population undergoes a change in function from cells that mediate baseline levels of innate protection through phagocytosis and production of proinflammatory cytokines, In actuality, virus-induced IFN-g increases MHC class II expression

while downregulating alveolar macrophage expression of the scavenger receptor MARCO. Given that murine alveolar macrophages normally suppress adaptive immune responses, their alteration on day 7 of influenza infection, along with type 1 IFN-mediated inhibition of neutrophil recruitment, may be a mechanism that evolved to enable enhanced induction of specific anti-influenza T cell memory in the respiratory tract, even if it temporarily sacrifices innate defense against bacterial pathogens. This new paradigm ought to eventually enable the creation of innovative immune intervention methods for the comprehensive management and prevention of subsequent bacterial infections following influenza.

In study by Adrienne G. Randolph et al, In this multicenter PICU cohort, MRSA-coinfected infants with influenza-related acute respiratory failure had more severe illnesses than children with other bacterial infections or no bacterial co-infection, and they were nine times more likely to pass away. Within 24 hours of PICU admission, anti-MRSA drugs were linked to positive hospital outcomes. A child's risk of death was 5.5 times higher when early vancomycin was used as their only anti-MRSA treatment than when early vancomycin along with the early use of another MRSA-fighting medication.

In study by E. Cuquemelle _ C. Brun-Buisson et al, We present data on 103 patients with severe A/H1H1 influenzae pneumonia, of which nearly 50% had documented bacterial co-infections without receiving prior antibiotic therapy; Streptococcus pneumoniae was the predominant cause of co-infections. A PCT level of 0.8 lg/l or higher was found to be necessary to distinguish between isolated viral and mixed (bacterial and viral) pneumonia in the 52 individuals in whom PCT was assessed.

In study by Amreeta Dhanoa et al, In comparison to past studies, the rate of bacterial co-infection among our H1N1 hospitalised patients was higher (28 percent). In a large laboratory study conducted in the United States, co-infection rates with bacteria were shown to be similar to our analysis, while virus copathogen detection was only very infrequent. In contrast to earlier studies' findings that patients with H1N1 infections tended to be younger, those over 50 had a higher frequency of bacterial co-infection in our study. bacterial infections are still a Infections that are of concern can coexist and significantly affect mortality in prior influenza pandemics; their involvement in the ongoing H1N1 pandemic is still developing. Bacterial lung infections have been linked to an increase in fatal H1N1 cases, according to recent postmortem research.

A more recent study contradicted a previous study that found bacterial co-infection was not a significant factor in the development of severe illness.

In study by Dalva Assuncao Portari MANINI et al, In subjects from three different So Roque, SP, Brazil localities, it was discovered that Stenotrophomonas maltophilia co-infected 21.11 percent of the thirteen confirmed influenza virus in samples isolated from pigs, horses, and humans (working as veterinarians or feeding the animals) from locations a and c during the influenza season. At the time of these experiments, the confirmed influenza samples at site b did not show signs of bacterial co-infection. There was no evidence of influenza (negatives) in the final 34/47 samples gathered. As a result of the bacterial protease and elastase cleaving and activating the HA of these viruses, this co-infection led the influenza virus to worsen. This was evident from the strong cytopathic effect of the infected cell cultures. It was determined that co-infection between bacteria and the influenza virus is possible and poses a risk to susceptible hosts. Co-infection that

leads to respiratory tropism of the influenza virus, such as that caused by Stenotrophomonas maltophilia protease, represents a strong mutual aid, facilitating either opportunist bacterial invasion into the respiratory tract or exacerbation of the viral infection through the cleavage activation of the HA influenza.

In study by Alexandre Elabbadi et al , S bacterial co-infection rates in critically ill adult patients with severe COVID-19 pneumonia. All patients admitted to the Tenon University-teaching hospital's intensive care unit (ICU) between February 22 and May 7 of 2020 who had severe COVID-19 pneumonia that had been confirmed in the lab were included. Within 48 hours of ICU admission, samples of the respiratory system were collected. 101 patients were sent to the ICU for severe pneumonia caused by COVID-19 during the study period. On arrival to the ICU, the

majority of patients (82.2 percent; n = 83) had intubations and were being mechanically ventilated. 20 respiratory tract samples were collected overall (19.8%) within the first 48 hour.staphylococcus Nearly half of the early-onset bacterial etiologies were attributed to the primary pathogen, aureus. We discovered a high incidence of early-onset S. aureus-predominant bacterial co-infection during severe COVID-19 pneumonia.

In study by Leili jia et al, Failed antibacterial resistance, synergistic immunological pathogenicity, and failed tolerance are only a few of the factors that contribute to increased mortality after influenza-associated bacterial co-infections. Because it is still a relatively new idea in animal immunology, tolerance needs to be given more attention in order to fully understand how it affects co-infection. Co-infections with viruses or bacteria make it more difficult to treat either infection.

For instance, it is unknown if antiviral medications that reduce viral load have a impactconcomitant bacterial contamination Similarly, it is unknown if treatments to reduce human inflammatory responses to bacterial co-infection are effective. In order to choose the best therapeutic strategies to address the main issue, it may be crucial to distinguish between failed resistance and failed tolerance. It is conceivable to create new recombinant vaccines that contain both influenza and bacterial antigens because, while by unidentified processes, mortality during co-infection can be reduced when bacterial infection occurs prior to influenza challenge.

In study by Kevin J. McHugh.et al In this research, we show the value of utilising an unique outbred mouse line to investigate the genetic phenotype of viral and bacterial pneumonia severity. We can draw correlative conclusions about the characteristics of severe illness aetiology by studying a genetically heterogeneous animal population. The definition of determinants, or biomarkers, of severe disease that may be connected to morbidity and death, is a particular use of

this method. Examining markers of increased clearance or lower morbidity can provide provide mechanistic insight into immunological host defence processes. The most recent new H1N1 pandemic caused numerous Studies were undertaken to investigate the link between serum cytokines and the severity of the disease A strong connection between IL-6 levels and influenza severity emerged as the main consistent conclusion in all research. Our mouse study found a strong correlation between ongoing IL-6 production and higher morbidity. IL-6 has been demonstrated to be crucial for the host defence against the influenza virus in mice studies. Increased neutrophil mortality was seen in IL-6 receptor- and IL-6-deficient animals. compared to WT mice, the lung damage was worse and the viral persistence was higher. Furthermore, IL-6 -/- mice displayed

decreased CD4+ T cell memory responses to influenza virus, possibly as a result of increased regulatory T cell activation. These findings indicate that inhibiting IL-6 during influenza virus infection is unlikely to be a successful treatment strategy. However, the level of IL-6 production could serve as a helpful biomarker for the development of severe disease. TNF- was also found to positively correlate with the severity of the flu in human.

TNF- was also overexpressed in our mouse model and showed a substantial connection with increased morbidity during blood tests in addition to IL-6.

In study by Gustavo Palacios.et al In both the current and prior influenza pandemics, S. pneumoniae has been linked to both morbidity and mortality. However, this study is the first to show the predictive value of non-invasive antemortem S. pneumoniae infection identification, and it may offer guidance for therapeutic therapy. Secondary bacterial infections are thought to contribute to H1N1 influenza morbidity and mortality. Acute bacterial pneumonia-like histopathologic features were frequently found when lung tissue samples from deceased 1918

influenza cases were analysed. Lung samples from 96 fatal 1918 influenza pandemic victims were cultured after death and found to include S. pneumoniae (23.2% S. aureus (7.3%), H. influenzae (18.0%), and emolyticus (180.0%) (4.7 percent) The presence of S. pneumoniae in NPS predicts a severe illness outcome in our investigation of H1N1pdm sufferers from Argentina. S. pneumoniae exposure has an especially high risk for people aged 6 to 55. In fact, using a multivariate logistic regression model that takes into account the presence of S. pneumoniae along with other viruses outside influenza and a chi-square test, the severity of disease in this low risk category can be

predicted with 90.97% accuracy.), S. medical condition at risk. The pathophysiology of the influenza virus and S. pneumoniae working together is outlined. It has been shown by Madhi and colleagues that vaccination against S. pneumoniae lowers the incidence of pneumonia brought on by influenza A, RSV, and parainfluenza viruses. Influenza neuraminidase has been demonstrated in animal models to Remove sialic acid residues to reveal the respiratory epithelium's pneumococcal receptors. In fact, neuraminidase potency and an influenza virus strain's ability to cause pneumonia are connected.

In study by Amber M. Smith et.al ki We infected groups of mice with either the H1N1 subtype influenza A virus A/Puerto Rico/8/34 (PR8) or a variant expressing the 1918 PB1-F2 protein (PR8-PB1-F2(1918)), and then seven days later with either type 2 D39 or type 3 A66.1 of the two S. pneumoniae strains, in order to address the mechanisms and determine the influences of pathogen dose and strain on disease. We found that after bacterial infection, virus titers initially rise and then steadily fall. Bacterial titers rise quickly to high values and remain high. Utilizing a To investigate the linked interactions and research the predominate regulating mechanisms, use a netic model. We

propose that increased viral release from infected cells causes viral titers to rebound in the presence of bacteria, whereas impaired alveolar macrophage function causes an increase in bacterial titers. Initial bacterial dosage has an impact on dynamics, while the expression of the influenza 1918 PB1-F2 protein has no such effect. Our model offers a platform for studying the interactions between the pathogens during co-infections and reveals dynamical variations dependent on inoculum size and strain.

In study by Denise E.Morris et al Viral infection helps bacterial infection in several ways, including by exposing or offering more sites for adhesion, reducing immune responses, and causing cell and tissue death, which promotes bacterial growth and the development of invasive infection. Therefore, bacterial infection has the potential to affect clinical outcomes and disease severity. Virus and bacterial co-infection can, of course, benefit one another, promoting viral infection, which is harmful for the general public's health. Even if antibiotics can lessen the effects of , co/secondary bacterial infection, we still need to better understand the interactions between viruses, Understanding all illness pathways, including those involving microorganisms and their host especially in view of the rise in antibiotic resistance and the adaptability and resistance to vaccine-induced immunity of microorganisms. In order to inform clinical treatment and development, particularly in the context of an influenza epidemic or pandemic, it is crucial to analyse the strains and types of bacteria and viruses that are spreading among and continuing to be transmitted across the general populace.

In study by Rhiannon R. Penkert et al The only cytokine or chemokine that was reduced in VAD animals as compared to controls was RANTES. Because RANTES can be produced by and can control T cells, low RANTES production can be both a cause and an effect of T-cell dysfunction.

Therefore, the low expression of RANTES shown in naive VAD mice may have contributed to the poor recruitment of T cells during influenza infection, which may explain the decreased expression of RANTES late in infection. The aberrant B-cell responses in VAD mice were accompanied by alterations in cytokine/chemokine production and inadequate T-cell recruitment. Although B cells

were seen in the lungs of VAD mice, but they were poorly organised, which may help to explain why VAD is frequently associated with low antibody production. The poor B-cell organisation seen in our study may be explained by the low CD4+ T-cell frequencies, while vitamin A can potentially directly affect B-cell formation and function, making them more susceptible to shocks. Although vitamin A has been studied as an anti-inflammatory in vitro, its effects in vivo are frequently stimulatory rather than inhibitory of adaptive immunity. When vitamin A encourages functional CD4+ T cells, CD8+ T cells, and B cells in the respiratory tract may stop the spread of the pathogen, averting cell death and immunopathology. Viral clearance is impaired in the absence of vitamin A, and inflammation does not heal effectively. Another contentious issue is the administration of high-dose VASs to hospitalised patients with respiratory illnesses.

A benefit was demonstrated among patients hospitalized with measles in the developing world. Before acquisition of new clinical data, a cautious approach may be to encourage adequate dietary intake of vitamin A and to reserve VASs for individuals who cannot access vitamin-rich foods.

In study by Ignacio Martin loeches et al, According to the findings, co-infection is now found in one out of every six critically sick patients who are brought to the ICU and have a severe influenza virus infection. This co-infection rate has been rising over the past few epidemics. Almost all patients (with or without co-infection) received antibiotic medication, making co-infection with influenza an independent risk factor linked to greater ICU mortality. Surprisingly, the

administration of the proper antibiotic medication was not linked to a better result. Both epidemiological and translational research should focus more on the pathogenicity of influenza and

the intricate host-pathogen interactions in patients who have co-infection.

AIMS

AND

OBJECTIVE

AIM OBJECTIVES:

(1) To estimate the prevalence of influenza disease with secondary bacterial infection.

(2) To establish a relationship between the disease outcome of secondary bacterial infection in viral influenza patients.

RATIONALE

The objective to do this study is to establish the correlation between influenza infection and secondary bacterial infection the study will comprise of various research articles,orginal articles and review articles based on the topic.

MATERIALS

AND

METHODS

METHODOLOGY

AREA OF STUDY: Virology and bacteriology.

RESEARCH OF DESIGN: Qualitative and Quantitative.

DATA TYPE: secondary mode of data collection.

a)Data from various journal.

b)Data from books.

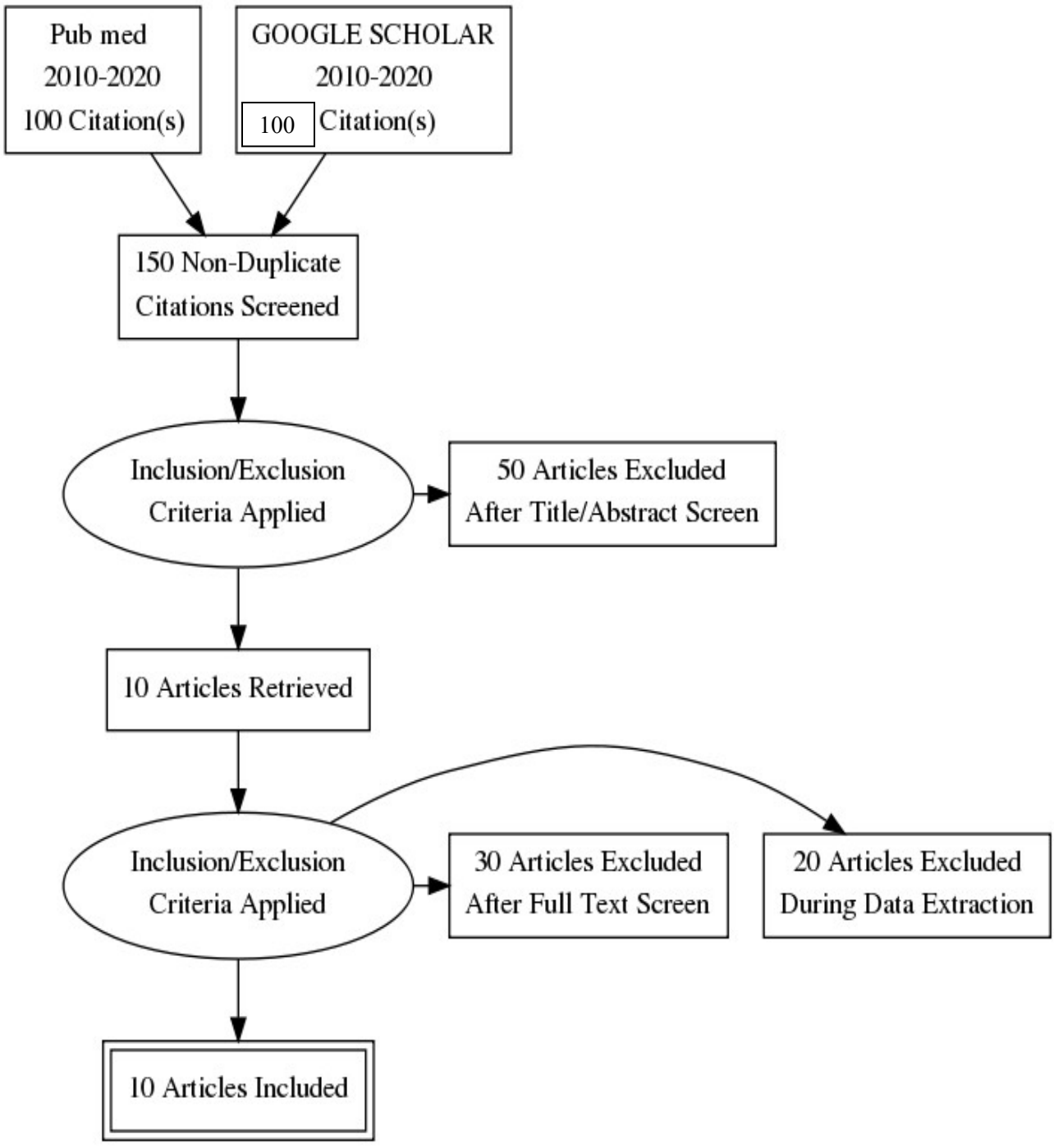
c)Online data from various literature reviews.

RESEARCH TOOL: secondary data from published report of articles.

TIME FRAME: All the studies in indexed journal from 2010 to 2020.

SEARCH ENGINE: Pub med, Google scholar.

ETHICAlCLEARENCE: Were applied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After Title/Abstract Screen
10 Articles Retrieved
Inclusion/Exclusion
Criteria Applied
30 Articles Excluded
After Full Text Screen
20 Articles Excluded
During Data Extraction
10 Articles Included

OBSERVATION

AND

RESULT

S.No.	AUTHOR	YEAR	COUNTRY	STUDY FINDING
1.	Ignacio Martin-Loeches1,2* Et.al	2016	Berlin Heidelberg	There were 482 (16.6%) co-infected patients out of 2901 ICU patients with influenza. From 11.4 percent (110/968) in 2009 to 23.4 percent (80/342) in 2015, there were more incidences of co-infection (P 0.001). Patients with co-infection tended to be older (adjusted odds ratio (aOR) 1.1, 95 percent confidence interval 1.1-1.2; P 0.001) and more frequently immunosuppressed due to prior HIV infection (aOR 2.6; P 0.001) or medication (aOR 1.4; P = 0.03). Co-infection was a risk factor on its own for ICU mortality (aOR 1.4; P 0.02), 28-day mortality (aOR 1.3; P = 0.04), and hospital mortality (aOR 1.9; P 0.001).
2.	Rhiannon R. Penkert, Et.al	2021	America.	The immune system was out of balance in naive VAD mice lungs. The frequency of neutrophils increased, and RANTES—a chemokine important for T-cell homing and recruitment—which is regulated on activation of normal T cells produced and secreted—was significantly reduced. Failures in CD4+ T-cell recruitment and B-cell organisation into lymphoid tissues in the lung were seen in VAD mice following influenza virus infection. VAD animals had slower viral clearance and higher viral titers than control mice. Innate cell subsets and pro-inflammatory cytokines were overexpressed in the lungs. Arginase, however, a sign of alternatively activated M2 macrophages,

3.	Denise E. Morris1 Et.al	2017	Malaysia	The fourth-leading cause of death worldwide is lower and upper respiratory infections. Respiratory infection epidemic and pandemic outbreaks are a serious medical concern because they frequently result in significant sickness and a high mortality toll, usually within a brief period of time. A significant contributor to epidemic and pandemic infection is influenza. Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus have been described as the most frequent causes of bacterial co/secondary infection, which further enhances morbidity and mortality of influenza infection. It is critical to track the epidemiology of pathogens in circulation to guide therapeutic development and treatment, especially in the midst of an influenza epidemic or pandemic, given the rise in antibiotic resistance and vaccine evasion.
4.	Amber M. Smith Et.al	2013	United States of America	.Influenza lung titers for PR8 and PR8-PB1 both start off exponentially rising to maximal titers of 3:2|107 TCID50/ml lung homogenate and 3:2|108 TCID50/ml lung homogenate, respectively. Mice injected with PR8 saw viral titers peak at 72 hours after inoculation (p.i.), whereas mice injected with PR8-PB1- attained high titers (equal to the peak of PR8) a little sooner at 48 hours p.i. However, PR8-PB1- Through day 4 after injection, F2(1918) readings are still high. Then, as the mice start to recover, the viral titers of both strains start to fall.

5.	Gustavo Palacios1 Et.all	2009	Canada	MassTag PCR was used to check for the presence of 33 viral and bacterial respiratory pathogens, as well as NPS samples from 199 H1N1pdm-positive patients, which were collected between June 23 and July 4 as part of an investigation into the pandemic H1N1 influenza outbreak in Argentina. All samples were tested using the WHO-approved Real Time PCR H1N1pdm assay to ensure that H1N1pdm was present before MassTag PCR experiments began.
6.	Kevin J. McHugh1 Et.al	2013	United States of America	in the context of mouse influenza (A/ We selected to create a novel model for influenza virus infection in a recently accessible outbred mouse line in order to most effectively explore the molecular profile of influenza virus infection severity in mice. We used Jackson Laboratories Diversity Outbred (JDO) mice to do this. As an enhancement over current outbred colonies, Jackson Laboratories just debuted this unique line. In order to protect founder genomes and prevent allelic loss, JDO mice were created using an unique outbreeding technique. The Collaborative Cross mice from which the JDO founders were descended (CC). The CC is a sizable collection of inbred mouse strains produced through an eight-way cross between a batch of mice that comprises specimens from three different strains descended from wild animals. Recent studies utilising CC mice have looked on severity markers. infection by the virus PR/8/34). To maximise allelic variation across the entire genome, we have adopted the JDO model in this study. Jackson Laboratories provides an array chip to map more than 620,000 single

				nucleotide polymorphisms, which is an additional benefit (SNP). In the future, this would enable us to execute SNP. analysis on mice with interesting phenotypes in response to influenza virusand/or co infection.
7.	Yingzhi Liu et al,	2021	Hong Kong	St 8451 (53.1%) clinically suspected and 1,087 (6.8%) laboratory-confirmed viral-bacterial co-infections were found in 15,906 patients with respiratory viral infection. The three most prevalent bacterial pathogens in the group with laboratory-confirmed co-infections were Streptococcus pneumoniae (123/1087), Pseudomonas aeruginosa (180/1087), and Haemophilus influenzae (226/1,087, 20.8 percent), among all bacterial species. respiratory viruses and methicillin-resistant or non-pneumococcal streptococci c The greatest mortality rate in this sample was linked to aphylococcus aureus (9/30, or 30%), and 13/48, or 27.1%. Those with laboratory-confirmed co-infection had higher 30-day mortality (p = 0.028) and ICU admission rates (p 0.001) compared to patients in other infection groups. These findings persisted even after propensity score matching was used to control for potential confounders. Additionally, the mortality rate was noticeably greater among individuals with co-infections that were proven in the lab. ompared to

				patients with bacterial infection alone.
8.	Masafumi Seki et al.	2007	Fukuoka	In comparison to individuals with bacterial pneumonia alone, those with influenza virus infection were more likely to have complications with chronic lung illnesses. The two groups' heart rates and body temperatures were likewise statistically different. The severity of pneumonia, as assessed using the criteria of the Japan Respiratory Society (JRS) and/or the Infectious Diseases Society of America (IDSA), as well as CRP levels, were all significantly worse in patients with bacterial pneumonia who were also infected with the influenza virus than in patients with bacterial pneumonia alone.

9.	Adrienne G. Randolph et al,	2018	Boston	ant171 children (127 influenza A, 43 influenza B). Children with influenza-MRSA pneumonia were older than those with non-MRSA (N = 61) or no (N = 79) bacterial co-infections (N = 30, 87 percent previously healthy). In comparison to either group, influenza-MRSA was linked to higher rates of leukopenia, acute lung damage, vasopressor use, extracorporeal life support, and mortality (P .0001). MRSA increased the risk of influenza-related death from 4.3 percent to 40 percent (relative risk [RR], 9.3; 95 percent confidence interval [CI], 3.8-22.9). If treatment included a second antibiotic, death was 12.5% (N = 2-16) of 29/30 MRSA-infected kids who received vancomycin during the first 24 hours of admissioni-MRSA antibiotic compared to 69.2 percent (N = 9/13) with vancomycin monotherapy (RR, 5.5; 95 percent CI, 1.4, 21.3; P =.003). Initial trough levels were unaffected by vancomycin dosage; 78 percent were less than 10 g/mL.
10.	Catia Cill_oniz	2012	Barcelona	CAP experienced a 19 percent prevalence of influenza A H1N1 infection during the pandemic era (n, 667). 42 patients (or 33 percent) out of the 128 we evaluated had bacterial co-infection. Streptococcus pneumoniae (26, 62 percent) and Pseudomonas aeruginosa were the most frequently isolated bacterial pathogens (6, 14 percent). Chronic obstructive pulmonary disease

				(COPD) and an increase in platelet count were predictors of bacterial co-infection. Nine percent of patients in hospitals passed away. Mortality risk factors included septic shock and age more than 65. mechanical ventilation is required, too. Although individuals with bacterial co-infection had greater Pneumonia rates at presentation

DISSCUSION

Although there has long been knowledge of the risk that bacterial co-infections in influenza patients provide, the extent of co-infection has not been carefully investigated. Clinicians can better balance the goal to reduce bacterial infection-related patient morbidity and death with the effects of inappropriate antibiotic usage on both the patient and society by being aware of the possibility of bacterial co-infection in hospitalised influenza patients. We conducted a systematic review and meta-analysis of studies published since 1982 to determine how frequently bacterial co-infection occurs in patients with laboratory confirmed influenza.

Clinicians continue to struggle in separating viral from bacterial infections. The misuse of antibiotics in individuals with viral illnesses is a well-known consequence of this diagnostic ambiguity. If a patient has influenza-related pneumonia or is thought to have a bacterial infection, the CDC advises using both antiviral drugs and antibiotics at the same time. However, as other observational studies have demonstrated, influenza patients admitted to the hospital are more likely to be given antibiotics than antiviral drugs. According to our research, while hospitalised patients with moderate to severe influenza may also have bacterial and viral pathogen infections, the majority of patients are probably not going to. In light of this, even though recognising and treating possible bacterial co-infections is crucial, especially community-acquired Clinicians should think about treating potential underlying viral processes as well, especially for high-risk patients, when treating pneumonia where bacteria are difficult to identify. Our research also suggests that routine cultures are advised in patients hospitalised with influenza, particularly those who started antibiotic therapy empirically, in order to prevent the overuse of antibiotics. Based on the microbiological findings, antibiotic medication may then be reduced as needed. Consequently, the study does not

represent the vast majority of influenza patients, including asymptomatic individuals, who are hospitalised. This points up a hole in the existing literature because it is still unclear how often outpatients with confirmed influenza have bacterial co-infection. Collecting or finding a bacterial sample. This lack of statistically significant variation may be the result of unrecorded differences in the studies, such as genetic variations in the populations, regional variations in the severity of viral or bacterial illness, unrecorded patient comorbidities, treatment variation, or as previously mentioned, antibiotic use. Lastly, despite our best efforts, we were unable to explain the notable variation between trials. It could not be explained by variations in the age, year, location of study enrolment, study design, study size, or procedure of the patients. The high heterogeneity and lack of statistically significant covariates also indicate the need for further research to better understand bacterial co-infection rates, pathogen-specific outcomes, the impact of increased testing for both bacterial and viral pathogens, and the effectiveness of interventions, such as increased antiviral drug use. These are especially crucial in view of recent discoveries that suspected community-acquired pneumonia infections were more frequently discovered to contain viral pathogens than bacterial pathogens.

CONCLUSION

Although the findings were extremely varied, we discovered that bacterial co-infection of hospitalised patients with influenza is frequently common. S. pneumoniae and S. aureus were the two main co-infecting species in the investigations, although numerous additional organisms were also discovered to be infectious. In order to prevent exposing patients to the hazards of extended needless antibiotic usage, healthcare providers should take into account the possibility of bacterial co-infection in patients hospitalised with influenza. Possible co-infection with When choosing the best antibiotics, MRSA should be taken into account, especially for community-acquired pneumonia infections. Therapy should be stopped or scaled back as needed based on the microbiological results. In the final analysis, the frequency of co-infection in the total influenza patient population, including outpatients, should be better described.

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unique	aeruginosa coinfection.	
unique	However, no definitive relationship has been established.	
unique	Even though oseltamivir and empirical antibiotics were administered early, our pati....	
unique	One study found that after using peramivir, patients with complicated influenza had....	
unique	Peramivir may be an option for treating acute influenza infection. Because P.	
unique	aeruginosa is a pathogen that can co-infect with influenza A(H1N1)pdm09, clinician....	
unique	in mind when treating patients who have influenza-associated pneumonia and severe I....	
unique	A timely antiviral agent and antibiotic use could save a life.	
unique	The 1918 influenza (H1N1) pandemic killed over 50 million people worldwide (Johnson....	
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unique	Similarly, during the 2009 influenza pandemic, bacterial coinfection was positivel....	
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unique	In patients in intensive care units, bacteria such as Streptococcus pneumoniae (S.	
unique	P), group A streptococcus (GAS), Staphylococcus aureus, and Haemophilus influenzae (H.	
unique	I) aggravate their illness (Estenssoro et al.	
unique	, 2010; Farias et al., 2010; Rice et al., 2012).	
unique	Antibiotic use may reduce influenza-related deaths by limiting bacterial coinfections.	
unique	However, as bacterial antibiotic resistance rises, IAV-caused bacterial coinfectio....	
Plagiarized	diseases (20).	Compare