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Multidrug Resistance in Microorganisms Causing Ventilator-Associated Pneumonia: A Literature Review

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ABSTRACT

Purpose: *Studying Multidrug Resistance (MDR) in Ventilator Associated Pneumonia (VAP) is an essential for several key reasons. Firstly, it's critical for enhancing patient outcomes and public health. Understanding the basic mechanisms of MDR helps in developing new treatments and infection control methods. Knowledge of MDR prevalence and patterns aids in choosing the right emperical antibiotic therapy, crucial for patient survival, as incorrect initial treatment is linked to higher mortality in severe cases like VAP. Research in this area broadens our understanding of bacterial resistance, host- pathogen dynamics and the impact of antibiotic uses, paving the way for new diagnostics, therapies and prevention strategies. Effective management of MDR in VAP can also leads to reduced hospital stays and lower healthcare cost by minimizing the need for expensive and toxic alternative antibiotics.*

Design/Methodology/Approach: *Understanding and management of MDP in VAP contributing to improved healthcare practices and patient outcomes.*

Findings/Result: *Based on different studies, prevalence of MDR pathogens, antibiotic resistance patterns, risk factors, genetic mechanism of resistance, treatment efficiency, patient outcomes, infection control effectiveness, economic impacts, emerging trends, antibiotic stewardship can easily be understood. It is crucial for improving treatment protocol, infection control and policies, ultimately enhancing patients care in critical control settings.*

Originality/Value: *Advances in genomic sequencing have enabled more detailed studies into the genetic basis of antibiotic resistance. This provides insight into how resistance gene is acquired and spread among bacteria. This helps in choosing the right treatment protocol at the earliest.*

Paper Type: *Literature review*

Keywords: Multi Drug Resistance, Ventilator Associated Pneumonia, Prevalence, Epidemiology, nosocomial infection.

1. Introduction:

A major problem in the treatment of illness, particularly infectious diseases and cancer, is Multi Drug Resistance (MDR). It describes the occurrence in which a cell or a collection of cells grows resistant to a variety of medications that would have otherwise worked well against them. The efficacy of medical therapies is severely hampered by this resistance. Multidrug resistance is a common occurrence in infectious illnesses namely bacterial infections, wherein gems develop resistance to a numerous drug. The decreasing efficacy of conventional antibiotic therapies due to this is a global problem that necessitate the use of stronger, more costly, and frequently hazardous medications. One of the primary mechanisms of attaining MDR is by over expressing certain Efflux pumps in the cell membrane. Medications are aggressively exported from the cells by these pumps, which lowers the intracellular concentration and effectiveness of the medication. The P-Glycoprotein (P-gp) which is encoded by gene MDR 1 in human beings, is considered as a well-known example for Efflux pumps [1] [2]. The development of novel medications that can circumvent or inhibit resistant mechanisms, the use of combination drugs to delay the onset of resistance and the implementation of personalised medicine technique to customise treatments depends on the unique resistance patterns of particular infections which are important aspects of the research on MDR [3].

A kind of lung infection known as Ventilator Associated Pneumonia (VAP) affects patients using mechanical ventilation breathing equipment at the hospitals. As the name suggests, it mostly affects patients who are on a ventilator, usually with a tracheostomy or endotracheal tube. VAP is a major problem in critical care units (ICUs) since it is linked to greater morbidity, longer hospital stays, higher healthcare expenses, and a higher fatality rate. It usually develops 48hrs or more after intubation. Because patients in ICUs frequently have severe illness and/or compromised immune system, which makes them more vulnerable to infections, the condition is especially difficult for them [4].

The aspiration of stomach or oropharyngeal contents into the lower respiratory tract, which is colonised with potentially harmful microbes, is the pathophysiology of VAP. Because of the endotracheal tube and the mechanical ventilation settings, this might result in pneumonia in a patient whose immune system is compromised. Prolonged mechanical ventilation, history of antibiotic exposure, the existence of underlying chronic lung disease and immobility are risk factors of VAP. Although the organism causing VAP might be different, they frequently include bacteria such as Pseudomonas aeruginosa Staphylococcus aureus which includes Methicillin Resistant Staphylococcus aureus (MRSA) and other gram-negative organisms [5].

The symptoms of VAP include fever, productive cough and raised white blood cell count which are non-specific and can be associated with a various number of other illnesses, making diagnosis difficult. As a result, a mix of clinical, radiographic and microbiological data are used in diagnosis. The management of ventilated patients has a strong emphasis on preventing VAP. Appropriate antibiotic treatment, informed by local microbiological patterns and specific patient variables is crucial when VAP is suspected or confirmed [6].

2. Related Works:

2.1 Ventilator Associated Pneumonia

VAPs identification as a separate clinical entity can be linked to the wider advancement and growing application of mechanical ventilation, which gained popularity in 20th century, especially following World War II. With the development of positive pressure mechanical ventilators in the 1950s and their growing application in Critical Care Units (ICUs) novel respiratory problems in intubated patients become apparent [7]. During the 1960s and 1970s, the risk of pneumonia in patients receiving mechanical ventilation increased due to the development of critical care medicines and ventilator-dependent patient care. Factors contributing to this increased risk included the presence of an endotracheal tube, decreased mucociliary clearance and the possibility of secretion aspiration [8].

Table 1: Review on Ventilator Associated Pneumonia (VAP)

S. No.	Work	Focus	Reference
1	Epidemiology of VAP	Bacterial pathogens, epidemiology and mortality	Craven, (2000). [9]
2	Epidemiology, etiology, and diagnosis of hospital-acquired pneumonia and ventilator-associated pneumonia in Asian countries	Etiology, risk factors, prevention, diagnosis, management and prevention of VAP	Chawla, (2008). [10]
3	Risk and prognostic factors of ventilator-associated pneumonia in trauma patients	Assess the risks and prognostic factors with respect to immunological responses.	Cavalcanti, (2006). [11]
4	Does this patient have Ventilator Associated Pneumonia?	Routine bedside evaluation coupled with radiographic information for the diagnosis	Klompas, (2007) [12]
5	Treatment Guidelines and Outcomes of Hospital-Acquired and Ventilator-Associated Pneumonia	Prediction of microorganism, selection of adequate antibiotic	Torres et al. (2010). [13]
6	Prevention of Ventilator associated Pneumonia: An Evidence-Based Systematic Review	Semi-recumbent positioning, sucralfate and aspiration of subglottic secretions and oscillating beds	Collard, et al. (2003). [14]

2.2 Multi Drug Resistance in VAP

Microorganisms such as bacteria, fungi, virus and parasites can become resistant to many medications or antibiotics, a condition known as Multi Drug Resistance (MDR), which poses a serious threat to the public health. This resistance develops as a result of genetic changes of acquisition of resistance gene, and it is frequently made worse by the overuse and abuse of antibiotics in agriculture and human medicine. With illness that were formerly easily treatable become more difficult to control, MDR results in longer hospital stays, greater medical expenses and higher fatality rate. A multimodal strategy is needed to combat MDR including, prudent antibiotic usage, better infection control procedures, more surveillance and continuous research into novel treatment options. The WHO and other global health organisations are actively involved in creating plans to deal with this danger to global health, highlighting the necessity of concerted worldwide action [15].

Multidrug resistance (MDR) in Ventilator-Associated Pneumonia (VAP) is a significant clinical challenge. The development of MDR in VAP is largely attributed to the overuse and misuse of antibiotics, along with the hospital environment, where resistant strains can thrive and spread. Managing MDR in VAP requires a combination of strategies, including stringent infection control practices, careful antibiotic stewardship to prevent the emergence of resistance, and the development and use of novel antimicrobial agents. Early and accurate diagnosis, along with targeted antibiotic therapy based on susceptibility patterns, is crucial for effective treatment and control of MDR in VAP cases [16].

Table 2: Review on Multidrug Resistance in VAP

S. No.	Work	Focus	Reference
1	Epidemiology of multidrug-resistant Gram-negative pathogens isolated from ventilator-associated pneumonia in ICU patients	Prevalence of extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases and metallo-β-lactamases (MBLs) and their drug resistance profile.	Gupta, et al. (2017). [17]
2	Management and prevention of ventilator-associated pneumonia caused by multidrug-resistant pathogens	Selecting appropriate antibiotics, optimizing dosing and using timely de-escalation based on antimicrobial sensitivity data	Grgurich et.al, (2014). [18]
3	Multi-drug resistant ventilator associated pneumonia: risk factors and outcomes	investigate MDR pathogens' effect on the VAP patients in order to improve the treatment choice and outcome	Hosamirudsari, et al. (2018). [19]
4	Preventing Ventilator-Associated Pneumonia in Adults: Sowing Seeds of Change	Multidisciplinary prevention team and risk reduction	Donald. (2006). [20]
5	New treatments of multidrug-resistant Gram-negative ventilator-associated pneumonia	Eravacycline, cefiderocol and probably plazomicin	Poulakou. (2018). [21]
6	Pathogenesis-Targeted Preventive Strategies for Multidrug Resistant Ventilator-Associated Pneumonia: A Narrative Review	Oral hygiene with Chlorhexidine (CHX), CHX body washing, selective oral decontamination (SOD) and/or digestive decontamination (SDD), multiple decontamination regimens, probiotics, subglottic secretions drainage (SSD), special cuff material and shape, silver-coated endotracheal tubes (ETTs), vaporized hydrogen peroxide	Cotoia, et al. (2020). [22]
7	Ventilator-Associated Pneumonia: Epidemiology and Prognostic Indicators of 30-Day Mortality	co-morbid malignancy, Simplified Acute Physiology Score, Sequential Organ Failure Assessment score and delayed inappropriate emperical antibiotic treatment	Inchai, et al. (2018). [23]

3. Objectives:

For a number of reasons, it is essential to research MDR in VAP. In ICUs, where patients are frequently very sick and susceptible to infections, VAP is a serious health risk. Treating infections caused by MDR organism is particularly difficult. The following are the objectives of studying MDR in VAP:

(1) To understand the pathogen and its mechanism of resistance

(2) To improve diagnosis technique

(3) To optimize antibiotic uses

(4) To prevent the spread of MDR infections

(5) To improve patient outcomes

(6) To understand risk factors

(7) To enhance patient and public awareness

4. Literature survey:

Ventilator-Associated Pneumonia (VAP) is a severe infection in mechanically ventilated patients, exacerbated by multidrug resistance (MDR), leading to higher mortality, extended hospital stays, and increased healthcare costs. MDR in VAP is caused by complex bacterial mechanisms, including genetic mutations and biofilm formation, and is exacerbated by antibiotic misuse. Diagnosing MDR VAP is challenging due to traditional culture methods' limitations, but molecular diagnostics show promise. Treatment involves a combination of antibiotics, with current applications being limited. Prevention focuses on strict infection control practices, reducing mechanical ventilation duration, and potential vaccine development. Global collaboration is crucial for effective management. A multidisciplinary approach is needed, including ongoing research, novel therapeutic developments, enhanced diagnostics, and robust antibiotic stewardship education. Tackling MDR VAP is crucial for patient health, antibiotic effectiveness, and healthcare system integrity.

Emori et.al, (1993) stated nosocomial infections in the US affect around 2 million patients annually, with the increasing presence of antimicrobial agent-resistant pathogens and high-risk patients in hospitals posing challenges to prevention and control. The growing number of antimicrobial agent-resistant organisms, particularly vancomycin-resistant Enterococcus spp. and Pseudomonas aeruginosa resistant to imipenem, is problematic. The active involvement and cooperation of microbiology laboratories are crucial for infection control programs, including surveillance and epidemiologic purposes [24].

Gould (1994) analysed multiple resistant gram-negative bacteria pose a significant threat to clinical practice due to the lack of new antibiotic classes, widespread resistance, and rapid spread of plasmid-mediated cephalosporinases. Increased use of prophylaxis in immunosuppressed and intensive care patients and the use of new broad-spectrum agents in the community exacerbate the problem. To contain antibiotic resistance, more directed and restricted antibiotic use, better patient education, improved surveillance of sensitivity trends, and better infection control techniques are necessary. The multifactorial nature of illness in many patients complicates the issue, necessitating further study of risk factors and preventative and therapeutic measures [25].

Rello et.al, (1960) explained the aspiration of microbes colonising the oropharynx is the main method that germs enter lower airways in people on mechanical ventilation. Most infections and colonisations of the lower respiratory tract in patients on intubation are caused by a small number of species. For the causative flora of respiratory infections, factors such the underlying condition, duration of intubation, and previous antibiotic treatment are important. During the first week following intubation, the most common respiratory pathogens in critically sick patients are unencapsulated Hemophilus influenzae, Streptococcus pneumoniae, and methicillin-sensitive Staphylococcus aureus. Pseudomonas aeruginosa in particular is a Mult resistant bacteria that causes the majority of pneumonia-related fatalities. Prompt identification and suitable antibiotic treatment are essential in defining the consequences [26].

Wunderink (1995) says that VAP is linked to increased mortality due to virulent pathogens like P. aeruginosa. Inadequacies in antibiotic therapy may contribute to apparent failure. Factors such as resistance, inadequate antibiotic levels, anatomic limitations, and superinfection can cause antibiotic failure. Unrelated factors include misdiagnosis, SIRS, and host immunocompetency. Patterns of apparent failure can help determine the cause, but tracheal aspirate cultures and portable chest radiographs are insufficient for determining the cause. More accurate tests, such as quantitative bronchoscopic cultures and chest CT scans, are often required to avoid spiralling emperical antibiotic therapy [27].

Craven (1997), says that diagnosis is often clinical, but quantitative techniques are more specific for ventilator-associated pneumonia (VAP). Bacterial pathogens can be from endogenous flora, other patients, staff, visitors, or environmental sources. Aspiration is a major route for bacteria entry into the respiratory tract. Recognizing risk factors and overcoming barriers to prevention can reduce HAP rates and associated morbidity and mortality. Practical and easy-to-implement prevention strategies are essential in this cost-containment era [28].

Quinn (1998), in his review examines the role of Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, and Burkholderia cepacia as opportunistic pathogens, with a common feature of resistance to multiple antibiotics. These organisms can cause device-related infections, are resistant to disinfectants, and can spread from patient to patient. It highlights new clinical syndromes, such as P. aeruginosa infections in AIDS patients and also carbapenem's role in selecting A. baumannii, S. maltophilia, and B. cepacia's unique niche [29].

Bonten (1999), explains VAP and its diagnosis using clinical, microbiological, and radiographic criteria, but these methods have low specificity, leading to unnecessary antibiotic use. Bronchoscopic techniques, such as protected specimen brush and bronchoalveolar lavage, have higher specificity but their impact on patient care and costs remains uncertain. Prevention relies on basic infection control practices, with topical nonabsorbable antibiotics consistently reducing VAP incidence but disappointing patient survival and the possibility of antibiotic-resistant bacteria selection [30].

Chalfine et.al, (2000) describe nosocomial pneumonia as a controversial disease due to its lack of standard diagnostic criteria, leading to inappropriate use of broad-spectrum antibiotic therapy and the emergence of multiresistant bacteria. Most pneumonias are endogenous, especially in mechanically ventilated patients, with a higher rate of multiresistant bacteria. Factors influencing antibiotic resistance include hospital stay duration, onset time, prior therapy, and local microbial ecology. Emperical antibiotic treatment must be prescribed before culture results [31].

Vincent et. al, (2001) says about the risk factors include ICU stay duration, mechanical ventilation, trauma diagnosis, and illness severity. Early diagnosis and treatment can be aided by understanding these factors. Preventative strategies include limiting airway colonization and improving host defence mechanisms. Non-invasive ventilation, semi-recumbent nursing, stress ulcer prophylaxis, and selective digestive decontamination are effective methods. Early nutrition can improve host defence, while immune stimulatory therapies like interferon and granulocyte colony stimulating factor require further research [32].

Heininger et.al, (2002) explains on investigations focused on outcome variables have improved the database to estimate diagnostic and therapeutic management strategies. This knowledge has diminished the importance of the discussion on how to diagnose the pneumonia. His review summarizes recent data on epidemiology and mortality, risk factors and prevention, diagnosis, microbiology and antimicrobial treatment of ventilator-associated pneumonia [33].

Napolithano (2003) says that the nosocomial infections are an important cause of morbidity and mortality in US hospitals. The cost to the country is enormous, with >$4.5 billion being spent annually on the treatment of patients with nosocomial pneumonia. According to the American Society of Microbiology, approximately 70% of nosocomial infections are caused by organisms resistant to ≥1 antimicrobial agent. In addition to extended-spectrum β-lactamase–producing *Klebsiella pneumoniae* and *Escherichia coli*, and vancomycin-resistant enterococci (VRE), other problems include vancomycin-intermediate *Staphylococcus aureus* (VISA) and *Staphylococcus epidermidis*, penicillin-resistant *Streptococcus pneumoniae*, methicillin/oxacillin-

resistant staphylococci, and multidrug–resistant *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Enterobacter* species. Antimicrobial resistance is becoming one of the most important problems of the early 21st century, and it is imperative to find ways to reduce these problems [34].

Jain et.al, (2004) Acinetobacter baumannii is a global issue causing infections such as pneumonia, bacteraemia, meningitis, urinary tract infections, and skin and soft tissue infections. Its high mortality rate is due to resistance to most commercial antimicrobials. The development of new agents and reappraisal of older compounds is necessary for optimal treatment. Eradication requires good infection control, prudent antibiotic use, and effective antimicrobial therapy. Alternative therapies like colistin, ampicillin/sulbactam, and tetracycline are potential but not yet proven [35].

Szabo et.al, (2005) says that late-onset, ventilator-associated pneumonia (VAP) is caused by Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae, and Acinetobacter spp. These organisms are resistant to multiple antibiotics in ICUs. Antibiotic resistance in VAP may outstrip pharmaceutical manufacturers' ability to develop new antibiotics due to bacteria's rapid multiplication and ability to pass resistance mechanisms [36].

Jackson et.al, (2006) finds that recent literature explores infection prevention approaches and guidelines for clinicians. Studies show the high cost, morbidity, and mortality of infections in intensive care units, particularly ventilator-associated pneumonia. Potential management options include advances in diagnosis methods like bronchoscopy and inflammatory markers, and treatment methods like short-course regimens and 'de-escalation' for antibiotic prescribing. Further research is needed to develop effective preventive, diagnostic, and therapeutic strategies to improve patient outcomes [37].

Chastre et.al, (2007) explained large, randomized, controlled trial found that an 8-day antibiotic regimen was not associated with excess mortality or more episodes of recurrent pulmonary infection in patients with microbiologically confirmed ventilator-associated pneumonia (VAP). Multidrug-resistant pathogens emerged less frequently in the 8-day group, and the regimen was not associated with excess mortality in the subgroup with VAP caused by non-fermentative Gram-negative bacilli, mostly Pseudomonas aeruginosa. Pending confirmatory studies, on 8-day course of antibiotic therapy may be appropriate for many patients with VAP, provided initial treatment is appropriate, clinical course is favourable, and extreme vigilance is maintained after stopping antibiotics [38].

According to Blot (2008) severe nosocomial infections and multidrug resistance (MDR) negatively impact patients in intensive care units due to high disease severity and acute illness before infection onset. However, attributable mortality can be limited by implementing general infection prevention measures, preventing cross-transmission, and restricting antimicrobial use. Early recognition of sepsis and prompt initiation of emperical antimicrobial therapy are crucial. The choice of therapy should be based on local bacterial ecology, resistance patterns, risk factors for MDR, and patient colonization status. Adequate doses of antimicrobial agents and elimination of infection sources, such as contaminated devices or leakages, are also important [39].

As per the article of Kuti (2009) the American Thoracic Society and Infectious Diseases Society of America's guidelines recommend emperical antibiotic therapy for ventilator-associated pneumonia (VAP). However, these guidelines lack guidance on how institutions can develop a strategy for emperical antibiotic treatment. His review article suggests a hospital-specific approach, including a multidisciplinary group, real-time MIC data, and emperical dosage strategies. A proper de-escalation strategy is crucial for managing antibiotic choices and dosages, and continuous feedback is essential for maintaining compliance and reevaluating emperical antibiotic choices. This review article emphasizes the importance of implementing these strategies in hospitals [40].

According to Chastre et.al, (2010) aerosolization of antimicrobial agents may be a viable option for treating ventilator-associated pneumonia (VAP). However, its use in daily practice is yet to be proven. The efficacy of aerosolized antibiotics should be evaluated in a superiority trial, targeting patients with microbiologically proven VAP caused by potentially multidrug-resistant strains. Until these trials are completed, antibiotic aerosolization should only be recommended for multi drug resistant VAP patients with no effective intravenous regimen [41].

Jean (2011) refers about combination regimens which are being explored to overcome drug resistance. β-lactams or tigecycline combinations may be effective for managing MDR or PDR Acinetobacter baumannii pneumonia. Vancomycin plus rifampicin is effective against MRSA pneumonia, which responds poorly to vancomycin monotherapy. Parenteral colistin is suitable for MDR A. baumannii pneumonia. Linezolid may be the drug of choice for MRSA-VAP treatment. The role of tigecycline monotherapy in managing MRSA and Enterobacteriaceae pneumonia needs careful evaluation [42].

Grgurich et.al, (2012) explains that VAP due to MDR pathogens has increased in the last decade, with risk factors including advanced age, immunosuppression, broad-spectrum antibiotic exposure, and prolonged invasive mechanical ventilation. Methicillin-resistant Staphylococcus aureus and Gram-negative bacteria can cause VAP, with Pseudomonas aeruginosa, Acinetobacter baumannii, carbapenemase-producing Enterobacteriaceae, and extended-spectrum β-lactamase producing bacteria being particularly difficult. Proper management and evidence-based strategies are crucial to reduce VAP burden and healthcare costs [43].

Wilke et.al, (2013) says that Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are common conditions in intensive care units (ICUs), with Germany experiencing approximately 18,900 and 4,200 cases annually. A review of current guidelines on HAP and VAP, including strategies for individual patient risk and medication for initial intravenous antibiotic treatment (IIAT), found that correct choice significantly impacts clinical and economic outcomes (44).

According to Montero et.al, (2014) Multidrug resistant (MDR) bacteria pose a significant challenge in treating ventilator-associated pneumonia (VAP), particularly by Gram-negative bacilli (GNB). The lack of antibiotics against these pathogens and the lack of new antimicrobials in the pharmaceutical industry make treatment a challenge. Emperical therapy should be prescribed based on local susceptibilities, with colistin and tigecycline being unique options. Tigecycline should be used with an initial bolus of 200 mg followed by 100 mg every 12 hours. Vancomycin is the treatment of choice for

pneumonia due to MRSA, although linezolid may provide a higher rate of clinical cure. Initial antibiotic treatment should be reassessed and simplified based on culture results [45].

Bailey et.al, (2015) says that Gram-negative and gram-positive microorganisms are linked to VAP. MDR VAP is a significant problem, impacting survival outcomes. The study reviews optimal antibiotic choices for treating patients, discussing challenges of intravenous, inhaled, monotherapy, and combination therapies [46].

The study done by May (2016) explores the use of aminoglycosides in empiric antibiotic therapy for ventilator-associated pneumonia. It found that aminoglycosides improve clinical outcomes in patients at high risk of infection with antibiotic-resistant gram-negative bacilli and those with severe illness. In critically ill populations, short-duration therapy and high-dose extended-interval dosing can improve therapeutic efficacy while limiting nephrotoxicity. Therefore, aminoglycosides should be considered for empiric treatment [47].

According to Brotfain et.al, (2017) Acinetobacter baumannii, a multidrug resistant gram-negative bacterium, is often associated with ventilator-associated pneumonia (VAP) in critically ill patients. Patients in the ICU often develop A baumannii bacteraemia, which can worsen outcomes. The ICU mortality rate is higher in patients with VAP having A baumannii bacteraemia compared to nonbacteraemic patients. Independent risk factors for in-hospital mortality include age >65 years, an Acute Physiology and Chronic Health Evaluation II score higher than 20, a Sequential Organ Failure Assessment score higher than 7, and the presence of comorbid diseases like COPD and chronic renal failure [48].

Rhodes et.al, (2018) says VAP patients are at risk for antibiotic failure and under-dosing due to altered pharmacokinetic parameters. With few antibiotic agents approved in the last 15 years, the problem is expected to worsen. Rapid identification technologies, phenotypic methods, new therapeutic strategies, and novel treatment paradigms have evolved to improve treatment outcomes for VAP. However, clinical data supporting alternative treatments and adjunctive therapies remains sparse. Conscientious stewardship of new and emerging therapeutic agents is needed to ensure their effectiveness in the future [49].

The review done by Sarda et.al, (2019) discusses strategies for treating the three most prevalent resistant Gram-negative organisms causing VAP: Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae. Existing evidence focuses on bloodstream infections, and there are no recommendations for VAP treatment by multi-drug resistant Gram-negative bacteria, especially for combination regimens. The approval of new drugs is needed for effective and safe alternatives. Rapid identification technologies, phenotypic methods, and new therapeutic strategies have evolved to improve treatment outcomes, but clinical data supporting alternative treatments remains sparse [50].

Cotoia et.al, (2020) proposes that the increasing problem of multidrug resistant (MDR) organisms has led to a reduction in treatment options. His narrative review summarizes 27 original articles from the last 15 years, focusing on pathogenesis-targeted strategies to prevent MDR-VAP. The most convincing evidence came from interventions directly addressed against key factors of MDR-VAP pathogenesis, especially when implemented into bundles. Further research is needed to identify the most effective combination [51].

The review done by Xu et.al, (2021) critically examines new developments in Nosocomial Pneumonia diagnosis and antibiotic treatment, including lung ultrasound and low radiation computed tomography. Recent developments in rapid microbiological confirmation, such as syndromic rapid multiplex Polymerase Chain Reaction panels, are discussed. The use of volatile compounds or electronic nose as a diagnostic tool is also discussed. The review also discusses antibiotics approved for Nosocomial Pneumonia management in the last decade [52].

Bassetti et.al, (2022) says that new antibiotics, such as ceftobiprole, ceftolozane–tazobactam, ceftazidime–avibactam, meropenem–vaborbactam, imipenem–relebactam, and cefiderocol, have been approved for treating HAP and VAP. These agents have high activity against multidrug-resistant gram-negative pathogens, making them promising for preserving and enhancing antibiotic armamentarium. However, the efficacy of these agents in real-life scenarios is still a challenge. Further investigation is needed to determine the potential for monotherapy in patients with infections by MDR gram-negative pathogens. Positioning and differentiation of new treatment options and optimizing available therapeutic options are crucial for incorporating these drugs in daily clinical use. In conclusion, new agents hold promise for treating HAP and VAP, and their use should be vigilant to ensure their longevity in the antibiotic arsenal [53].

According to Alnimr (2023) prompt antimicrobial therapy is crucial for better outcomes, and understanding antimicrobial resistance in VAP is crucial in the era of evolving clones. His review focuses on risk factors for adult VAP and novel microbiological tools, highlighting evidence-based knowledge about resistance mechanisms in clinical settings, particularly Gram-negative pathogens. It also discusses evidence-based antimicrobial management and prevention of drug-resistant VAP, emerging predictive microbiology concepts, and VAP's relevance in COVID-19 [54].

In a study done by Hossein et.al, (2024) Acinetobacter baumannii, was explained as a major cause of ventilator-associated pneumonia (VAP). It is highly resistant to antibiotics, making control and treatment difficult. His study examining the prevalence of multidrug-resistant A. baumannii isolated from VAP patients from 2011 to 2020 found a final prevalence of 0.38. Asia and Africa had higher and lower prevalence rates, respectively. The overall prevalence rates of MDR, XDR, and PDR A. baumannii were 0.71, 0.73, and 0.40, respectively. Males had a higher prevalence of A. baumannii than females. VAP was directly related to different years, continents, drug resistance, and gender. VAP is crucial in ICUs, and implementing infection control standards and proper antibiotic use is essential for preventing MDR A. baumannii [55].

5. Factors CONTRIBUTING THE DEVELOPMENT OF MDR IN VAP:

The misuse and overuse of antibiotics in hospitals contributes to the development of multidrug-resistant (MDR) pathogens. the high-risk environment of intensive care units, particularly ventilators, increases the risk of infection with resistant bacteria. patient factors, such as chronic lung diseases, prolonged hospital stays, and previous antibiotic exposures, also contribute to the risk. inadequate infection control practices can lead to cross-contamination between patients, healthcare workers, and hospital equipment, promoting the spread of MDR pathogens. Biofilm formation, particularly on medical device surfaces, protects bacteria from antibiotics and immune system attack, promoting resistance. genetic adaptations of pathogens, such as mutations or exchanging genetic material. This allows them to survive in the presence of antibiotics. Selection pressure, lack of new antibiotics, and inadequate diagnostic techniques further drive resistance. Global health challenges, such as international travel and patient transfer, can also spread MDR bacteria across regions and countries. Addressing this issue requires a multifaceted approach, including stringent infection control practices, antibiotic stewardship programs, rapid and accurate diagnostic methods, and ongoing research for new therapeutic options.

6. How to control the development multidrug resistance in vap?

Multidrug resistance (MDR) in ventilator-associated pneumonia (VAP) can be controlled through a comprehensive approach that includes infection control practices, antibiotic stewardship programs, early and accurate diagnosis, prevention, regular surveillance, optimizing ventilation practices, education and training, limit use of invasive devices, isolation precautions, research and development, collaboration and communication, and patient and family education.

To prevent the spread of MDR organisms, healthcare facilities should implement strict infection control protocols, such as hand hygiene, PPE use and regular cleaning and disinfection of equipment and surfaces. Antibiotic stewardship programs should be developed and adhered to ensure the appropriate use of antibiotics. Early and accurate diagnosis can help administer the most effective antibiotics and reduce unnecessary use of broad-spectrum antibiotics.

Preventing VAP involves evidence-based practices such as elevating the head end of the bed, oral care with chlorhexidine, and minimizing sedation. Regular surveillance helps track trends, identify outbreaks early, and implement targeted interventions. Optimizing ventilation practices, minimizing mechanical ventilation duration, and providing ongoing education and training for healthcare professionals can help reduce MDR incidence and improve patient outcomes.

Tailoring the approach to the specific context of the healthcare setting, considering factors like local antibiotic resistance patterns and available resources, is also essential.

7. Conclusions:

Multidrug resistance (MDR) in ventilator-associated pneumonia (VAP) is a complex issue influenced by factors such as antibiotic overuse, hospital environment, patient-specific factors, and the adaptability of pathogenic microorganisms. It is crucial to implement antibiotic stewardship and robust infection control practices to prevent the spread of MDR organisms in healthcare settings. Enhanced diagnostic strategies are essential for rapid and accurate identification of pathogens, limiting the use of broad-spectrum antibiotics that contribute to resistance development.

Continuous research and development are needed to combat MDR in VAP, including the development of new antimicrobial agents, alternative therapeutic strategies, and innovative diagnostic tools. A multidisciplinary approach involving clinicians, microbiologists, pharmacists, and infection control specialists is necessary. Future research should focus on understanding the molecular mechanisms of resistance, exploring the role of the microbiome in VAP, and developing targeted therapies less likely to promote resistance. Implementing machine learning and artificial intelligence in predicting MDR outbreaks could offer new avenues for pre-emptive interventions.

In conclusion, MDR in VAP is a significant and evolving threat in healthcare, requiring a coordinated and comprehensive approach. Continuous vigilance, innovative research, and best practices in patient care and antibiotic use are essential for effective addressing of this challenge.

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