Section A-Research paper

An Overview about Antibiotic resistance among Ventilation Acquired Pneumonia Patients

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Abstract

Hospital-acquired pneumonia (HAP) is defined as an infection of the pulmonary parenchyma in patients who acquire the condition at least 48 hours after admission to the hospital or within 14 days after discharge from the hospital. Ventilator-Associated Pneumonia (VAP) represents a significant sub-set of HAP occurring in Intensive Care Units (ICUs) and is defined as pneumonia that occurs more than 48 to 72 hours after tracheal intubation and is thought to affect 10% to 20% of patients receiving mechanical ventilation for more than 48 hours. In critically ill patients, the susceptibility of the bacteria isolated in VAP depends on the duration of stay in the ICU and on MV as well as the previous use of antibiotics. VAP has been classified into early and late onset. Early-onset VAP occurs within less than 96 hours of ICU admission and is generally due to antimicrobial-sensitive bacteria.Late-onset VAP occurs after 96 hours of ICU admission and may be caused by an MDR pathogen. Resistance genes may be transferred to bacterial species capable of causing kinds of infections other than the original one. Successful genes may then be further selected and transferred to new hosts and in that process ,being amplified and established as important resistance genes, especially if the selection pressure of antibiotics continues. As an example, resistance to sulfonamides has been found throughout the world encoded by only two resistance genes. Antibiotic resistance genes carried in bacterial chromosomes and genetic elements have been suggested as potential emerging environmental pollutants.

Keywords: Ventilation Acquired Pneumonia, Antibiotic resistance

Introduction

Hospital-acquired pneumonia (HAP) is defined as an infection of the pulmonary parenchyma in patients who acquire the condition at least 48 hours after admission to the hospital or within 14 days after discharge from the hospital **(1).**

Ventilator-Associated Pneumonia (VAP) represents a significant sub-set of HAP occurring in Intensive Care Units (ICUs) and is defined as pneumonia that occurs more than 48 to 72 hours after tracheal intubation and is thought to affect 10% to 20% of patients receiving mechanical ventilation for more than 48 hours **(2**).

VAP, the most common and fatal nosocomial infection with serious complications such as empyema, septic shock, and multiorgan failure, which are observed in approximately 50% of HAP patients, especially those hospitalized in ICU **(1).**

1.1 Epidemiology

HAP and VAP represent one of the most common hospital-acquired infections, carrying significant morbidity and risk of mortality.

The risk is between 3 and 10 times higher compared to patients who do not get mechanical ventilation (MV), with the incidence rate of VAP in MV patients reported to vary from 9 to 27% according to study in 2019. **(3).**

The microbial resistance in hospitals worsens the occurrence of VAP and may result in significant consequences in association with increasing healthcare consumption and, case-fatality rates ranging from 20 to 50% **(4).**

VAP is one of the most dreaded nosocomial infections. VAP appears to have low attributable mortality ,but if caused by MDR pathogens is associated with a significant attributable mortality.Potential MDR pathogens include P. aeruginosa, Acinetobacter spp, ESBL-producing Enterobacteriaceae, Klebsiella-producing carbapanamase strains, Stenotrophomonas maltophilia, and MRSA **(5).**

In critically ill patients, the susceptibility of the bacteria isolated in VAP depends on the duration of stay in the ICU and on MV as well as the previous use of antibiotics. VAP has been classified into early and late onset. Early-onset VAP occurs within less than 96 hours of ICU admission and is generally due to antimicrobial-sensitive bacteria.Late-onset VAP occurs after 96 hours of ICU admission and may be caused by an MDR pathogen **(6).**

Risk factors of MDR pathogens include prior antibiotic use within the preceding 90 days, frequency of antibiotic resistance in the community or hospital, and the immunocompromised state .

Different studies have described a high rate of VAP due to MDR pathogens in episodes occurring in the first days of MV, highlighting the importance of local ecology **(7).**

Diagnosing VAP is difficult because it requires clinical data assessment, radiological findings and microbiological results. There are no foolproof tools to determine whether the patient has a VAP. When the clinical suspicion of VAP is high, empirical antimicrobial therapy must be initiated early as possible because both delayed and inadequate treatments have been associated with increased rate of morbidity and mortality **(6).**

Current guidelines recommend empirical coverage of GNB with a third or fourth generation Cephalosporin, piperacillin-Tazobactam or Carbapenem in combination with Fluoroquinolone or Aminoglycoside.

Resistance genes may be transferred to bacterial species capable of causing kinds of infections other than the original one. Successful genes may then be further selected and transferred to new hosts and in that process ,being amplified and established as important resistance genes, especially if the selection pressure of antibiotics continues. As an example, resistance to sulfonamides has been found throughout the world encoded by only two resistance genes. Emergence of resistant strains in hospitals occurs when a patient infected with resistant bacteria is transferred to the hospital from another facility, by patient-to-patient transfer, through selection caused by antibiotic use, and by transfer of resistance genes. Factors as, overcrowding, limited capacity and poor sanitation make the situation worse in many low and middle-income countries. Moreover, healthcare-associated infections are a problem worldwide **(8).**

Mechanisms

Mutation of bacterial genes lead to the rise of resistance in bacteria also known as vertical evolution. This resistance genes are transferred by mobile genetic elements, also known as horizontal gene transfer. Antibiotic resistance genes have mechanisms that make it impossible for an antibiotic to work properly. Different mechanisms of resistance affect different classes of antibiotics and antimicrobials. For example, beta-lactams are destroyed by the enzyme beta-lactamase, which breaks the beta-lactam ring **(8).**

Macrolides, aminoglycosides and glycopeptides antibiotics mechanisms are prevented by the change of the antibiotic ribosomal binding site. This leads to a decrease of its binding capacity. Resistance to Tetracyclines, Quinolones and quaternary ammonium compounds is caused by genes resulting in formation of efflux pumps that expel the antibiotic before it reaches the ribosomal target. Antibiotic resistance genes carried in bacterial chromosomes and genetic elements have been suggested as potential emerging environmental pollutants. **(7)**

The mobile genetic elements such as plasmids, integrons, transposons and insertion sequences are responsible for the carrying of the antibiotic-resistant genes among different groups of bacteria. Plasmids are extra chromosomal deoxyribonucleic acid (DNA) molecules that can multiply autonomously from the chromosomal host DNA. Plasmids can be mobile, encoding conjugative transfer genes for movement between bacteria of the same or different species, including commensal and pathogenic bacteria. **(8)**

Plasmids are essential vectors for accumulating and passing by multiple resistance genes. Multiple resistance plasmids often contain resistance genes found within integrons, insertion sequences and transposons, coding for different resistance mechanisms to antibiotics, heavy metals and quaternary ammonium compounds. **(9)**

Resistant plasmids are common among MDR pathogens, such as Staphylococcus aureus, Enterococcus species, Clostridium difficile, Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli and Salmonella enterica **(10).**

MRSA is a well-established infectious organism in the healthcare environments. Recently, it has been found also as community acquired, known as, community associated-MRSA (CA-MRSA)**.** Not much is known about the emergence of CA-MRSA strains. However, the common methods of MRSA transmission in humans are direct transmission through direct contact and indirectly by contact with contaminated inanimate objects, fomites and colonized animals, such as farm animals and pets. **(11).**

MDR bacteria are capable of spreading from one country to another. This is seen in the recent emergence of the New Delhi metallo-beta-lactamase (NDM-1) bacterial pathogens encoding resistance to the last-line group of Carbapenems. NDM-1 strains have been reported to originate in India in 2008 and did spread to many countries as England, USA and Canada**. (11).**

Empirical treatment of VAP due to MDR pathogens should be based on knowledge of local ecology. A strategy combining early high doses of effective agents with subsequent simplification in the light of microbiologic information is recommended.

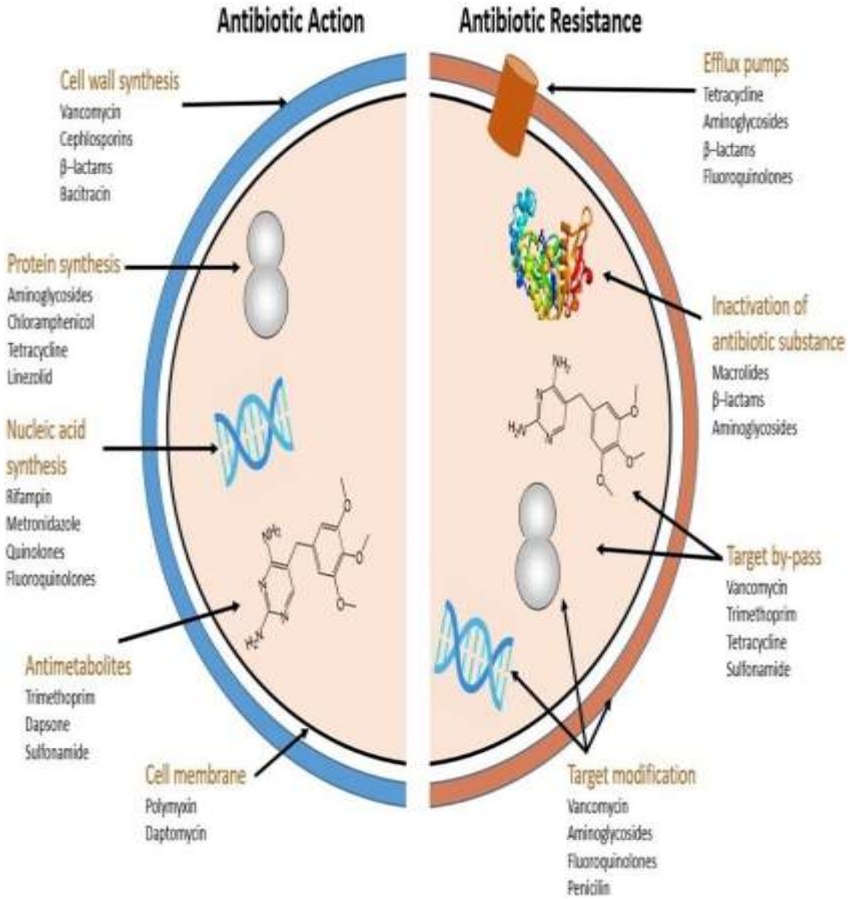

Figure (1) : Antibiotics resistance .

Antibiotics for MDR-GNB

Carbapenems

Carbapenems have been effective for VAP for many years. Imipenem, meropenem and Doripenem have similar spectrum ,but Doripenem is the most active carbapenem against P.aeruginosa.

Optimization of Carbapenem dosages (extended infusion of Meropenem or Doripenem) improve pharmacokinetic and pharmacodynamic target and is associated with higher rate of clinical cure in VAP **(12).**

Dual-carbapenem therapy (Ertapenem plus Meropenem or Doripenem) protect against Klebsiella pneumoniae carbapenemase (KPC)-producing K. The beneficial effect may be related to the KPC enzyme's preferential affinity for Ertapenem , Doripenem or Meropenem degradation and allowing the action of this Carbapenem **(13).**

A successful recovery with the use of this combination in a patient with bacteremic VAP due to pan-resistant KPC-producing K. pneumonia has been recently reported.

Colistin

Polymyxins are a group of polypeptide cationic antibiotics. Only polymyxin B and polymyxin E (colistin) are used in clinical practice.

colistin is antimicrobial with the greatest level of in vitro activity against multi-drug resistant GNB ,including A.baumannii, P aeruginosa, ESBL-producing Enterobacteriaceae or Klebsiella-producing carbapanamase strains **(14).**

Some GNB such as Proteus spp, Providencia spp, Morganella morganii and Serratia marcescens are resistant.

Doses of colistin have been recommended as loading dose of 9 million international unit (IU) and 4.5 million IU 12-hourly because colistin displayed a half-life that was significantly long in relation to the dosing interval.

Tigecycline

Tigecycline is broad spectrum antibiotic with potent in vitro activity against anaerobic and aerobic Gram-positive bacteria and Gram-negative pathogens with the exceptions of P.aeruginosa and Proteus ssp. Tigecycline is active against A. baumannii, including some colistin-resistant strains**.** Episodes of A.baumannii VAP treated with Tigecycline had a statistically significant excess of mortality in comparison to patients treated with Colistin. The excess mortality of Tigecycline was significant only among those with MIC >2 μg/mL but not for those with MIC ≦ 2 μg/mL. All isolates were susceptible to Colistin **(15).**

Dose of Tigecycline approved for intra-abdominal and skin and soft tissue infections (50 mg every 12 h with a loading dose of 100 mg) does not achieve adequate concentrations for pulmonary infections, which need 200 mg followed by 100 mg every 12 h achieved the greatest rate of clinical cure. Tigecycline is also active against MRSA, clinical cure of cases of MRSA was lower with Tigecycline than with the comparator in the clinical trial that evaluated this antibiotic in HAP, so we do not use Tigecycline for MRSA pneumonia and specific antibiotic against this Gram-positive bacterium is necessary **(15).**

Antibiotics for resistant Gram-positive cocci

Empirical coverage of MRSA is less troublesome. Vancomycin has been considered the treatment of choice for pneumonia due to MRSA. Almost all MRSA isolates are susceptible to vancomycin. However, an interesting issue to keep in mind is the MIC of MRSA to vancomycin. Several studies in patients with MRSA pneumonia or bacteremia (mainly from lung sources) have observed a higher rate of treatment failure and mortality in episodes with MIC ≥ 1.5 mg/L treated with vancomycin.

Current guidelines recommend a loading dose of 25-30 mg/kg followed by vancomycin dosages of 15-20 mg/kg given every 8-12 hours for patients with normal renal function **(16).**

Linezolid has been shown to have a better pharmacokinetic profile than vancomycin. Multipul studies concluded that linezolid therapy was associated with significantly better clinical cure and survival rates than therapy with vancomycin in patients with MRSA in VAP **(17).**

Ceftaroline is Cephalosporin with broad Gram-positive activity, including MRSA. Its Gram-negative activity includes common respiratory pathogens and members of the Enterobacteriaceae. This new Cephalosporin has a promising role in the treatment of VAP but clinical data are not currently available. It should be used in combination with another antimicrobial to cover GNB such as P.aeruginosa or ESBL-producing Enterobacteriaceae. **(17).**

Antibiotic resistance (ABR) is a normal evolutionary process in the environment where antibiotics use is abundant and haphazard, thus causing an important selection pressure. Mutations that entail resistance provide competition to the microbes carrying it and are therefore favored in natural selection. The vast use of antibiotics in hospitals and the community over the last decades have accelerated this process causing a global health problem. Widespread resistance to antibiotics is not only creating difficult-to-treat infections associated with high mortality but also threatening major progresses in modern medicine like major surgery and cancer chemotherapy. Bacteria with resistance to broad-spectrum antibiotics are increasing, and with the emergence of MDR bacteria, there is a great fear that we are heading towards a post-antibiotic era. Resistance is spread between bacteria, humans and regions using transmission of resistance genes between bacteria (e.g., plasmids and transposons), poor sanitation and hygiene in hospitals and communities, and other factors such as global travel, trade and migration **(17)**.

Since the 2000s, bacteria of the family Enterobacteriaceae producing ESBL – enzymes providing resistance to almost all β- lactam antibiotics (like penicillin and cephalosporins) except carbapenems have emerged as an important cause of infections. **(17)**.

They have since spread all over the world and are often associated with multi-drug resistance ,including resistance to Co-trimoxazole, Aminoglycosides and Ciprofloxacin (Important antibiotics in the empirical treatment) (**16).**

Resistance genes may be transferred to bacterial species capable of causing kinds of infections other than the original ones. Successful genes may then be further selected and transferred to new hosts and in that process ,being amplified and established as important resistance genes, especially if the selection pressure of antibiotics continues. As an example, resistance to sulfonamides has been found throughout the world encoded by only two resistance genes. The emergence of resistant strains in hospitals occurs when a patient infected with a resistant bacteria is transferred to the hospital from another facility, by patient-to-patient transfer, through selection caused by antibiotic use, and by transfer of resistance genes. Factors as overcrowding, limited capacity and poor sanitation make the situation worse in many low and middle-income countries. Moreover, healthcare-associated infections are a problem worldwide **(12).**

Most studies are carried out in hospitals, often with cultures from severely ill patients where first-line treatment has failed. Community-acquired infections and infections treated in out-patientcare are underrepresented. This may massively increase the rates of ABR and further drive the use of broad-spectrum antibiotics, which in turn may further accelerate the process of evolution and spread of resistance. **(10).**

Table 1: treat VAP caused by MRD pathogens.

	Decalogue to treat VAP caused by MRD pathogens
1	Antimicrobials used in the empirical regimens should be chosen based on the local pattern of susceptibility.
2	Initiation of antimicrobial therapy should not be delayed in patients with ahigh probability of VAP ,especially if the infection originates from severe sepsis or septic shock.
3	In patients with no signs of severe sepsis or septic shock and no organisms present on Gram's staining, antimicrobial therapy can be withheld pending culture results.
4	When a high rate of episodes is caused by extremely resistant GNB, empirical use of Colistin and/or Tigecycline may be justified.
5	The inclusion of a Carbapenem (in extended infusion) in this empirical therapy seems reasonable especially for pathogens not covered by these antibiotics.
6	The addition of Vancomycin or Linezolid is recommended is Units with ahigh prevalence of MRSA

(>10% of episodes caused by MRSA).

7 The initial antibiotic treatment must be reassessed when the culture results are available. Depending on the clinical progress and microbiological findings, clinicians should adjust therapy accordingly.

Table 2

Recommended doses of antimicrobials use in VAP caused by MDR pathogens in patients with normal renal function

Antibiotic	Loading dose	Daily dose	Observations
Imipenem*	Not required	1 g/6-8 h	Extended or prolonged infusion is not possible due to drug instability
Meropenem*	Not required	1-2 g/8 h	Extended infusion (3-4 hours) is recommended.
Doripenem*	Not required	500 mg-1 g/8 h	Extended infusion (3-4 hours) is recommended.
Colistin*	4.5-9 UI	9 UI/day in 2 or 3 dose	Loading dose is necessary.
Tigecycline	200 mg	100 mg/ 12 h	Without approval by regulatory agencies.
Fosfomycin*	Not required	24 g/day (in four doses)	Always in combination therapy.
Vancomycin*	25-30 mg/kg (based on ABW)	15-20 mg/kg (based on ABW) every 8-12 hours	Monitor trough concentrations after the forth dose; serum trough levels of 15-20 mg/L for MRSA VAP.
Linezolid	Not required	600 mg/ 12 h	It should be changed to vancomycin in the directed therapy of patients with good clinical evolution and S aureus with vancomycin.

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