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A COMPREHENSIVE REVIEW ON RESISTANCE OF GRAM NEGATIVE NONFERMENTING BACILLI IN VARIOUS HOSPITAL ACQUIRED INFECTIONS.

Medical Microbiology

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KEYWORDS

NFGNB- Nonfermenter gram negative bacilli, NNIS- National Nosocomial Infection Surveillance, CDC- Center for Disease Control and Prevention, CAUTI- Catheter - associated Urinary tract infection,BSI- Bloodstream infection,ESBL- Extended spectrum beta lactamases, MBL- Metallobetalactamases, ESKAPE- Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanni, Pseudomonas aeroginosa and Enterobacter species

INTRODUCTION

The nonfermentative gram-negative bacilli are a group of aerobic, non–spore-forming bacilli that do not either use carbohydrates as a source of energy or degrade them through metabolic pathways other than fermentation.

The term nonfermentative gram-negative bacilli is used to mean all aerobic gram-negative rods that show abundant growth within 24 hours on the surface of Kligler's iron agar (KIA) or triple sugar iron (TSI) medium, but neither grow in nor acidify the butt of these media.[1]

It is a heterogenous group of organisms because these organisms do not fall into a well defined taxonomic group of bacteria, thus several different genera have been included in the group of non fermenting gram negative bacilli.[2]

They are ubiquitous in nature and found as saprophytes in nature, inhabiting soil, water and some are also found as commensals in human gut. Most of the NF-GNB exist as environmental commensals in hospital that inhabit in moist environments, detergents and IV fluids. They are resistant to multiple antibiotics.[3]

NFGNB accounts for nearly 12-16% of all bacterial isolates in a clinical microbiology laboratory.[4]

NFGNB were earlier considered to be only commensals or contaminants. But, the pathogenic potential of these organisms has recently been established beyond doubt because of their frequent isolation from clinical specimens and their association with the disease.(Benachinmardi KK, Padmavathy M, Malini J, et al 2014). [5]

In the National Nosocomial Infection Surveillance (NNIS) survey from the Centre for Disease Control and Prevention (CDC),infections caused by non fermenters is the fourth most common cause of hospital acquired infections.

Cousative Pathogen

The group of genera that are medically important includes predominantly pseudomonas and Acinetobacter species as well as less common organisms Stenotrophomonas,Burkholderia, Alcaligenes, Weeksella species., currently; Pseudomonas aeruginosa and Acinetobacterbaumanii are the most commonly isolated non-fermenters pathogenic for humans whereas infections caused by other species are relatively still infrequent.[5]

Non Fermenting Gram Negative Bacilli Can Cause Various Infections Including

1. Pseudomonas aeruginosa is a Gram-negative pathogen that is commonly associated with hospital-acquired infections,infections in immunocompromised hosts, and chronic infections in patients with structural lung disease such as cystic fibrosis"[6]. It is the most common cause of wound infection, ventilator associated pneumonia, cystic fibrosis, bacteraemia, infective endocarditis, skin and soft tissue infections, meningitis in post operative or post – traumatic patients, osteomyelitis and septic arthritis, urinary tract infection in catherized patients.[7]

It is estimated that P. aeruginosa has a prevalence of 7.1%–7.3% amongst all health care associated infections.[8,9]

In intensive care unit (ICU) patients, P. aeruginosais responsible for higher percentage of healthcareassociated infections. Healthcare-associated pneumonia (HAP) and ventilatorassociated pneumonia (VAP) are a significant source of stress on the healthcare system.[10]

P. aeruginosa accounts for 10%–20% of isolates in cases of VAP,second only to Staphylococcus aureus.[9]

P. aeruginosa is a common cause of nosocomial urinary tract infections (UTI), particularly catheter-associated UTI(CAUTI). P. aeruginosa accounts for approximately 10% of all CAUTIs, and up to 16% of UTIs in ICU patients [11]

Amongst healthcare-associated infections reported to the National Healthcare Safety Network at the Centersfor DiseaseControl and Prevention (CDC) from 2011–2014, 5.7% of surgical site infections were found to be secondary to P.aeruginosa, with breast and cardiac surgeries being the type of surgery most associated with P. aeruginosa [9]

P. aeruginosa is a known complication of and important pathogen in burn patients, with the moist environment of burn-wound patients believed to contribute to its predilection for burn patients.[12] Bloodstream infections (BSIs) due to P. aeruginosa are associated with high rates of morbidity and mortality.[13]

P. aeruginosais a critically important pathogen, and is a predominant cause of morbidity and mortality, in patients with cystic fibrosis.[14]

Emerging Resistance Profiles

Pseudomonas aeroginosa is a classic opportunist pathogen with innate resistance to many antibiotics and disinfectants.[15] It is the Members of non-fermenting gram negative bacteria show resistance to a wide range of commonly used antibiotics by several mechanisms like antimicrobial inactivating enzymes, reduced access to bacterial targets and point mutations that change targets or cellular functions.[16] The antimicrobial inactivating enzymes are beta lactamases including Extended Spectrum Betalactamases (ESBL), AmpC, Non-metallo beta lactamases and Metallobetalactamases (MBL).[17]

Pseudomonas aeruginosa belongs to the group of ESKAPE pathogens (Enterococcus faecium,Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species) that are common causes of life-threatening nosocomial infections among immunocompromised and critically ill patients.[17]

Clinical strains of P. aeruginosa resistant to many classes of

antimicrobial agents, including β-lactams, aminoglyco-sides and fluoroquinolones, are often isolated.[18]However, an increase in strains resistant to the third- and fourth-generation cephalosporins and carbapenems has become a serious clinical problem worldwide.[18,19] The primary cause of cephalosporin resistance in P. aeruginosa isolatesis the overexpression of the chromosomal AmpC enzyme (mainly resistant to ceftazidime) andthe production of the metallo-β-lactamases, MBLs (resistant to cephalosporins and carbapenems).[20,21] However, ESBL-positive P. aeruginosa strains that produce extended-spectrum-β-lactamases (ESBLs) are frequently isolate.[18,19]

Generally, ESBLs are a group of β-lactamases that hydrolyse penicillins and cephalosporins, including oxyimino-β-lactams (third- and fourth-generation of cephalosporins) and aztreonam, and are inhibited by β-lactamase inhibitors, such as clavulanic acid, sulbactam and tazobactam.[22]

All ESBL-type enzymes are categorized into two structural Ambler classes, A and D.

In P. aeruginosa strains, the ESBL enzymes from both these classes are observed, primarily β-lactamases from the PER, GES[18,23, VEB[18,24,BEL[18,19,25,and PME[26, family (belonging to class A) and from the OXA family (class D), named extended-spectrum class D β-lactamases (ES-OXAs) [18,19,24

2. Family Moraxellaceae

Genus Acinetobacter

Taxonomy- The genus Acinetobacteris currently classified in the family Moraxellaceae and consists of bacteria that are nonmotile, oxidase-negative, gram-negative coccobacilli. Acinetobacterspecies are encapsulated, nonmotile, aerobiccoccobacilli that are nonfermenters of lactose. The majority of infections are caused by the Acinetobactercalcoaceticus-baumannii complex, Which ncludes the Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter nosocomialis, and Acinetobacter pittiigenotypes.[27]

A variety of human infections are caused by Acinetobacterspecies including pneumonia (most often related to endotracheal tubes or tracheostomies), endocarditis, meningitis, skin and wound infections, peritonitis (in patients receiving peritoneal dialysis) and urinary tract infections. Sporadic cases of conjunctivitis, osteomyelitis, and synovitis have also been reported. It is now recognized that Acinetobacter spp. play a significant role in the colonization and infection of hospitalized patients.[28] They have been implicated in a variety of nosocomial infections, including bacteremia, urinary tract infection,and secondary meningitis, but their predominant role is as agents of nosocomial pneumonia, particularly ventilator-associated pneumonia in patients confined to hospital intensive care units.Acinetobacter spp, principally A. baumannii, have emerged during the past few decades as one of the most difficult nosocomial microorganisms to both control and treat. Acinetobacter spp colonize multiple sites and can persist on environmental surfaces for extended periods. A. baumannii is intrinsically resistant to several classes of antibiotics.Although carbapenems and aminoglycosides are considered the therapies of choice, A. baumannii strains that possess aminoglycoside-modifying enzymes and carbapenemases are increasingly reported.[29]

The National Nosocomial Infection Surveillance System implicated Acinetobacterspecies in7% of nosocomial pneumonias and 2% each of nosocomialblood stream, surgical site, and urinary tract infectionsin ICUs in the United States in 2003.[30]

Stenotrophomonasmaltophilia (previouslyclassified in the Pseudomonas andsubsequently the Xanthomonasgenus) is an importantcause of nosocomial pneumonia and bacteremia, particularlyin immunocompromised hosts.[31] The mortality rate of Stenotrophomonasinfections is close to 40%, with100% mortality reported in nosocomial pneumonia inimmunocompromisedhosts.[32,33] Th e Burkholderiacepaciacomplex, best recognized as causing respiratory infectionin patients with cystic fi brosis, consists of 17 closely related species.[34] These organisms can cause nosocomialoutbreaks of pneumonia and bacteremia in critically illpatients without cystic fi brosis,[35] and are sometimesassociated with contaminated medications and toiletries.[36,37]

Achromobacterxyloxidans (previously classified as Alcaligenesspecies) is ubiquitous in water environmentsbut is an uncommon nosocomial pathogen, causingpneumonia, bacteremia, and catheter-associated infections that disproportionately afflictimmunocompromisedpatients with underlying malignancy.[38,39] It, likeBurkholderia, has been isolated from aqueous solutionsused in health-care facilities, including IV and dialysissolutions, and it can colonize medical equipment.[40]

Mechanism Of Resistance:

Disruption of -lactam rings of antibiotics by enzymatic hydrolysis is the most common resistance mechanism among gram-negative bacilli. -lactamases are categorized into classes A to D based on molecular structure, and functionally into groups 1 to 3 based on the antibiotic they degrade.[42] In the latter system, group 1 -lactamases are encoded inthe chromosomes of many gram-negative bacilli; theyare more active against cephalosporins and aztreonam than penicillins but are only active against carbapenems at high concentrations. Group 2 enzymes, the serine -lactamases, are the largest and most structurally diverse group of -lactamases, many of which are encoded by plasmids and are, therefore, readily transmissible between species. Group 2 enzymes include several penicillinases inhibited by -lactamase inhibitors, such as sulbactam, clavulanic acid, or tazobactam; the ESBLs(discussed subsequently); enzymes that hydrolyze extended-spectrum cephalosporins; and most recently, the serine carbapenemases. Group 3 enzymes, the metallo- -lactamases, are distinguished from other -lactamases by their requirement for zinc at their enzymatic binding site. These enzymes are potent hydrolyzers of carbapenems and are not inhibited by -lactamase inhibitors. Group 3 enzymes were first described as chromosomal genes in nonfermenting bacteria but, in recent years, have become encoded by transposons and plasmids, thus greatly increasing their interspecies transmissibility and prevalence.

Extended-Spectrum –Lactamases:

β-lactamase enzymes production is the most common mechanism of developing drug resistance to β-lactamantibiotics among Gram-negative bacteria.[42]

Extendedspectrum β-lactamase (ESBLs) and Amp-C β–lactamasemediated resistance are of increasing clinical concern.[43] ESBLs are group of enzymes which confers resistanceto extended spectrum cephalosporins, aztreonam, andoxyimino β-lactams and are inhibited by β-lactamaseinhibitors such as clavulanic acid, sulbactam, andtazobactam.[44] These enzymes are commonly found in Enterobacteriaceae and other Gram-negative organismssuch as Pseudomonas aeruginosa[45] and are encoded bymutated TEM1, TEM2 and SHV genes on plasmids.[46]

The spread of these ESBLs andAmp-C β-lactamase producing strains limits the use ofβ-lactam class of antibiotic, causing serious therapeuticfailures, compelling use of more broad spectrum andexpensive drugs.[47]

The ESBLs arose in Europe from single amino-acidsubstitutions in TEM and SHV group 2 b -lactamases inthe 1980s, temporally corresponding to the introduction of third-generation cephalosporins. ESBLs becameprevalent in the 1990s and are now ubiquitous worldwide,with 300 individual enzymes described.[48]

Themost common ESBLs belong to the TEM, SHV, and, beginning in the 2000s, the CTX-M family. The CTX-MESBLs appear to have been acquired from a nonpathogenic Enterobacteriaceae.[49]

In addition, the TEM and SHV ESBLs arebeing replaced by the CTX-M strains in most countries.Human gut carriage is thought to represent the largestreservoir of ESBLs, but other documented sourcesinclude rivers, wild and domesticated animals, and retailfoods.[50]

Table-1 Classification Of β- lactamases

CLASS	DRUG	SPECTRUM OF ACTIVITY
LACTAM+ LACTAMASE INHIBITORS	• Ampicillin-sulbactam • Amoxicillin-clavulante • Cefoperazone-sulbactam • Ceftazidime-avibactam • Ceftolozane- tazobactam • pipercillin-tazobactam • meropenem - vaborbactam	spectrum of respective - lactam drug plus active againstlactamase producing bacteria

Infection and colonization by ESBL-carrying path ogensoccur most commonly in hospital and ICU settings and are associated with length of stay, prior b -lactam or fluoroquinolone use, comorbidity and severity of illness,and presence of indwelling devices (eg, central venouscatheters, endotracheal tubes, urinary catheters, and gastrostomy tubes).[51,52] Once exclusively a cause of hospital-acquired infections, ESBL organisms increasinglycause community-acquired infections in patients with recent health-care contact.[53,54]

Carbapenemase:

Carbapenemase are a type of beta-lactamase enzyme released from GNB to defend themselves against carbapenem anti-biotics and tend to give resistance to all penicillins and cephalosporins.

A. baumannii and MDR P. aeruginosa are the current critical organisms for research and innovation of new drugs.

Mechanisms Of Carbapenem Resistance Among CR-NF-

Carbapenem resistance among CR-NF can be mediated by multiple different mechanisms, including carbapenemase production, decreased permeability due to porin mutations, overexpression of efflux pumps, and changes in penicillin-binding proteins.[55,56]

- One such resistance to β-lactam drugs is attributed to decreased permeability of the outer cell walls,which reduces the entry of the antibiotics through the porinchannels to reach their sites of action.[57]
- In addition, the excessstimulation of the efflux pumps serves as another mechanismthat removes the antibiotic from its site of action before theonset of the action.The active pumps comprise around three proteins, driven by the proton motive force producedby the respiratory enzymes and oxidative phosphorylation.[58]
- The mutational transformation of the target alsocauses resistance to the antibiotic. The resistance obtained againststreptomycin, quinolones, and other antibiotic groups has beenanalysed to be caused by a series of mutations that can occur in thegene that encodes the target protein, the protein of drug transportor activation.[59]
- However, the most common form of resistanceis contributed by hydrolysis, where the molecule is broken downor modified, rendering it inactive. The βlactam-hydrolyzingenzymes are the group of enzymes involved in the hydrolysis of theantibiotic. Penicillinases, cephalosporinases, extended-spectrumβ lactamase ESBLs, and most recently, the mannose-bindinglectin MBLs are some of the important enzymes.[60]

Classes Of Carbapenemase:

Carbapenemase is the enzyme produced by certain bacteria that can break down carbapenem, making them ineffective. These enzymes are classified into different classes based on genetic and functional characteristics.

Class A carbapenemases, are chromosomally encoded by the SME, NmcA, SFC-1, BIC-1, PenA, FPH-1, and SHV-38 genes and plasmid-encoded by KPC,GES, FRI-1 genes, or by both.[61]

Among these, the best-known KPC was isolated in most of the clinical enterobacterial species,such as P. aeruginosa and A. baumannii.

These enzymes reduce susceptibility to the imipenem for the bacteria sensitive to it and allow hydrolysis of a wide variety of β-lactams.

Class B of the Ambler group are the most clinically relevant carbapenemasesand are divided into three subclasses: B1, B2, and B3. The B1 subclass is responsible for most cases and frequently comprises Verona integrin-encoded MBL (VIM), imipenemase (IMP), and New Delhi MBL (NDM).[63.Class D carbapenemasesare a group of enzymes discovered in A. baumannii and K. pneumoniae human strains.[63]

The OXA-48 and related variants are of clinical relevance.[64] Class C carbapenemases are not considered carbapenemasesbut possess a low potential for the hydrolysis of carbapenem and can contribute to carbapenem resistance combined with diminished outer membrane permeability or efflux pump overexpression.[65,66]

Treatment Strategy For Non Fermenters:

The treatment of drug-resistant non-fermentersis among the most challenging problems in contemporarymedicine, because these organisms often do not respond to most cephalosporins, penicillins, or fluoroquinolones. β-lactams are an appropriate first choice for non lactose fermenters.Among carbapenems, imipenem-cilastatin or meropenem are active against many Pseudomonas and Acinetobacter species, whereas ertapenem has poor activity against non-lactose fermenters and should not be used against these pathogens. For organisms that retain sensitivity to β-lactams, the role of combination antibiotic therapy, typically with a β-lactam and aminoglycoside, remains undefined: Clinical studies have not shown any benefit from combination therapy over monotherapy if the organism is sensitive to the selected antibiotic.[67,68]

Combination therapy is appropriate for the treatment of infections caused by carbapenem-resistant Pseudomonas and Acinetobacter species. Polymyxins are effectiveagainst most of these organisms in vitro and constitute a mainstay of therapy. The addition of aerosolized to IV colistin has been reported as beneficial in pneumonia caused by such highly resistant isolates in some studies, but not others.[69,70]

Tigecycline is active against most Acinetobacter, but not Pseudomonas, species. For Acinetobacter species, the sulbactam component of ampicillin-sulbactam can be an effective therapy.[71] Other choices, including aminoglycosides (most often amikacin), aztreonam, fosfomycin, andrifamycins, may be considered, based on sensitivity testing.

Table No.2

PERCENT OF PATHOGEN THAT TESTED NON SUSCEPTIBLE TO OTHER TYPES OF ANTIBIOTICS					
Antibiotics	2013	2014	2015	2016	2017
Any fluoroquinolone	98%	93%	97%	92%	89%
Any extended-spectrum β-lactam	80%	75%	81%	79%	75%
Ampicillin/sulbactam	62%	62%	59%	64%	61%
Trimethoprim/ sulfamethoxazole	84%	74%	81%	77%	66%

Table No. 3 This Following Table Summarizes The 2019 Ar Threats Report Estimates, And Comparesion-

Resistant germ	Threat estimated 2019 report	Year-to-Year Comparison Provided, 2019 report	ResistantInfection Increase/ Decrease, 2019 report
Carbapenem-resistant Acinetobacter (formerly multidrug-resistant Acinetobacter)	8,500 cases & 700 deaths	Cases over time from 2012–2017	**Decrease**
Multidrug-resistant Pseudomonas aeruginosa	32,600 cases & 2,700 deaths	Cases over time from 2012–2017	**Decrease**

CONCLUSION:

Antimicrobial resistance is an important global concern for public health authorities due to their increasing multidrug resistant infections burdening a country's health and social economy. This reviews study shows the importance of highly prevalent Nonfermenters gram negative bacilli.

Resistance among these clinical isolates emphasize the need for strict adherence to the concept of the "reserve drugs" and antibiotic therapy that should be formulated or modified after following the culture and sensitivity analysis. This will help for a proper treatment to the patient and prevent the misuse of the available antibiotics, thereby the spread of drug resistance in the bacteria. The prevalence of Extended spectrum lactamases resistance and carbapenem-resistant among NFGNB is now considered as threat to the hospital setting due to their ability to cause severe and life-threatening infections; hence, it is necessary to perform regular monitoring, reporting, and documentation of cases of drug resistance in the hospitals.

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