NON-FERMENTING GRAM-NEGATIVE BACTERIA - LET'S BE CAUTIOUS

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Abstract: Non-fermenting Gram-negative bacteria are a taxonomically diverse group of aerobic nonspore forming bacteria, the majority of which are able to survive for extended time periods under adverse environmental conditions - dry, cold or warm. They are widely distributed in the environment including soil, water, plants and various other sources. In the hospital environment, they may be isolated from humidifiers, ventilator machines, nebulizers, dialysis fluids, saline solution, disinfectants and medications. They can be part of the transient physiologic flora and can be also found as commensals on the human skin or in the gut. These opportunistic pathogens possess a highly variable level of virulence as a major virulence factor is the ability of biofilm production which facilitates attachment to various surfaces, resistance to phagocytic activity and other host immune factors, protection from antimicrobial activity and enhanced spread across surfaces through bacterial motility. The accurate identification of these bacteria to species level is absolutely important for appropriate patient management. The molecular methods for identification are emerging as alternatives for phenotypic identification methods of these microorganisms and have provided a number of changes in taxonomy, but also contributed important insights into their epidemiology and clinical importance. The non-fermenting Gram-negative bacteria group includes organisms from diverse genera, the most prevalent among which are *Pseudomonas, Acinetobacter, Stenotrophomonas, Burkholderia, Alcaligenes, Weeksella, Flavimonas, Achromobacter, Elizabethkingia*, etc. Non-fermenting Gram-negative bacteria rarely causes disease in healthy individuals. However, in recent years these bacteria have emerged as important healthcare-associated pathogens. They cause infections in critically ill, immunocompromised or cystic fibrosis patients and are particularly associated with severe urinary tract infections, wound infections, ventilator pneumonia, meningitis, surgical site infections and bloodstream infections significantly increasing morbidity and mortality among the patients. A major issue for the physicians in terms of non-fermenting Gram-negative bacteria infection treatment and control is the emerging challenges of multi-drug resistance, both intrinsic and acquired among them and the rapid emergence of resistance to novel antimicrobial compounds raises concerns about the clinical reliability of these agents which in turn leads to prolonged hospital stay and greater healthcare costs.
Keywords: Non-fermenting Gram-negative bacteria, antimicrobial resistance, virulence factors.

1. INTRODUCTION

Non-fermenting Gram-negative bacteria (NFGNB) are a taxonomically diverse group of strictly aerobic nonspore forming bacteria. They do not use carbohydrates as a source of energy and do not break down them through other metabolic processes (14). The majority of NFGNB are able to survive for extended time periods under adverse environmental conditions - dry, cold or warm. They can be part of the transient physiologic flora and can be also found as commensals on the human skin or in the gut (14). Due to the highly variable level of virulence and their multidrug resistance, over the last few decades these opportunistic pathogens have become increasingly important as human pathogens.

2. TAXONOMY

Molecular identification methods are becoming more popular than phenotypic identification.of NFGNB and have provided a number of changes in taxonomy, but also contributed important insights into their epidemiology and clinical importance. As more data is gathered, the taxonomy of this group of microorganisms is still being updated. The non-fermenting Gram-negative bacteria group includes microorganisms from diverse genera, the most prevalent among which are *Pseudomonas, Acinetobacter Stenotrophomonas, Burkholderia, Alcaligenes, Weeksella, Flavimonas, Achromobacter, Ralstonia, Roseomonas, Sphingobacterium, Elizabethkingia*, etc.

3. EPIDEMIOLOGY

The non-fermenting Gram-negative bacteria are widely distributed in the environment including soil, water, plants and various other surfaces and foods such as dairy products, poultry and frozen foods. They may be isolated from medical devices such as humidifiers, ventilation systems, dialysis and saline solutions, disinfectant substances and

medications in addition to healthcare workers' skin and have the ability to spread horizontally (23). They present a challenge as they are also resistant to numerous disinfection substances commonly used in the hospital settings (37).

4. INFECTIONS

Non-fermenting Gram-negative bacteria rarely causes disease in healthy individuals. However, in recent years these bacteria have emerged as important healthcare-associated pathogens (22). They cause infections in critically ill, immunocompromised or cystic fibrosis patients and are particularly associated with severe urinary tract infections, wound infections, ventilator-associated pneumonia, meningitis, surgical site and bloodstream infections significantly increasing morbidity and death rate among the patients.

5. MOST COMMON ISOLATED NON-FERMENTING GRAM-NEGATIVE SPECIES AND THEIR ANTIBIOTIC RESISTANCE PROFILE

Pseudomonas spp. and *Acinetobacter* spp. have the higher isolation rates compared to all other non-fermenting Gram-negative species.

Pseudomonas aeruginosa is able to colonize a wide range of different places it is metabolic flexible and has a broad capacity of environments adaptation (38). Its high adaptability and ubiquity can also be demonstrated by the fact that it can infect a variety of hosts. *P. aeruginosa* one of the main causative agents of healthcare-associated infections, including acute breathing disorders and bacteremia (2). In addition, it can cause chronic infections in individuals with immune deficiencies and underlying diseases like chronic obstructive pulmonary disease, cystic fibrosis, cancer HIV infected patients, or those with burns or surgical wounds. These infections are the leading cause of morbidity and mortality in intensive wards (19,32,41). *P. aeruginosa* possesses a variety of virulence factors which facilitate the infection and obstruct the treatment. Among these factors are different enzymes, motility capacity, biofilm formation especially when found on prosthesis, catheters, or the lungs and the cell-cell signalization (quorum sensing) that regulates the expression of these factors (12,15). Due to its high virulence and low susceptibility to a great number of antibiotics, the *P. aeruginosa* is stated into 2 main groups of microorganisms – ESKAPE *(Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, P. aeruginosa, and Enterobacter spp.)* and TOTEM (TOp TEn resistant Microorganisms), which include the currently most significant multidrug-resistant human pathogens (33,29). The increased intrinsic resistance of *P. aeruginosa* to antibiotics is due to its low permeability of the outer membrane, the production of enzymes that modify the antibiotic molecules, and the abundance of efflux pumps responsible for multidrug resistance (25,45). These bacteria have been found to have a wide sublethal selective window to different antibiotics (for example ciprofloxacin or tetracycline), under which resistant mutants can emerge (34,35). In addition to intrinsic and genetically acquired, stable antibiotic resistance, the resistance phenotype can also be temporarily acquired without requiring genes alterations, as seen in the formation of biofilms (6). One of the main virulence factor of *P. aeruginosa* is its capacity to form a biofilm in the host. That contributes to the ability of the microorganism to inhabit various ecological niches, facilitates binding to various surfaces, resistance to phagocytic activity and other host immune factors, and reduce the efficacy of antibiotic treatment regimens which can lead to the development of chronic and persistent infections in the host's tissues or prosthetic devices (12). Depending on the features of the infection, fluoroquinolones (ciprofloxacin), polymyxins, and carbapenems are preferred antimicrobials for treatment of *P. aeruginosa* infections; aminoglycosides (tobramycin) are also commonly used, along with cephalosporins or combinations of β-lactam and β-lactamase-inhibitor (e.g. piperacillin/tazobactam or ceftazidime/avibactam) (2,11).

Acinetobacter spp. are the other non-fermenting Gram-negative resistant bacteria causing health care associated infections. *Acinetobacter baumannii* is one of the most prevalent species and other ones such as *Acinetobacter pittii* and *Acinetobacter nosocomialis* have been also often isolated in hospitalized individuals (44). *A. baumannii* is ubiquitous microorganism, opportunistic pathogen associated with infections of the respiratory system, bloodstream, wound, skin and soft tissue, urinary tract and central nervous system. It possesses wide range of intrinsic resistance determinants, and can easily acquire new mechanism of antimicrobial resistance. Several efflux pumps including MDR efflux pumps, are its primary determinants of intrinsic antibiotic resistance (8,21). Numerous mobile genetic elements, including integrons, transposons, and plasmids, are present in its genome, which may contribute to the pathogen's ability to acquire antibiotic resistance (10). Furthermore, mutations in genes encoding outer membrane proteins also promote antibiotic resistance and alter the virulence of this microorganism (42). Additionally, *A. baumannii* possesses also multiple β-lactamases (28). Carbapenems-resistant *Acinetobacter* spp. is considered a top priority that requires novel antibiotics

S. maltophilia is considered now as a frequent NFGNB that causes infection in hospital wards (43). Although it is mainly a hospital-acquired pathogen, community-acquired infections are becoming more common (36). *S. maltophilia* usually affects immunocompromised patients with previous pathologies such as cystic fibrosis, HIV

infection or cancer, respiratory ventilation, permanent catheters, therapy with immunosuppressant or corticosteroids, as well as patients hospitalized for prolonged periods in intensive care units and those administered previous broad-spectrum antibiotics therapy (4). *S. maltophilia* is mostly associated with lung infections and acute exacerbations of chronic obstructive pulmonary disease, followed by bloodstream infections. Not as often, it causes skin and soft tissues infections, infections of biliary and urinary system, endocarditis, intra-abdominal and central nervous system infections (31). Treating *S. maltophilia* infections can be challenging due to intrinsic resistance mechanisms to the majority of antibiotics that this microorganism possesses (24). In the *S. maltophilia* genome have been found many genes encoding determinants of resistance to variety of antibiotics such as β-lactams, cephalosporins, macrolides, fluoroquinolones, aminoglycosides or carbapenems (7,30). Two inducible β-lactamases and aminoglycoside-modifying enzymes that provide low susceptibility to a number of aminoglycosides have been found in the bacteria (39). In addition, *S. maltophilia* has chromosome-encoded multidrug resistance efflux pumps involved in intrinsic resistance to β-lactams, quinolones, tetracycline and polymyxin B (3). The overexpression or mutations of all these elements can contribute to acquired resistance (13). Another significant feature of *S. maltophilia* linked with its antibiotic resistance is its ability to form biofilms and attaching to surfaces, including medical devices. The treatment of choice of *S. maltophilia* infections is currently trimethoprim/sulfamethoxazole or the more effective combination of trimethoprim/sulfamethoxazole and ciprofloxacin, ceftazidime, tobramycin or tigecycline (40,47). Ticarcillin/clavulanate, ceftazidime in combination with fluoroquinolones are an effective option in case of trimethoprim/sulfamethoxazole resistant infections (4).

Burkholderia cepacia complex is another NFGNB. Its taxonomy is complicated and changing (9). The complex is formed by nine genomovars and the group or taxon K split into two species - *Burkholderia contaminans* and *Burkholderia lata*) (9,20). *Burkholderia* spp. colonize and infect patients with chronic respiratory illness. *Burkholderia cenocepacia, Burkholderia multivorans, B. contaminans* are known to cause disease in cystic fibrosis patients and once infected, it is extremely hard to eliminate (27). *B. pseudomallei* is the causative agent of melioidosis and is responsible for abscesses formation in not only in lungs but also in kidney, skin, heart, muscles, etc. Due to efflux pumps and inducible β-lactamases *Burkholderia cepacia complex* is associated with low susceptibility to carboxypenicillins, first and second generation cephalosporins, tetracycline and tobramycin and possess intrinsic resistance to polymyxins which are the last option (26).

Another NFGNB are *Achromobacter* spp. *Achromobacter xylosoxidans* is an important nosocomial pathogen even it is found in a variety of water environments (5). It is an opportunistic pathogen that emerges as causative agent of infections in cystic fibrosis patients (1). Due to the presence in the *A. xylosoxidans* genome of genes encoding efflux pumps responsible for multidrug resistance it is intrinsically non susceptible to several antibiotics such as cephalosporins, carbapenems, quinolones, chloramphenicol, tetracyclines, etc. (16). Moreover *A. xylosoxidans* possess also β-lactamases and shows greater resistant to carbapenems (16,46).

Infections caused by non-fermenting Gram-negative bacteria have a worse prognosis than those caused by sensitive pathogens due to the increased antimicrobial resistance of these microorganisms and the limited, sometimes nonexistent therapeutic options. In the last few decades, the treatment of NFGNB infections related to healthcare settings primarily relied on single therapy with polymyxin or polymyxin-based combined protocols (17,18).

6. CONCLUSION

The rapid emergence of resistance even to novel antimicrobial compounds among the non-fermenting Gram-negative bacteria leads to prolonged hospital stay, higher healthcare costs and higher rates of morbidity and mortality among patients and definitely raises concerns. Appropriate screening of NFGNB in hospitals, their accurate identification, routine assessment of their antibiotic susceptibility profiles is absolutely important for efficient treatment of patients and limiting the emergence of multidrug resistance. The increased rate of isolation of these resistant NFGNB is a clear indication that there is a need of rapid implementation of antimicrobial stewardship policies and comprehensive microbiological surveillance programs in the hospitals.

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