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## **Non-fermenters – Emerging Health Care Pathogens**

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### **Abstract**

Aerobic nonfermenting gram-negative bacilli (nonfermenters) are a heterogeneous group of organisms that are either incapable of utilizing carbohydrates as a source of energy or degrade them via oxidative rather than fermentative pathway. These organisms are common inhabitants of soil and water. Nonfermenters can cause a vast variety of infections and account for approximately 15% of all Gram negative bacilli cultured from clinical specimens. Their infection are endogenous or exogenous origin, depending on several factor such as use of immunosuppressant substance, abusive use of wide spectrum antimicrobial agents, prolong surgical procedure and inadequate instrumentation. Pseudomonas cause endocarditis, osteomyelitis, urinary tract infections, gastrointestinal infections, meningitis, and, commonly septicaemia. Acinetobacter has emerged as an important nosocomial organism causing infectious outbreaks in critically ill patients leading to high mortality and morbidity. Burkholderia cepacia shows fast

growth on immune-depleted patients - like cystic fibrosis patients (CFPs). *Sphingomonas paucimobilis* can produce biofilms or attach to preexisting biofilms, where they become integrated and survive for days. Most infections caused by nonfermenters have been nosocomial, often related to contamination of hospital equipment or fluids and have occurred in immunocompromised hosts. Non-fermenting Gram-negative bacilli are innately resistant to many antibiotics and are known to produce extended spectrum  $\beta$ -lactamases and metallo  $\beta$ -lactamases. This review article highlights the different clinical conditions caused by the nonfermenters.

**Keywords:** Nonfermenters, *Pseudomonas*, *Burkholderia cepacia*, *Acinetobacter*, *Sphingobacterium*.

## **Introduction**

Nonfermenter Gram negative bacilli were considered to be a contaminant in past have now emerge as an important health care pathogen. The term nonfermentative Gram-negative bacilli means all aerobic gram-negative rods that show abundant growth within 24 hrs on the surface of Kligler iron agar (KIA) or Triple sugar iron (TSI) medium, but neither grow in nor acidify the butt of this media [1]. Aerobic nonfermenting gram-negative bacilli (nonfermenters) are a heterogeneous group of organisms that are either incapable of utilizing carbohydrates as a source of energy or degrade them via oxidative rather than fermentative pathway [2]. This group includes organisms from diverse genera like *Pseudomonas*, *Acinetobacter*, *Alcaligenes*, *Burkholderiacepacia*, *Sphingobacterium*, *Agrobacter* *Weeksiella*, etc. These organisms are common inhabitants of soil and water. They also exist as harmless parasites on the mucus membranes of humans and animals. Though primarily regarded as contaminants or incidental organisms, they are becoming increasingly important as opportunistic pathogens in immunocompromised patients. They can also cause infection by gaining access to normally sterile body sites through trauma [3]. Nonfermenters can cause a vast variety of infections and account for approximately 15% of all Gram negative bacilli cultured from clinical specimens [4]. Non-fermenters may differ in their pathogenic potential and transmissibility and many are multidrug resistant. For this reason, accurate identification of non-fermenters to species level is important for appropriate patient management [4]. Their infection are endogenous or exogenous origin, depending on several factor such as: use of immunosuppressant substance, abusive use of wide spectrum antimicrobial agents, prolong surgical procedure and inadequate instrumentation [5]. In recent year due to liberal and empirical use of antibiotics, nonfermentative Gram-negative bacilli are emerge as a important health care associate pathogen. They have been incriminated in infections such as a septicemia, meningitis, osteomyelitis, pneumonia, Urinary tract infection and surgical site infection. Non-fermenting Gram-negative bacilli are innately resistant to many antibiotics and are known to produced extended spectrum  $\beta$ -lactmases and metallo  $\beta$ -lactmases [6].

## **Clinical Conditions caused by Nonfermenters**

### ***Pseudomonas***

The genus *Pseudomonas* of the *Pseudomonadaceae* family, are motile gram-negative aerobic bacteria, 2 – 4  $\mu\text{m}$  long plump-shaped rods, with polar flagella which have an important role in pathogenicity [7] .

They are non-spore forming and can produce pigments, such as pyocyanine (green-blue) and pyorubrin (yellow-green) fluorescence [7]. *P. aeruginosa* can produce a large variety of extracellular toxins, including exotoxin A and enterotoxins [8]. As opportunistic pathogens, *Pseudomonas* spp. often invades the host tissue and cause infection and bacteremia in immunocompromised hosts (e.g., HIV/AIDS, cystic fibrosis, bronchiectasis, and severe chronic obstructive pulmonary disease, burns, malignancy, or diabetes mellitus) [9]. The common site of infection is the lower respiratory tract, and severity ranges from colonization without immunological response to severe necrotizing bronchopneumonia; such severe infection in patients with cystic fibrosis is almost impossible to eradicate once established in the airways [10]. Pseudomonal pneumonia often develops from oro-pharyngeal contamination or secondary bacteremia, and is also a common cause of nosocomial ventilator-related pneumonia in intensive care settings. Infections also include endocarditis, osteomyelitis, urinary tract infections, gastrointestinal infections, meningitis, and, commonly, septicemia [11]. *P. aeruginosa* is the most common agent associated with infection and inflammation during contact lens wear. The bacteria colonize on lenses and produce proteases to kill or invade corneal cells, an infection that can lead to scarring and vision loss [7]. *P. aeruginosa* can also readily colonize on open burn wounds, causing infections, abscesses, and sepsis, with edema and discoloration of unburned skin at wound margins and green pigment in subcutaneous fat [12]. They exhibit intrinsic resistance to several antimicrobial agents, including most  $\beta$ -lactams, and they often carry acquired resistance determinants that further reduce their spectrum of susceptibility [13].

### **Acinetobacter**

Acinetobacter species are aerobic gram-negative bacilli that can cause healthcare-associated infections and can survive for prolonged periods in the environment and on the hands of healthcare workers [14]. Acinetobacter has emerged as an important nosocomial organism causing infectious outbreaks in critically ill patients leading to high mortality and morbidity [15]. It has become one of the top seven pathogens threatening the current health care delivery system, particularly the intensive care setting [16]. Because of its remarkable ability to colonize patients and the nosocomial environment, it causes hospital

outbreaks due to cross-transmission between patients [17]. It is associated with ventilator acquired pneumonia (VAP), blood stream infection (BSI), urinary tract infection (UTI) and central nervous system (CNS) infection in neonates. *Acinetobacter* is considered as an organism with low virulence but issues such as critical illness/immunocompromised status, prematurity, low birth weight, endotracheal intubation, parenteral nutrition, intravascular catheterization and broad spectrum antibiotic therapy are known risk factors for *Acinetobacter* spp. septicemia [18]. *Acinetobacter* infections have become increasingly difficult to treat because of the emergence of strains resistant to all drugs or all but 1 commonly prescribed antimicrobial drug [19]. *Acinetobacter* spp. resistance against broad-spectrum cephalosporins, b-lactam agents, aminoglycosides and quinolones. Resistance to carbapenems is also being increasingly reported [20].

### **Burkholderia**

*Burkholderia cepacia* is a bacterial complex composed of opportunistic pathogens with high pathogenicity, living in various environments. Being aerobic and chemoorganotrophic with optimal temperature similar to the human body, this bacterium shows fast growth on immune-depleted patients - like cystic fibrosis patients (CFPs). Cystic fibrosis is an autosomal recessive disease, more severe when accompanied by this infection. The risk factors of this bacterium are due its capacity of direct transmission (as nosocomial infection or social contact with infected patients), but new information shows the possibility of indirect transmission [21]. Cystic fibrosis is the most common autosomal genetic disease in North America, affecting 1 in 2,000 individuals among Caucasians [22]. This disease is caused by mutations affecting the cystic fibrosis transmembrane conductance regulator protein - CFTR - and is characterized by chronic malfunction of lung, pancreatic insufficiency and high levels of chloride in sweat. Its high mortality index is evident when lung and spleen are affected, but other organs can also be affected. The persons affected die by progressive bronchiectasis and chronic respiratory insufficiency [23].

### **Sphingomonas**

*S. paucimobilis* is a gram-negative, slightly motile, non-fermentative, oxidase positive opportunistic

pathogen that rarely causes infections in humans, and forms yellow-pigmented colony in blood agar. It is found in nature, notably in water and soil [24]. Varieties of *Sphingomonas* are widely used in biotechnology due to their ability for synthesis and decomposition of macromolecules [25]. In various studies, *S. paucimobilis* has been shown to be a causative agent of infection in immune-compromised patients, and in hospital acquired postoperative endophthalmitis, septic shock, septic arthritis and osteomyelitis [24]. *Sphingomonas paucimobilis* can produce biofilms or attach to preexisting biofilms, where they become integrated and survive for days, weeks or even longer, depending on the biology and ecology of the organism and the environmental conditions [26].

### **Sphingobacterium**

*Sphingobacterium multivorum* is a ubiquitous Gram-negative saprophytic bacillus naturally present in the environment like soil, plant material, and water [27]. It has been associated with septicemia in immunocompromised patients [28] and respiratory tract infections in patients with cystic fibrosis [29]. Cases of nonnecrotizing soft tissue infection due to other *Sphingobacterium* species have also been reported [30]. In the present case, the patient was relatively immunocompromised by long duration of septicemia and non-healing wounds at many sites on the skin, and *S. multivorum* is a well-known risk factor for skin and soft tissue infection [31].

### **Stenotrophomonas maltophilia**

*Stenotrophomonas (Xanthomonas) maltophilia* is a ubiquitous, aerobic, non-fermentative, gram-negative bacillus that is closely related to the *Pseudomonas* species [32]. *S. maltophilia* is not highly virulent, nevertheless several factors may promote its ability to colonize the respiratory tract and plastic surfaces, such as catheters and endotracheal tubes. These include a positively charged surface as well as flagella and fimbrial adhesion, the latter have been associated with biofilm formation [33]. The outer membrane lipopolysaccharide (LPS) plays a role in colonization and resistance to complement-mediated cell killing, and its lipid A moiety can stimulate peripheral blood monocytes and alveolar macrophages to produce TNF $\alpha$ , which plays a role in the pathogenesis of airway inflammation [34]. *S. maltophilia* produces a number of extracellular enzymes, whose contribution to virulence is currently uncertain [35].

### **Alcaligenes faecalis**

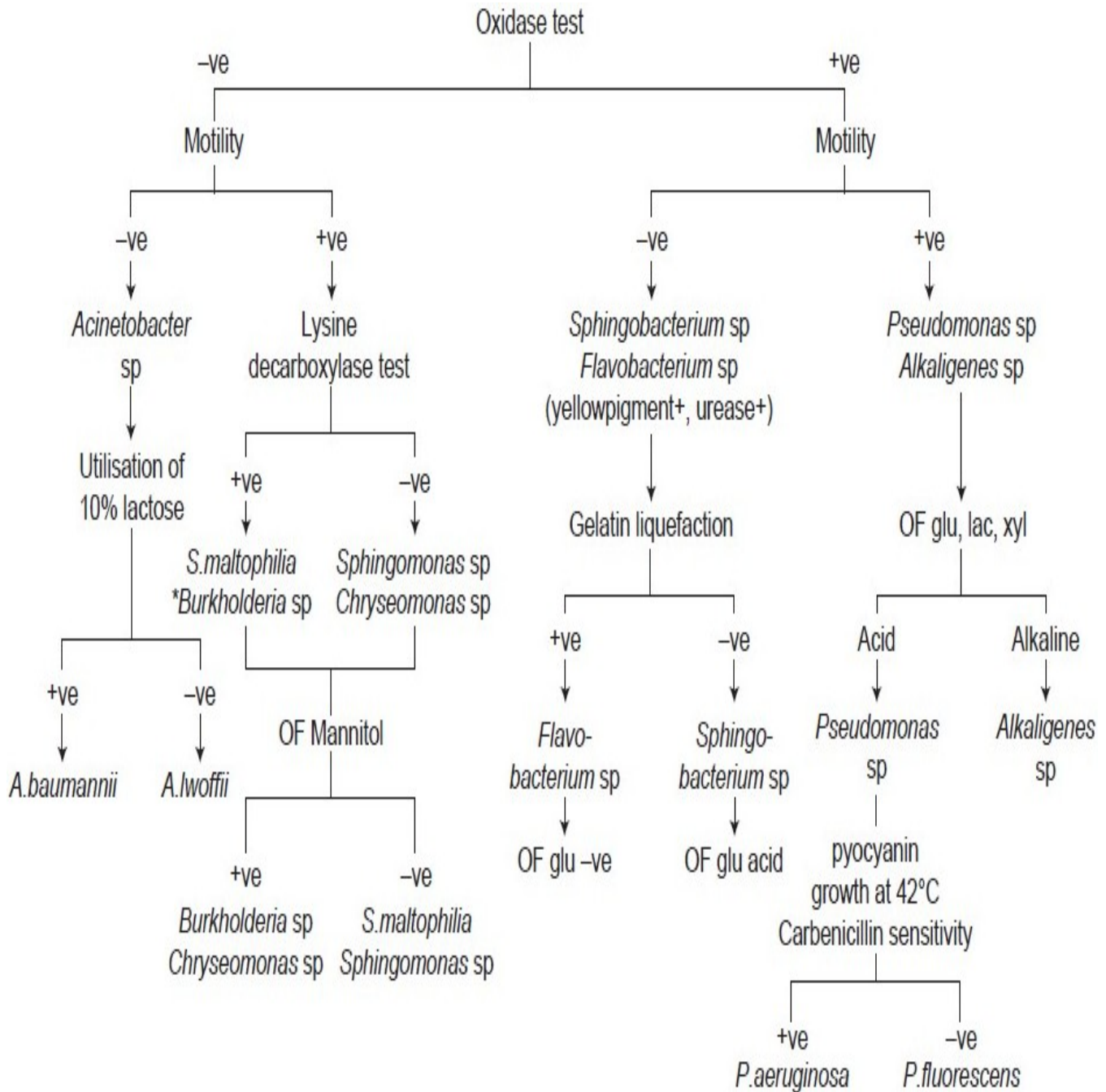
*Alcaligenes faecalis* is an aerobic, glucose-non-fermenting, Gram-negative bacillus, ubiquitous in soil and water but rarely isolated from humans [36]. Most infections caused by this bacterium have been nosocomial, often related to contamination of hospital equipment or fluids and have occurred in immunocompromised hosts [37]. Most strains appeared to display multiple resistance to numerous antibiotics, including  $\beta$ -lactams (amoxicillin, ticarcillin and aztreonam), aminoglycosides and quinolones but were susceptible to combinations of amoxicillin or ticarcillin plus clavulanic acid and to the cephalosporins [37].

### **Achromobacter group**

In this group *Ochrobactrum anthropi* and *Rhizobium radiobacter* are the species most commonly encountered in the clinical setting. For the both *R. radiobacter* and *O. anthropi*, bacteremia is the most common type of infection peritonitis, endocarditis, meningitis, urinary tract infection and pyogenic infections are much commonly encountered. Cellulitis and abscess formation typify the infections resulting from the traumatic introduction of CDC group EF-4b into the skin and subcutaneous tissues[38].

### **Conclusion**

Nonfermenters can cause a vast variety of infections and account for approximately 15% of all Gram negative bacilli cultured from clinical specimens. Non-fermenters may differ in their pathogenic potential and transmissibility and many are multidrug resistant. They have been incriminated in infections such as a septicemia, meningitis, osteomyelitis, pneumonia, Urinary tract infection and surgical site infection. *Acinetobacter* has emerged as an important nosocomial organism causing infectious outbreaks in critically ill patients leading to high mortality and morbidity. *Stenotrophomonas maltophilia* is not highly virulent, nevertheless several factors may promote its ability to colonize the respiratory tract and plastic surfaces, such as catheters and endotracheal tubes. So most of the nonfermenters are known to cause nosocomial infections in immunocompromised hosts and are resistant to many antibiotics and are known to produced extended spectrum  $\beta$ -lactmases and metallo  $\beta$ -lactmases.





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