

New Targets for Treatment, Prevention and Control of Carbapenem-Resistant *A. baumannii* Isolates Causing Nosocomial Infections

Introduction

Acinetobacter spp. are among the most frequent causes of nosocomial bacterial infections. This genus have gained increasing attention as different members of the family show multiple virulence factors that cause clinical infections with high rates of mortality but also the possibility of industrial applications due to the production of some enzymes useful for bioremediation [1]. Up to know 41 distinct validly named species [2], although there are a number of strains of provisional termed genomic species, several with not validly name and others of an unknown taxonomic status [3].

Acinetobacter baumannii is undoubtedly the species showing the highest clinical relevance although during the last years *A. pittii* and *A. nosocomialis* (also known as the *A. baumannii* group) are also emerging as nosocomial pathogens [1,4,5]. Two main features contribute to the great interest of *A. baumannii* over the other related species: first, the ability of clinical isolates to develop multidrug- resistance acquired by either mutations or genetic elements such as plasmids, transposons, or resistant islands and second, the ability to colonize almost any surface and survive in the environment making it very difficult to eradicate from clinical settings [1,4].

During the last decades *A. baumannii* has emerged as one of the most dangerous pathogens and a priority of the World Health Organization. It has been currently added to the hit-list of most important hospital pathogens known as "ESKAPE" [6]. Clinical cases typically involve ventilator-associated pneumonia and septicaemia with high rates of mortality, and also endocarditis, meningitis, burn and surgical wound infections, and urinary tract infections. Bacteriemia is very common in elderly immunocompromised patients being pneumonia the main source of the majority of cases. Nosocomial pneumonia affects patients in intensive care units with a rate of mortality of 30 to 75% [1,5]. Risk factors to acquire *Acinetobacter* infections include major surgery, malignant diseases or burns, immunocompromised patients such as the elderly, neonates with low birth weights, and patients with prolonged illnesses. Predisposing factors are malignant diseases, trauma, prolonged antibiotic treatment, prolonged intravenous lines, post operations, urinary catheterization, mechanical ventilation, parenteral nutrition and long hospitalization.

The emergence of nosocomial infections caused by *A. baumannii* is a result of different factors:

- a) a succesful adaptation to adverse environmental conditions
- b) the long persistence on dry surfaces
- c) the resistance to antibiotics
- d) increasement of immunocompromised patients
- e) plasticity of their genome

Ecology

Acinetobacter spp. are mostly free living saprophytes found ubiquitously in nature but the precise environmental reservoirs are unknown (Doughary). Generally considered part of the normal flora of the skin and mucosa of the pharynx, human respiratory secretions, urine, rectum and other clinical samples. They are the only group of gram-negative bacteria that may be natural residents of the human skin with carriage rates of 42.5% in healthy individuals and as high as 75% in hospitalized patients. Generally the species most frequently isolated are *A. johnsonii*, *A. lwoffii*, *A. radioresistens*, *A. baumannii*, *A. calcoaceticus*, *A. haemolyticus*, *A. pittii* and *A. nosocomialis*. Colonization of the intestinal tract is controversial but some authors suggest and report that there is the most important reservoir of resistant strains [1,4].

The *A. baumannii* has been reported to inhabit soil and aquatic environments. The organism has also been isolated from different sources such as freshwater ecosystems, raw sewage and wastewater treatment plants and activated sludge, vegetables, fruit and animal sources, it has also demonstrate its ability to grow on crude oil and it has also been isolated from lice collected from homeless people. Several studies have shown that strains of *A. baumannii* can adhere to human cells and form biofilm on abiotic surfaces what enhaces its capacity of survival en the environment (on fingertips and inanimate objects such as glass, plastic, and other environmental surfaces) even after exposure to dry conditions and nutrient starvation during extended periods of time [1,4].

Volume 2 Issue 4 - 2015

Editorial

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Received: August 7, 2015 | Published: August 13, 2015

In the hospital environment *A. baumannii* is the most important species. It has been isolated from ventilator tubings, arterial pressure monitoring devices, humidifiers, washbasins and also from the skin of healthcare personnel, mattresses, pillows and in all types of ventilator equipment and moist situations such as sinks and tap water. Hospital food could also be a potential source of *A. baumannii*. Some strains also survive exposure to commonly used disinfectants like chlorhexidine, gluconate and phenols, particularly those not used in the appropriate concentrations and is able to survive much better, compared with other gram-negatives, on fingertips or on dry surfaces when tested under simulated environmental conditions [1,4,6].

It is clear that the emergence of nosocomial and community-acquired infections due to *A. baumannii* is mainly a result of high adaptability to adverse environmental conditions and the ability to persist for months in dry and harsh environments. They are able to survive on moist and dry surfaces and some strains have been found to be tolerant of soap.

Pathogenesis and Virulence

Multiple virulence factors have been described in *A. baumannii* but little information is known about the contribution to its pathogenicity. The pathogenic mechanisms are little understood or studied and the precise mechanisms involved in the establishment and progression of infections by this species are unclear. Among the most important pathogenic mechanisms and virulence factors are:

- a) twitching motility mediated by a type IV pilus and adherence to biotic and abiotic surfaces due to the production of structures such as pili and forming biofilms
- b) surface polysaccharides forming capsules, extracellular polysaccharidae (PNAG) and LPS structures
- c) OmpA which induces the apoptosis in epithelial cells and degrades chromosomal DNA and is also implicated in resistance to complement and biofilm formation
- d) Outer Membrane Vesicles containing multiple virulence factors (OmpA, proteases, phospholipases, LPS, lipoproteins, bacterioferritin, catalase, etc.)
- e) Phospholipases, important for human serum resistance, epithelial cell invasion, etc
- f) enhanced virulence in the presence of ethanol not only assimilated as carbon source but also due to increased expression of some factors related to stress responses
- g) Penicillin-binding proteins; g) siderophores for iron uptake
- h) quorum sensing systems related to production of biofilm and other virulence mechanisms
- i) antimicrobial resistance to almost all commonly used antibiotics
- j) genomic plasticity and versatility due to the diversity of genomic islands and mobile structures such as plasmids, integrons and *ISAb* elements [1,4].

Emergence of carbapenem-resistant clones causing nosocomial infections

During the last years *Acinetobacter baumannii* has become resistant to almost all commonly used antimicrobial agents, including β -lactams, aminoglycosides and quinolones and isolates showing multidrug or pan-resistant phenotype are described in the clinical setting worldwide. In no organism is the antibiotic panresistant paradigm more evident than in *Acinetobacter baumannii* that has acquired resistance genes to virtually all antibiotics capable of treating Gram-negative bacteria. The continuing rise in the number of such isolates is of great concern as there are no new antibiotics development resulting most of the infections fatal [7,8].

For resistant isolates, carbapenems are the last therapeutic option due to their good activity and low toxicity but resistance to this group of antibiotics has been increasing during the last years. Although alterations to PBPs, loss or decreased expression of OMPs and efflux systems can confer resistance to carbapenems, in *Acinetobacter baumannii* the most important mechanism is the production of carbapenemases. Several classes of beta-lactamases have been identified in *A. baumannii*:

- a) class A which includes the majority of the extended-spectrum beta-lactamases (ESBL) TEM, SHV and CTX-M families and GES and KPC carbapenemases
- b) class B metallo-beta-lactamases of the IMP, VIM, SIM and NDM families
- c) class C, ADC enzymes (also referred to as AmpC enzymes)
- d) class D beta-lactamases that are by far the most prevalent in *A. baumannii* [7].

There are five well known families of OXA-type carbapenemases that have been found in *A. baumannii*: the OXA-23-like, OXA-40-like, OXA-51-like, OXA-58-like and OXA-143-like [9] and a sixth group recently described and named OXA-235 [10]. All *A. baumannii* isolates possess an inherent class D beta-lactamase gene bla OXA-51 but they can additionally produce more. While other carbapenemases are commonly found to be located on class 1 integrons, bla NMD and the OXA-type enzymes genes are frequently been associated with *ISAb* elements and located on plasmids which facilitates the overexpression and transferability of the resistance genes [11]. To add to this a number of resistance islands *AbaR* have been identified among multidrug-resistance isolates belonging to worldwide epidemic lineages.

Outbreaks of *A. baumannii* are often clonal and a large number of infections globally can be attributed to three of these lineages named WW1, WW2 and WW3 corresponding to the European clones I, II and III that are commonly resistant to carbapenems [11,12]. The reason why some lineages are particularly successful and spread internationally is unclear but it's clear that the selective advantage that multiple antibiotic resistance confer, appears to be driving their expansion. While the core genome of these lineages is stable, the accessory genome is more fluid [3,13,14].

Future Alternatives

The cost to control outbreaks can be staggering, and some institutions have been forced to close units in order to interrupt the transmission of *Acinetobacter*. There is a need to prevent transmission in the healthcare setting and keep the organism, especially multidrug-resistant isolates, from becoming endemic in an institution. To achieve this goal it is also important to control contamination of the environment, water or food. Careful personal and hand-hygiene should be observed. It is important that laboratories should embark on active surveillance to detect cultures and patients who are colonized with multidrug-resistant *Acinetobacter* as well as a community-based surveillance to determine carriage rates. Other measures successful in the control of outbreaks include isolation precautions for infected or colonized patients, patients' relatives and staff, environmental disinfection, antimicrobial control, and unit closure if needed.

Implementing control of WW clones is a priority as these multidrug-resistant clones serve as host for the multiple genetic elements (integrons, IS, pAs, transposons and plasmids) that confer their resistance phenotype. Strains belonging to these successful WW clones I, II and III are an effective vehicle for the dissemination of the elements vertically and acting as donors to transfer its resistance elements horizontally to other strains, species or genera. As the majority of isolates belonging to these clones locate the resistance genes on plasmids, identification of this structures and control of its transferability is needed [3,13-16].

Treatment of *Acinetobacter* infections should be individualized according to susceptibility patterns. Carbapenem resistance has been described as a global sentinel event making evident we need to implement effective intervention and control strategies. The ability of the OXA-type beta-lactamases to confer carbapenem resistance has had a huge impact on the ability to treat *A. baumannii* infections and the current situation suggests that the problem is set to increase [7,8,17]. As preservation of carbapenem efficacy is essential for continued success against this microorganism, we need to be very careful in the management of carbapenems and promote the combination of these antibiotics with β -lactamase inhibitors which could overcome strains with these resistance [17,18].

In summary, strategies searching for new classes of antibiotics and knowledge on pathogenicity mechanisms and virulence factors seemed to be promising. Research on novel antimicrobial agents does not seem very promising due to the ability of *A. baumannii* to develop a huge range of resistance mechanisms but investigation of novel antibiotic substances from natural sources should also be considered. The novel strategies to interfere with the pathogenicity and bacterial growth were opens up a challenging alternative. Some of these targets could be vaccines against PNAG, OmpA and OMV antigens, antibiotics against OmpA and interruption of quorum sensing signals for pathogenesis inhibition.

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