ACINETOBACTER MAIN CAUSE OF HOSPITAL ACQUIRED INFECTIONS: A REVIEW

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ABSTRACT

Hospital acquired infections (HAIs) are mostly caused by Gram-negative organisms and is one of the major issues in patient safety. These infections are often associated with the medical processes of hospitals such as invasive medical devices and various surgical procedures. Gram-negative organisms account for most infections in the hospital environment because of their ability to acquire resistant against multiple antibiotics. Through different mechanisms including the synthesis of β- lactamases, overexpression of transmembrane efflux pump, loss of porins, synthesis of antibiotic modifying enzymes, target mutations, ribosomal mutation or modifications, mutations in lipopolysaccharide structure etc. these organisms have developed drug-resistant property and the genes encoded in plasmids play a vital role in developing the resistant. Among all Gram-negative bacteria, *Acinetobacter baumannii* is an emerging pathogen that accounts for about 80% of all reported infections. Although other species of *Acinetobacter* are also often associated with HAIs. Acinetobacter is non-motile, obligate aerobic Gram-negative coccobacillus and are ubiquitous free-living saprophytes in soil and water. It is commonly transmitted through medical devices such as ventilators, urinary catheters and other invasive devices in hospitals but its ability to colonize on the skin of individuals often increases the rate of transmission through person to person contact. Patients admitted to Intensive Care Unit (ICU) are at the major risk of getting infected by *A. baumannii* and these includes pneumonia/ventilator associated pneumonia (VAP), bloodstream infections, wound abscesses, urinary tract infections etc.

Keywords: HAI, *Acinetobacter baumannii*, β- lactamases, VAP

INTRODUCTION

Hospital-acquired infection (HAI) also called nosocomial infection is a kind of infection which is acquired in the hospital by a patient in whom the infection was not present at the time of admission but emerged after discharging, and it also includes occupational infections among the staff of the organization [1,2]. Nosocomial infections are mostly caused by Gram-negative organisms and are one of the major issues in patient safety. HAIs are one of the major causes of death [3] which have worldwide prevalence and affect developed, developing, and resource-poor countries. The rate of morbidity and mortality is significantly increased and cause financial losses for health-care system. The study has revealed that within hospital it is mostly prevalent is intensive care units (ICUs) followed by acute surgical and orthopedic wards [4], approximately, 30% patients in ICU are affected by at least one nosocomial infection [5]. Most frequent causative agents are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Acinetobacter baumannii* (Ab). Over the last 15 years, Ab has emerged as a potent nosocomial pathogen. It became the second most common Gram-negative bacilli after *P. aeruginosa* to be isolated from clinical specimens, and they rank fourth after (*P. aeruginosa*, *S. aureus*, *K. pneumoniae*) as most frequent hospital-acquired infectious agents. From the last two decades, clinicians worldwide have identified *Acinetobacter* genus, especially Ab as a frequent organism associated with critically ill patients [6].

HISTORICAL ANALYSIS OF THE GENUS *ACINETOBACTER*

In the early 20th century (1911), a Dutch microbiologist, Beijerinck, isolated an organism from the soil by a culture medium that was enriched by calcium acetate and named it as *Micrococcus calcoaceticus* [7]. Similar organisms were described and allotted to 15 different genera and species over the following years. In 1954, Brisou and Pre´vot proposed the current taxonomic genus, i.e., *Acinetobacter*. In Greek, it means non-motile. Brisou and Pre´vot separated the non-motile organisms from those of motile organisms within the genus *Achromobacter* [8].

However, this was not widely accepted until Baumann *et al*. concluded that the previously isolated organisms belonged to a single genus for which the name *Acinetobacter* was proposed. These findings led the genus *Acinetobacter* for an official acknowledgment in 1971 by the Sub-committee on the Taxonomy of Moraxella and Allied Bacteria. In the 1974 edition of Bergey's Manual of Systematic Bacteriology, the genus *Acinetobacter* was listed, with the description of a single species, *Acinetobacter calcoaceticus* [7]. In the "Approved List of Bacterial Names," in contrast, two different species, *A. calcoaceticus* and *Acinetobacter lwoffii*, were included, based on the observation that some *Acinetobacters* were able to acidify glucose whereas others were not [10]. Current taxonomic nomenclature defined as *Acinetobacter* is within the family *Moraxellaceae* and order *Gammaproteobacteria*, which includes the genera *Moraxella*, *Acinetobacter*, *Psychrobacter*, and related organisms [9].

GENERAL DESCRIPTION OF THE GENUS *ACINETOBACTER*

They are Gram-negative nonmotile coccobacilli possess very minimum growth requirement. They are strictly aerobe and cannot tolerate anaerobic condition but can survive on a variety of surfaces and aquatic environment. *Acinetobacter* is non-fermenter but has oxidizing properties. They are catalase positive and oxidase negative organism. DNA contains 39-47% of G+C content. They are a part of the commensal flora of human and animal which are regular contaminants of the hospital environment. Up to 25% of healthy ambulatory adults exhibit cutaneous colonization by *Acinetobacter* and are the most common Gram-negative bacteria carried on the skin of hospital personnel [11].

SOURCE AND OCCURRENCE

They are ubiquitous in nature, and inhabitants of soil, water, and sewage water as well. They are found mostly in aquatic environment. About 97% of natural water sample has been isolated with *Acinetobacter* spp. The bacterial count reached up to 100/ml. The organisms have been found to represent 1.0-5.5% of the HPC flora in drinking-water samples and

have been isolated from 5% to 92% of distribution water samples [12]. In the USA, one survey from untreated ground water has been isolated with the *Acinetobacter* spp. found in 38% of water supplies. They are the producer of slime layer, and there are no differences in the slime production of *Acinetobacter* spp. isolated from water samples and clinical specimens. *Acinetobacter* spp. are the normal flora of skin and occasionally in the respiratory tract of healthy individuals. Ingestion of drinking water having *Acinetobacter* spp. do not cause gastrointestinal infections; however, it can cause non-gastrointestinal problems in susceptible patients and individuals associated with health-care settings. *Acinetobacter* spp. are susceptible to chlorine, so uses of disinfectants can limit the transmission of organism. In an epidemiological survey performed to investigate the colonization of human skin and mucous membranes with *Acinetobacter* species, up to 43% of non-hospitalized individuals were found to be colonized with these organisms while in hospitalized patients the carriage rate of *Acinetobacter* spp. were comparatively high, i.e., 75% [13]. The fecal carriage rate of *Acinetobacter* spp. were detected up to 25% by Dijkshoorn *et al.* and the predominant species were *Acinetobacter johnsonii* and *Acinetobacter* genomic species 11 [15]. Chu *et al.* found 53% of medical students and new nurses to be colonized with *Acinetobacters* in summer versus 32% in winter [16]. These seasonal variations are associated with the prevalence of Ab infections. Ab was recovered from 22% of body lice sampled from homeless people [14]. *Acinetobacters* are capable of surviving on inanimate substances for a longer period. Berlau *et al.* investigated vegetables in the United Kingdom and found that 30 of 177 vegetables (17%) were culture positive for *Acinetobacter* [17]. Interestingly, Ab and *Acinetobacter* genomic species 11 (each at 27%) were the predominant species, followed by *A. calcoaceticus* and *Acinetobacter* genomic species 3 (each at 13%), while *Acinetobacter* genomic species 13 was found only once. In Hong Kong, 51% of local vegetables were culture positive for *Acinetobacter* species, the majority of which were *Acinetobacter* genomic species 3 (75%), but one sample grew Ab [18]. Houang *et al.* found *Acinetobacters* in 22 of 60 soil samples in Hong Kong, and the most frequent species were *Acinetobacter* genomic species 3 (27%) and Ab (23%), with only one sample yielding *A. calcoaceticus* [18].

LOAD OF *ACINETOBACTER* SPP. IN HOSPITAL ENVIRONMENT

Several studies have shown the prevalence of *Acinetobacter* spp. in hospital environment but their rate of occurrence vary widely depending on the protective actions and safety measures taken by different hospitals. The presence of *Acinetobacter* spp. has been found in almost all part of hospital which includes sinks, floors, cupboards, linens, mattresses, ventilators, and respirators. Contamination of mattresses occurs through breaches in plastic covers that allowed water penetration and persistence of the organism in the wet foam of the mattresses. More recently, feather pillows were found to be contaminated with considerable numbers of *Acinetobacter* in an outbreak of infection in the Netherlands [19]. It suggests that these inanimate things play a major role in transmission of *Acinetobacter* spp. which contributes them to be a potent nosocomial pathogen. It has been reported that *Acinetobacter* cells can survive on dry surfaces for durations even longer than that found for *S. aureus* [20,21]. An epidemic strain of multi drug resistant (MDR) *Acinetobacter* spp. has been shown to survive for up to 6 days after inoculation on to dry filter paper, duration similar to that found with *S. aureus*, which persisted for 7 days while *P. aeruginosa* and *Escherichia coli* survives up to 24 hrs or less [22]. Their ability to survive in all most all inanimate substances and minimal nutritional requirements make them very common nosocomial pathogen associated with outbreaks. The outbreaks also occur when the patient has some underlying disease and various medical processes have implicated, for example, intravenous catheters, respirators, and peritoneal dialysis. [23].

ROUTES OF TRANSMISSION

Environmental sources and cross-transmissions are the most common cause of transmission of *Acinetobacter* infections. Possible routes include direct contact, burn and inhalation especially in ICUs where patients are on mechanical ventilation. In patients with *Acinetobacter* bacteremia, intravenous catheters have also been identified as a source of infection. Water baths and humidifiers are also a potent source of infection. The oral transmission (through ingestion) is not a usual source of infection.

FACTORS CONTRIBUTING TO ESTABLISH A WELL FORMED DISEASE

Acinetobacter infections are favored by these following factors:
• Ability to upregulate and acquiring resistance gene which enable them to resist mostly all common antibiotics used in health-care setting, and enable them to become MDR bacteria.
• They are part of commensal flora which facilitates the cross-transmission.
• Their nonfastidious property helps them to survive on various inanimate materials as well as in aqueous environment.
• Underlying disorders, for example, long-term diabetes mellitus, immunocompromised state such as in patients with HIV infection can enhance the risk of *Acinetobacter* infections.
• Drug therapies such as immunosuppressive drugs and antibiotics, chemotherapy, radiotherapy, current surgeries, endotracheal intubation, intravenous procedures, catheterization contribute toward easy development of infection as all mentioned procedures suppress the immunity and make a route for easy entry.

SPECIES OF MEDICAL IMPORTANCE

Several studies have revealed that among all the different species, Ab is the most common nosocomial pathogen found in mostly all clinical specimens and are associated with major complications, for example, respiratory tract infections, and septicemia. According to the data of Centers for Disease Control and Prevention, the species Ab accounts for nearly 80% of reported *Acinetobacter* infection. *Acinetobacter* genomic species 3 and 13TU have been implicated in nosocomial outbreaks while *A. johnsonii* has been associated with catheter-associated bacteremia. *A. calcoaceticus*- Ab complex [24,25] contains isolates that are mostly glucose acidifying. The majority of glucose-negative, nonhemolytic strains found in clinical specimens seem to be identified mainly as *A. lwoffii*, *A. johnsonii*, *Acinetobacter haemolyticus* is the species who shows hemolysis. Other groups seem to be implicated only occasionally in human infections.

CLINICAL CASES ASSOCIATED WITH *ACINETOBACTER* SPP.

Acinetobacter spp. are associated with various clinical cases which sometimes is often fatal. Their abundant occurrence in nature and minimal nutritional requirement make them a potent pathogen to cause a well-formed infection. They occur mostly in the ICUs, as most of the patients are on ventilation. A mechanical ventilator is a potent source of infection, and it contributes as a source of transmission. Ventilator-associated pneumonia and ICU-acquired pneumonia are frequent cases occurred in ICUs. Post-surgical abscess and wound infections, bacteremia and septicemia as a result of the surgical and medical process, urinary tract infections on catheterization, pleural effusion, peritonitis, and meningitis are associated with *Acinetobacter* infections.

HEALTH IMPACT OF *ACINETOBACTER* INFECTIONS

MDR strains are associated with critically ill patients. This property to resist approximately all common antibiotics set the mortality rate at a high level, i.e., 26-68% [26-28]. *Acinetobacter* infections and colonization are associated with increased mortality [29-31]. Other studies that rigorously controlled for severity of illness did not find *Acinetobacter* infection to be independently associated with increased mortality [26,32-34]. However, patients with deliberated underlying illness the organism can be responsible for high mortality rate individually. *Acinetobacter* infection is associated with increased morbidity and a prolonged length of hospital stay. The duration of hospital stay is directly associated with the related infections caused

by *Acinetobacter* spp. and MDR- *Acinetobacter* spp. Patients with *Acinetobacter* bacteremia had a 5 days excess length of mechanical ventilator dependence and ICU stay, compared with critically ill patients without *Acinetobacter* infection [33]. The severity of infections is depended on the length of hospital stay and degree of antibiotic-resistant.

MECHANISM OF ANTI-MICROBIAL RESISTANCE

Acinetobacter spp. are emerging as a potent threat to hospitalized patients as they are untreatable with the most common antibiotics. The trend to resist the drugs has been extremely enhanced form past two decades. Ab among all species has been developed itself as a most common and also as a super bug associated with nosocomial infections. Upregulation of innate resistance, for example, impermeable outer membrane and acquisition of resistance gene are two major skill used by this bacteria that helps it to become a deadly pathogen in mainly health-care facility. Their natural habitat is also contributing them to achieve easy transmission of infection. MDR - Ab is very common problem to the physician to treat the patients especially having respiratory problems and associated with ICU units. MDR - *Acinetobacter* can be defined in two ways, i.e., resistance to carbapenem or resistance to ≥3 classes of antibiotics [35]. Some strains are only treatable with polymyxin, but resistance to them is also been reported in literature. The rapid emergencies of resistant strains of *Acinetobacter* globally possess the treatment option limited and crucial. In three possible ways, they resist the drugs, i.e., production of enzymes that degrade the antimicrobial substances, mutation that changes the bacterial target sites, and alteration in cellular function, for example, efflux pump [36].

They produce a wide variety of β-lactamases, enzymes that degrade the β-lactam ring. This enzyme confers resistance to penicillins, cephalosporins, and carbapenems. They resist broad-spectrum cephalosporins by AmpC cephalosporinase enzyme that is encoded in chromosome [40,41]. Class B metallo-β-lactamases (MBLs) are expressed in certain strains which provide them to resist a wide range of antimicrobial agent including carbapenems [37]. MBLs are easily transferred among bacteria which possess a great chance to get resistant genes easily. *Acinetobacter* spp. are well known for their resistance capability through alteration in bacterial targets. Porin channels and outer membrane proteins are the way for the drug to reach their targets, alteration in these structures enabling them to be a deadly pathogen that resist all kind of drugs. Loss of proteins from the outer membrane is linked with carbapenem-resistant Ab (CR-Ab) [37]. Various efflux systems are associated with Ab, for example, AdeABC, AdeM, Tet(A), Tet(B). Resistance to colistin is thought to be mediated by changes in the bacterial cell membrane that interfere with the agent's ability to bind bacterial targets [38]. *Acinetobacter* spp. can acquire genes from *Pseudomonas* spp. *Salmonella* spp., etc. A study have shown an interesting fact that in France MDR - *Acinetobacter* strain consist of a resistance island containing approximately 45 resistant gene and that appeared to have been acquired from species of *Pseudomonas*, *Salmonella,* and *Escherichia* [39]. Another study has been done on CR property of Ab and a total of 51 clinically significant CR-Ab were isolated from different specimens including tracheal aspirate, blood, wound sample and urine during t 4 months. Modified Hodge's test detected carbapenemase production in 50 out of 51 (98%) isolates, whereas ethylenediaminetetraacetic acid-disk synergy test detected MBLs production in 48 out of 51 (94.1%) isolates [42]. These findings support that since last two decades Ab has been emerged as a potent nosocomial pathogen.

MANAGEMENT OF MDR-*ACINETOBACTER*

Like all living organisms, microbes face challenges to their own survival as in their environmental and ecological changes. Because of this reason they acquire, develop or evolve mechanisms that favor them to survive in their surroundings. Their short life cycle opens infinite opportunities for genetic mutation to occur. In the other hand, their ability to acquire gene and sharing genes among related and unrelated species facilitate their existence. These properties enable them to respond to environmental as well as ecological changes. Hence, the antibiotic therapy in the health-care system can actually change the ecological atmosphere which can trigger the development of resistant strains. Thus, the uses of antibiotics should be minded and only used at proper dose. Fishman has described some strategies by which these consequences can be controlled which include education, formulary restriction, streamlining, and antibiotic cycling. All of them restrict the unnecessary uses of antibiotics, uses of broad spectrum antibiotics, continuous use of one antibiotic which can limit the occurrence antibiotic resistant strains.

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America recommend two core strategies for antimicrobial stewardship programs as per 2007 guidelines which says that prospective audit of antimicrobial use with direct interaction and feedback to the prescribing physician and formulation restriction and pre- authorization requirements can lead to significant reductions in antimicrobial use. To manage the load of MDR-*Acinetobacter*, analysis of susceptibility and antibiogram are at the major concern. Each MDR-*Acinetobacter* isolate must be checked for susceptibility and it should be readily accessible by physicians. They are helpful in both patient care treatments and surveillance of MDR-*Acinetobacter*.

Antibiogram often deals with the drug pattern of many isolates derived from clinical specimens rather consider for a single isolate. Compilation of drug pattern is generally done by the microbiology laboratory using data from various units. In case of Ab, susceptibility results from different isolates are compiled during a specific period and must be updated annually. The resulting antibiogram suggests the choice of drug for treatment of *Acinetobacter* associated infections in that particular unit. They can be used by physician to control the infection when the susceptible result is yet not available for patients. It also used in monitoring the changes of drug susceptibility. In one study, isolate of Ab obtained from Brahmakumari Hospital was subjected to antibiotic susceptibility testing to get the antibiogram. None of isolates gave the zone of inhibition at all to cefotaxime, they so considered as extended spectrum beta-lactamases. A synergy of cefotaxime and *Terminalia chebula* has been tested and it has been observed that there was a zone of inhibition formed [43]. This study indicates that the combination of medicinal plant extracts and known antibiotics offers significant potential for the development of novel antimicrobial therapies [43].

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