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Review Article

Development of immunization trials against *Acinetobacter baumannii*

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ABSTRACT

Acinetobacter baumannii has recently crossed all lines once considered harmless, pushing its way as a nosocomial pathogen. It had acquired resistance to almost all available chemotherapies and mainly targets intensive care residents; causing pneumonia and major outbreaks with high mortality rates. This urged the need for preventive methods, which include infection control, non-specific immune-therapy, passive, and active immunization in order to offer vulnerable immune-compromised patients a flare in the dark. Several attempts were done for constructing effective vaccines with promising results. These are precisely classified, documented, and discussed in this up-to-date review.

Contents

1. Introduction

Hospital's laboratories are pointing to a new emerging Gram-negative bacilli named *Acinetobacter;* specifically *Acinetobacter baumannii*. The bacterium affects different human organs particularly the lungs, causing Ventilator-Associated Pneumonia (VAP) [1] which usually develops to septicemia in intensive care unit (ICU) residents [2]. It mainly infects the peritoneal cavity then rapidly disseminates to the lungs and spleen, it replicates to produce septic shock and might lead to associated bacteremia [2,3]. Infection is characterized by a rapid onset within 36 h, and progressive symptoms that leads to a mortality rate ranging from 40% to 60% [4]. *Acinetobacter* spp. are Gram-negative diplococcobacilli, non-fermentative, and are strictly aerobic bacteria [5]. They are catalase-positive, oxidase negative, and hard to destain, thus sometimes misidentified as being Gram-positive. Therefore, it has undergone many changes in taxonomy from *Neisseriaceae* to the family *Moraxellaceae* [6,7]. They are non-motile due

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to the absence of flagella, but they rather exert a twitching movement [8]. *Acinetobacter* genus is pervasive in nature between soil, water, human skin, throat, and respiratory tract colonization [9]. But this was pleaded against in the case of *A. baumannii* and its two relatives (*Acinetobacter calcoaceticus* and *Acinetobacter nosocomialis*) collectively known as ACB complex together with *Acinetobacter pittii* [10] that are only isolated from hospital-setting and are outbreaks-associated [7,11,12]. Recently, two more species were added to the ACB complex, those include *Acinetobacter seifertii* sp. nov. [13], and *Acinetobacter dijikshoornii* sp. nov. [14].

Although DNA-DNA hybridization can identify *Acinetobacter* genus [12], further advanced techniques are required to identify *A. baumannii* down to the strain level. Such techniques include amplified 16S ribosomal DNA restriction analysis, and high resolution fingerprint analysis [15]. However, those are complicated methods and are not present in common laboratories. Therefore, it is a hard mission to quickly identify *A. baumannii* in ICUs, and in times of outbreaks [16].

Moreover, *A. baumannii* possesses special pathogenic traits such as the ability to form biofilm, the production of siderophores, the presence of capsular polysaccharide and fimbriae, the cell to cell signals (Quorum Sensing), and the production of hydrolytic enzymes [17]. These virulence features facilitate its adherence and tolerance to desiccation on inanimate surfaces for more than 14 days [18]. All of these pathogenesis factors lead to persistent occupancy in hospitals, increase morbidity rates, and eventually lead to hospital cross transmission with persistent outbreaks [19].

2. Epidemiology

The incidence of nosocomial infection patterns are changing due to the emergence of new pathogens, along with changes in the antibiograms due to antibiotics abuse [20]. Based on the surveillance data, alerts were raised toward *A. baumannii* in particular due to its high persistence on inanimate objects in ICUs for months. In addition, *A. baumannii* rapidly acquired resistance against almost all potent antibiotics, thus adding days to ICU stay [21].

Outbreaks were correlated to seasonal factors, patient cases, and disasters times. *A. baumannii* was found to be more prevalent in late summer to early winter [7] rising up to 50% during the period of July to October [22] favoring humid and moist habitats [23]. *A. baumannii* was frequently reported in times of war, such as in Afghanistan and Iraq [24]. It was revealed that morphine used as analgesic in battlefields potentiates the growth of *A. baumannii* infections rather than trauma itself [25]. Not only in times of war did *A. baumannii* prosper, but also in natural disasters such as the 1999 Marmara earthquake aftermath [26] and Asia's tsunami in 2004 [27]. In general, patients at risk are those who are immunocompromised, elderly, premature neonates, and patients that had recently undergone surgery or experienced a major trauma or were previously admitted to contaminated ICUs [28,29]. Smoking and alcohol abuse makes patients more prone to community acquired *A. baumannii* pneumonia, especially in tropical areas [30].

3. Therapy and resistance

A. baumannii exhibits a natural occurring resistance to a range of antibiotics such as Amoxicillin (penicillins), narrow-spectrum cephalosporins, Ertapenem, Trimethoprim, and Chloramphenicol [31]. *A. baumannii* managed to acquire resistance genes against several classes of antibiotics through the transfer of plasmids, transposons, and integrons from other Gram-negative bacteria [32]. All contributed to *A. baumannii* resistance and the ability to expel aminoglycosides [19], rifampicin [33], quinolones [34], fluoroquinolones [35], tetracyclines [36], in addition to some disinfectants [37]. Therefore, different strains of multi-drug resistant (MDR) *A. baumannii* arouse in many countries all over the world and caused memorable outbreaks [38], with remarkable regional differences [39]. Tigecycline first showed a promising effect against MDR *A. baumannii* [40,41]. However, resistance to tigecycline has been reported since 2007 in Israel [42], and recently worldwide when used as monotherapy for a long time [43]. Alternatively, Colistin was found effective against Imipenem resistant *A. baumannii*. However, its use warranted due to its toxicity, side effects [44], cross-resistance with the host defenses that lead to the emergence of hypervirulent strains [45], reported resistance [46,47], and the worrisome hetero-resistance phenomenon [48]. Few novel classes of antibacterial agents currently show hope against *A. baumannii* such as peptide deformylase inhibitors (PDIs) and LpxC inhibitor, but they are still under trials with contradictory data [49–51].

The lack of effective treatment against *A. baumannii* introduced atypical therapeutic options [52], such as the use of bacteriophages [53], podophage [54], the intake of levamisole an anti-helminthic that is potent against *Acinetobacter lwoffii* [55], the use of nanoparticles generating nitric oxide [56], photodynamic therapy [57], and radio-immunotherapy. However, safety concerns still arise against their application [58]. Other methods can render MDR *A. baumannii* susceptible such as multidrug efflux inhibitor [59,60], anti-biofilms [61], quorum quenching [62], interference with the lipopolysaccharide (LPS) biosynthesis [63], the use of antimicrobial peptides [64,65], in addition to the use of several botanical preparations. However, all are still under trials along with reported resistance [66].

A British report highlighted that resistance to antibiotics will definitely increase regardless of their prescription pattern, adding societal cost of treatment of around £10 billion every year. This will impact the future of invasive procedures and surgeries, that require antibiotics as a standard regimen for prophylaxis [67]. Furthermore, a study revealed that patients infected with Imipenem-resistant *A. baumannii* had longer hospital stay of about 21 days and added an amount of $334,516 to hospital charges [68], with an increase in mortality rates by 25% in general hospital population and 50% in ICUs [69]. In a survey established in European countries from 2003 to 2009, *A. baumannii* showed to cause mortalities ranging from 3% to as high as 67% [70]. Thus, prevention right from the start has become a necessity.

4. Control and immunostimulants

The previous data declares a war whoop against superbug *A. baumannii*. The increased resistance of chemotherapeutics to both conventional and last resort antibiotics necessitates prevention. Infection control is an important pillar in patient care excellence especially ICUs residents, and is a key factor to decrease nosocomial infections in the society and maintain antibiotic stewardship [71]. A recent study came to a shocking conclusions that the gowns, gloves, and unwashed hands of health care providers themselves are frequently contaminated with MDR *A. baumannii* acting as reservoirs in the ICUs [72–74]. When *A. baumannii* colonizes the respiratory tract, it can disseminate horizontally by droplet infection to as far as 22-feet [75]. In addition to that, 25% of the hospital environment had persistent contamination for months even after multiple-cleaning treatments [76], due to its biofilm formation ability [77]. Although new approaches arose to control the biofilm formation of *Acinetobacter* [78–80], however they are all under primary trials. All these facts urge researchers to be directed towards immunotherapeutics as a lifebuoy to unmet medical needs. Immunotherapies include non-specific, passive and active immunization.