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Present Developments in the Creation of Sophisticated Acinetobacter Therapies

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Abstract

Acinetobacter baumannii is a common global source of infections linked to healthcare that have a high morbidity and fatality rate. Due to the fast emergence of multidrug-resistant and very drug-resistant strains of A. baumannii, the therapeutic management of these infections has become much more challenging. Therefore, the creation of innovative intervention techniques is desperately needed to counteract this infection, which is resistant to several drugs. One of the best medical treatments for infection management is vaccination, which also has the potential to prevent A. baumannii from developing multidrug resistance. Here, we focused on the three most crucial preclinical vaccine development steps: immunological correlates of protection, antigen selection, and model organisms for effectiveness assessment. We also highlighted current developments and future obstacles in the production of A. baumannii vaccines.

Keywords: Genomic analysis, Autoimmune disorders, Personalized medicine.

Introduction

Acinetobacter baumannii is a commonplace extracellular gram-negative bacterium that is linked to a significant number of healthcare-associated illnesses (HAIs) both in hospitals and the community (1). Additionally, infections resulting from natural disasters or battle wounds are often caused by *A. baumannii* (1, 2). The infection is often linked to a high morbidity and death rate and may cause a wide range of illnesses, including meningitis, pneumonia, and major bloodstream or soft tissue infections. The fast emergence of multidrug-resistant and highly drug-resistant strains of *A. baumannii* has made the medical management of these infections more challenging. Furthermore, *A. baumannii* frequently creates biofilms that are impervious to both host defensive mechanisms and antibiotic therapy. Therefore, the creation of innovative intervention techniques is desperately needed to fight and manage multidrug-resistant *A. baumannii* infections (3).

Epidemiology

New pathogens are emerging, which is causing changes in nosocomial infection frequencies. Abuse of antibiotics is also causing changes in antibiograms (4). *A. baumannii* was singled out for alerts according to surveillance data because of its high tenacity on inanimate items in intensive care units (ICUs) for extended periods (5). Furthermore, *A. baumannii* developed resistance to practically all-powerful antibiotics quickly, lengthening the duration of an ICU stay. Seasonal conditions,

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patient instances, and catastrophe dates were all connected with outbreaks. According to research, *A. baumannii* is more common in late summer to early winter, peaking at 50% from July to October and preferring wet and damp environments (5). Reports of *A. baumannii* were common during wartime, for example, in Afghanistan and Iraq. It was discovered that, as opposed to the trauma itself, morphine used as an analgesic in combat zones amplifies the spread of *A. baumannii* infections (5). *A. baumannii* did not only thrive during wartime but also natural calamities like the aftermath of the 1999 Marmara earthquake (5, 6) and the 2004 Asian tsunami (5, 6).

Therapy

Many antibiotics, including trimethoprim, amoxicillin (penicillins), narrow-spectrum cephalosporins, Ertapenem, and chloramphenicol, are naturally resistant to *A. baumannii* (7). *A. baumannii* was able to transfer plasmids, transposons, and integrons from other Gram-negative bacteria, which allowed it to acquire resistance genes against many types of antibiotics. The capacity to eject aminoglycosides, rifampicin, quinolones, fluoroquinolones, tetracyclines, and some disinfectants were all factors in *A. baumannii* resistance. As a result, many multi-drug resistance (MDR) *A. baumannii* strains have emerged and caused notable epidemics in numerous nations worldwide, with notable regional variations. The use of bacteriophages, prophages, levamisole, an anti-helminthic that is effective against *Acinetobacter lwoffii*, the use of nanoparticles producing nitric oxide, photodynamic therapy, and radio-immunotherapy were among the atypical therapeutic options brought about by the lack of an effective treatment for *A. baumannii*. Nevertheless, there are still safety issues with its use (8, 9).

Immunostimulants

One of the best medical treatments for infection management is vaccination, which also has the potential to prevent the pathogen from developing medication resistance (10). There are currently few viable antibiotics on the market or in the late stages of research that can be used to treat infections caused by *A. baumannii* that are resistant to several drugs. Therefore, the burden of *A. baumannii* infections would be significantly reduced by the development of safe and efficient *A. baumannii* vaccines for both active and passive vaccination. After being started by Pachon and McConnell, *A. baumannii* vaccine development for specific populations has started in several labs worldwide, and various experimental vaccination trials have been published (11). Several outstanding studies have lately assessed the requirements and financial benefits of an *Acinetobacter* vaccine, as well as the advancements in science and probable difficulties in *A. baumannii* vaccine development's clinical trials. Although advancements and efforts have been made, the development of *A. baumannii* vaccines has lagged behind that of other nosocomial pathogens (like Clostridium difficile, Staphylococcus aureus, etc.). Additionally, no *Acinetobacter* vaccine has entered a Phase I clinical trial to date, indicating the relative difficulties in creating safe and effective *A. baumannii* vaccines. Here, we focused on the three most crucial preclinical vaccine development processes while discussing current developments and future obstacles in the development of *A. baumannii* vaccines: correlations between antigen selection correlates of protection and animal models for efficacy evaluation (12).

Selection of vaccine antigens

The immunogen in the early investigations on the *A. baumannii* vaccine was inactivated whole cells or components of cells (OMVs and OMCs) (13). The findings of such investigations have amply supported the viability of developing vaccines against *A. baumannii*. Animals (mostly mice) immunized with those vaccines develop antigen-specific antibody responses, which protect against a challenge involving different clinical and ATCC typing strains of *A. baumannii*. The challenge results in significantly lower bacterial burdens in tissue and blood, as well as a reduction in the inflammatory responses that accompany it (14). Despite the vaccines' excellent efficacy, possible safety and regulatory issues restrict their clinical usage. Therefore, determining which antigens best elicit the protective immune response has a major positive impact on vaccination safety and production. However, the expected heterogeneity in O-antigen and CPS demonstrated by various *A. baumannii* strains and samples is likely to challenge the glycoconjugate method (15). Even though almost all *A. baumannii* serovars were found in the early research, more is needed to know how common these serovars are among clinical isolates. According to recent research, 13% of the 100 *A. baumannii* strains examined were recognized by a monoclonal antibody targeting *A. baumannii* K1 CPS, demonstrating the relative variety of this pathogen's surface carbohydrate antigens (16). To ascertain which serotypes are more likely to be connected with a certain illness or are very common, further epidemiological research would be required to identify the optimal vaccine candidate. In this context, various bacterial pathogens, including *A. baumannii*, generate poly-N-acetyl-b-(1-6)-glucosamine (PNAG), a surface exopolysaccharide. Researchers demonstrated that antiserum to 9Glc-NH(2)-TT was strongly opsonic against different unrelated clinical strains of *A. baumannii* that synthesize varying quantities of surface PNAG by

conjugating a synthetic that resembles PNAG to tetanus toxoid (TT) (17). More crucially, compared to mice given a placebo, treatment with those antisera dramatically decreased the amounts of bacteria in the blood and lungs, indicating that PNAG could be a viable antigen for eliciting protective antibodies that cover a wide range of serotypes. The use of protein antigens or multivalent glycoconjugate vaccines against extremely common *A. baumannii* serotypes, as in the situation of S. pneumoniae, are two additional methods to offer a comprehensive coverage of the various serotypes (18).

Immunological correlates of defense versus infections caused by *A. baumannii*

The development of *A. baumannii* vaccines has advanced significantly over the past five years. However, before a vaccine candidate can go into clinical trials, more work may need to be done to improve the vaccine's protective effectiveness in terms of survival rates and tissue and blood-bacterial burdens. This will thus need a deeper comprehension of protective immunity's processes and possible correlates of protection (19).

Experiments demonstrate the much-anticipated function that certain antibodies play in the vaccine-induced defense against *A. baumannii* infection. The following findings have been reported: (1) the protection against *A. baumannii* challenges was recapitulated by passive transfer of entirety sera from vaccinated or convalescent animals toward polyclonal or monoclonal antibodies toward the whole *A. baumannii* cells or its cell elements; (2) anti-OmpA antibody levels are associated with survival in mice; (3) opsonization of K1-positive *A. baumannii* strains, but not K1-negative varieties, with a specific monoclonal antibody significantly enhanced neutrophil-mediated bactericidal action in vitro; and (4) vaccinations of B cell-deficient mice were unable to elicit a protective immunity toward subsequent *A. baumannii* challenges. Conversely, the mechanism behind antibody-mediated defense against *A. baumannii* needs to be better understood (20). Research has shown that immunological sera promote *A. baumannii* opsonophagocytic death but not complement-mediated death. Conversely, some research has shown that the opposite is true. It was also rather surprising to learn that FcRg-/- mice maintained the immunity established by the immunization (21).

Animal models for developing a vaccination against *A. baumannii*

The employing of animal models with clinical significance is essential to the effective creation of vaccines, as it is in the majority of vaccine studies and development (22). The mouse continues to be the most often utilized laboratory animal species for assessing the effectiveness of the *A. baumannii* vaccine. The first mouse models were created using either virulence-enhancing (like porcine mucin) or immunosuppressive (like cyclophosphamide) drugs to guarantee or promote the growth of a persistent infection. Replicable *A. baumannii* infections in immune-competent and traditional mouse strains have been successfully created by several organizations recently (23). *A. baumannii* pneumonia and wound infection in rats also resemble many features of clinical illness in humans. Immunocompromised animals mimic the conditions of human *A. baumannii* infections, which typically occur in immunocompromised individuals; conversely, the employing of immune-competent animals would allow the identification of the critical immune components that are essential to the host's response toward *A. baumannii* infection. Using multiple animal models could facilitate the development of secure and efficient *A. baumannii* vaccines (24).

The *A. baumannii* vaccine study group must rationally choose suitable animal models for vaccine efficacy evaluation in addition to standardizing vaccine immunity and effectiveness evaluation procedures (such as the time intervals between vaccinations and challenge, as well as the challenge varieties, doses, and routes, among other things) to compare the experimental vaccines' efficacies across laboratories (25). Regarding this, it was observed that the quantity of OmpA utilized in vaccines has a significant influence on the immunodominant epitope protection and immune responses elicited; a high dose promotes a Th2-biased response, while a low dose induces a balanced Th1/Th2 response. This may account for the variations in the vaccine's protective efficacies reported by various (26). The evaluation of protection against challenges posed by different clinical isolates in addition to challenges by homologous strains in several *A. baumannii* vaccination trials are positive as they help determine the vaccine candidate's overall level of protection. Nonetheless, the majority of the research could have described the challenge strains' serotypes or genetic diversities. Apart from the previously reported strain-specific changes in surface carbohydrate antigens, there is also significant heterogeneity in the proteomic patterns and biological functions of OMVs derived from several *A. baumannii* strains (27, 28).

Conclusion

As an aggressive, resistant superbug, *A. baumannii* has become more widespread, creating outbreaks that have led to high rates of morbidity and mortality, particularly in people who are already vulnerable. Because *A. baumannii* is difficult to identify, it

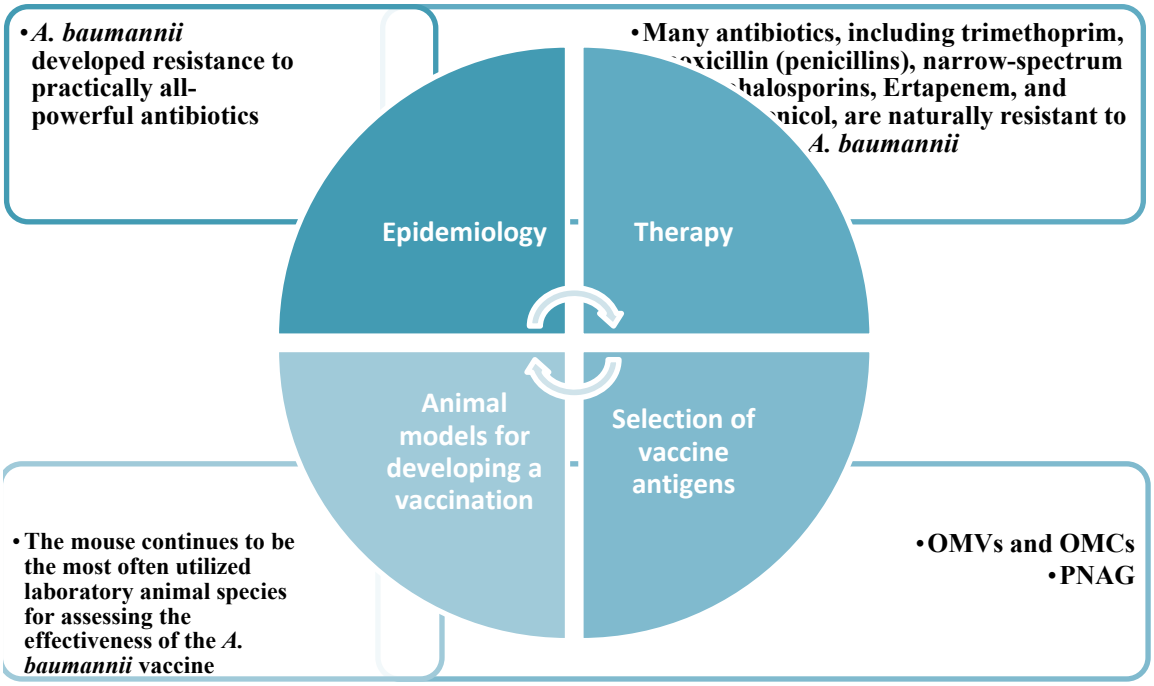

Fig1. Acinetobacter baumannii treatment flowchart.

takes time and expensive equipment, especially when trying to save lives. The rapid development of antibiotic resistance in *A. baumannii* makes it difficult to control and has already ended the antibiotic golden age. The supply of new antibiotics to combat the *A. baumannii* invasion has run out, and all other treatments are still in the research and development stage and will take years to reach the market. Therefore, ending the vicious cycle from its inception makes perfect sense in addition to infection management. Although the Australian group's groundbreaking work using in silico techniques to screen *A. baumannii*'s antigenic determinants was a good first step toward identifying effective epitopes, it was not entirely successful because *A. baumannii* contains some immune-dominant antigens that may obscure other effective antigens in the pathogen.

Furthermore, polysaccharide epitopes are never predicted by in-silico-based techniques; only protein epitopes are. Consequently, the mere use of those suggested epitopes would not be very beneficial, and more research using binding methods is required to provide a powerful vaccination against *A. baumannii*. In light of the trial-and-error nature of miss-guided empirical vaccine manufacture, it is evident now how important epitope screening techniques are. Relatively fewer antigen candidates for *A. baumannii* have been found and made accessible for vaccine development than other infections. On the other hand, the development of novel antigen candidates is probably going to happen more quickly now that *A. baumannii* research has exploded and we know more about the pathogen's virulence factors and molecular pathogenesis. Furthermore, two more epidemiological findings on the serotype prevalence of clinical *A. baumannii* separates are crucial for the logical design of glycoconjugate vaccines with broad serotype coverage, even though it was acknowledged that a vaccine targeting even a small number of *A. baumannii* strains may still be beneficial.

Therefore, given the current state of vaccine development technology, which includes reverse vaccinology, immunoproteomics, glycomics, and other innovations, there is a good chance that within the next five to ten years, multicomponent *A. baumannii* vaccines with well-defined compositions, high-efficacies, wide coverage, and favorable safety profiles will be put through clinical trials.

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Author contributions

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent to publication

Not applicable.

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