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Approach to Optimise the Treatment of Bacterial Infections: Combined Antimicrobial Therapy with Enhancers of Innate Immunity

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Looking for New Strategies for the Treatment of Bacterial Infections

Antimicrobials (ATM) themselves are the source of the evolutionary pressure that eventually renders obsolete. Dissemination of resistance is given by the inappropriate use of ATM by clinicians in human and veterinary medicine and agricultural community [1].

At the present the responsible of invasive infections in intensive care units were characterised as multi-resistant strains as *Pseudomonas aeruginosa*, *Acinetobacterbaumannii*, *Escherichia coli* and *Klebsiella pneumoniae* carrying extended spectrum β-lactamases or carbapenemases. ATM usage has continued to select pathogens resistant to newer ATMs considered to be treatments of last resort [2]. Cephalosporins were traditionally useful for the treatment of *Staphylococcus aureus* (SA) infections although their usefulness is nowadays reduced by the emergence and worldwide dissemination of Methicillin-Resistant Strains (MRSA) [3]. Contributing to the antimicrobial resistance problem is self-medication with freely available over-the counter antibiotics. Also their use as growth promoters in food animals such as cattle, pigs and chickens have produced the emergence of multi-resistant strains as enterococci vancomycin resistant [4].

The role of immune system in invasive infections is pivotal for helping the ATM therapy. The systemic inflammatory response in human sepsis is primarily attributable to highly conserved microbe derived macromolecules that feature surface patterns not found in human tissues. The intelligent use of immunomodulators will likely be individualized based upon specific laboratory and/or clinical findings that predict those patients most likely to benefit [5].

Development of New Antimicrobial Agents with Bactericidal Activity

In some cases bacteria have been able to develop simultaneous resistance to two or more antibiotic classes, making the treatment of infections caused by these microorganisms extremely difficult, very costly and in many instances associated with high morbidity and mortality [6]. New mechanisms of resistance have resulted in the simultaneous development of resistance to several antibiotic classes creating very dangerous Multidrug-Resistant (MDR) bacterial strains, some also known as "superbugs" [7].

In recent years, the number of new antibiotics licensed for human use in different countries has been lower than in last 30 years. In addition, there has been less innovation in the field of antimicrobial discovery research and development. The pharmaceutical industry, large academic institutions or the government are not investing the necessary resources to produce the next generation of newer safe and effective antimicrobial drugs.In many cases, large pharmaceutical companies ended their anti-infective research programs due to economic losses.

In the final analysis, however, the problem of antibiotic resistance will not be solved with the creation of many more or stronger, bactericidal antimicrobials. If past history is in any way a good predictor of future history, microorganisms will consistently continue to adapt to their environment by developing resistance to newer antibiotics and serious infections caused by these bacteria will continue to pose a major challenge for clinical practice. It will take a collaborative effort among industry, academia and government for us to strike a "balance" in the war against pathogenic bacteria. ATMs addressed to clear the infection caused by gram positives as MRSA (daptomycin and linezolid) have been introduced in last decade as well as the third generation semi-synthetic tetraciclyne, tigecycline. In the same address Telavancin (glycopeptide) and Ceftobiprole (fifth generation Cephalosporin), were developed for controlling gram positive resistant infections. Unfortunately, developing of new antimicrobials active against gram negative bacteria are not expected for the next years [1].

Use of Traditional Antimicrobial Therapy with Innate Immunity Enhancers

Modern antimicrobial therapy involves the strengthen interaction among Microbiology, Pharmacology and Immunology, as well as the severity of the infectious diseases.

Antimicrobial resistance is a serious concern worldwide in Human and Veterinary Medicine, since it is responsible of most of the therapeutic failures in bacterial infectious diseases. For this reason the development of new therapeutic alternatives became in a global emergency, being pivotal the understanding of how the immune system may be manipulated for controlling some bacterial diseases, using different immunomodulators as novel therapy.

The immunomodulation is a therapeutic approach by which is intending to modulate the auto-regulation process of the defense system. In infectious disease therapy, the immune response balance-reinstatement may increase the resistance, decreasing the severity of infection and shorting the recovery period-time. The modulation of immune response may occur by direct or indirect mechanisms, by mean of the interaction between of an immunomodulator and the immune cell system.This interaction stimulates or inhibits the release of a messenger biological possessing immunomodulatory activity [8,9]. The mode of action of many immunomodulatory compounds is not

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fully elucidated, but generally their main target cells in the immune system are lymphocytes T and B cells, monocytes/macrophages, granulocytes and NK cells [9].

Immunomodulators of prokaryotic source, in immunotherapy, are given by the administration of non-pathogenic or attenuated form of microorganisms. Bacterial compounds named PAMPS, as lipopolysaccharides, lipoteichoic acid, flagellin andbacterial DNA, serve as ligands for the pattern recognition receptors expressed on immune effector cells, known as Toll-Like Receptors (TLRs) [5]. Other PAMPS recognizer elements as myeloid cell antigen CD14, participating on the innate immune response.

In a clinical trial undertaken in Veterinary Medicine, *Mycobacterium phlei* Cell Wall Extract (MCWE) demonstrated high efficacy (70-80%) in endometiritis *Streptococcus zooepidemicus´* infected susceptible-mares when given at single dose alone, intravenously (IV) and intrauterinely, [10]. Mares who failed treatment with MCWE alone were subjected to another trial. The therapeutic strategy was undertaken combining an IV single dose of MCWE given at 0 h with an IV single dose of Enrofloxacin (EFX) 5 mg/kg given 12 h after MCWE administration. A bacteriological cure of 80% of the mares involved in this study was observed [11]. A novel approach to antimicrobial therapy is to recognise the beneficial aspects of antibiotic accumulation inside the immune cells and to consider these cells as 'drug delivery devices' [12,13]. Mobile phagocytes travel to, and accumulate at, the site of infection and could be a practical vehicle to deliver suitable concentrations of antibiotics (e.g., Fluorquinolones) to infected tissues. The 12 h timing delay would theoretically synchronise a potentiated interaction between the highest plasma concentration of EFX and the maximal IL-1 stimulation of phagocytes. It seems logical to expect that this timed dosing approach optimised the pharmacokinetic process and was responsible for the higher post-treatment efficacy.

Enterococcus faecalis CECT7121 is a non-pathogenic strain, proposed as immunomodulator. This probiotic, modulates the innate immune system response by inducing the synthesis of IL-12 and IL-10, two pivotal cytokines for the maintenance of the host's immune homeostasis [14,15].

Preclinical trails madein Balb-C mice challenged with *Salmonella enteritidis*, showed that peritoneal macrophages from animals treated with *E. faecalis* CECT7121 and stimulated with *Salmonella* were able to respond releasing high levels of inflammatory cytokines, compared with untreated animals. The differences observed in the pattern of cytokines released by macrophages from both groups of animals support modulation of the immune system at the systemic level [16].

Other studies have demonstrated the usefulness of the Isolation of *E. faecalis* CECT7121 cell wall extract (PEF7121), when used in combination with EFX (more used in veterinary medicine) and its active metabolite ciprofloxacin–CFX-(more used in Human Medicine) in a mice- septic shock model induced by *Salmonella enteritidis*. The outcomes observed in this study, demonstrated a potentiation on the therapeutic effect when the combination PEF7121+CFX or EFX were given. A significant potentiation has been observed after the combination with CFX (40% of surveillance), followed by 20% of surveillance, after combination with EFX, whilst the surveillance values obtained after separated administration, ranged 10%. The results obtained in this trial indicate that IL-10 production was proportionally higher (3.25:1) when compared with IL-12. The evaluation of the anti-inflammatory response IL-10-mediated after assessing concentrations post-stimulations, separated and combined with PEF7121 or *Salmonella*, resulted in a significant production of IL-10. However, the in vitro stimulation of the combination PEF7121+*Salmonella enteritidis* decreased the IL-10 concentration levels three folds [17]. This correlated with several studies which evidenced that patients with septic shock showed in the last stage, higher levels of IL-10, which also correlated with patient´s death [18]. The presence of PEF7121 with decreasing of IL-10 obtained in this assay may result favorable on the septic shock evolution.

The results of clinical trials of traditional immunomodulatory therapies as treatment with anti-endotoxins, antagonists to specific mediators, arachidonic acid metabolites, reactive oxygen species, immunoglobulins granulocyte colony-stimulating factor IFN-γ and immunonutrition have been disappointing more than encouraging the antimicrobial therapy [19-21]. New strategies such as the use of bacterial wall extracts create new expectations in the treatment of severe infections.

As conclusion, the use of innate immunity enhancers may be useful for combining with traditional ATM therapy in moderate and severe bacterial infections. The complementary use of immunomodulators with suitable ATM must be given at different administration time in a therapeutic regimen to obtain the potentiation. This field of research is attractive and has potential interest, since due to the high amount of uncontrolled variables involved in pre-clinical and clinical trials, more rational studies need to be carry-out for each disease in particular.

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