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HYPOTHESIS: Is a Failure to Prevent Bacteriolysis and the Synergy Among Microbial and Host-Derived Pro-Inflammatory Agonists the Main Contributory Factors to the Pathogenesis of Post-Infectious Sequelae?

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INTRODUCTION

Why Have Clinical Trials of Sepsis Been Unsuccessful?

It is disconcerting that entering the third millennium, severe microbial infections and their sequelae e.g., sepsis, septic shock, ARDS, "flesh-eating syndromes," still claim the lives of numerous patients annually. Furthermore, it is of great interest that while immunomodulating agents have proved beneficial in the treatment of inflammatory conditions such as rheumatoid arthritis, a large series of clinical trials which have been conducted in the last decade and which have mainly tested only single immunomodulating agents as therapies for septic shock, have been mostly unsuccessful. In 1996, Verhoef et al. (1) have stated that reviewing the literature on sepsis therapies "the area of immunomodulation has now become an area of more realism and the results of early trials have forced investigators to go back to the drawing board to re-investigate the whole concept of immunotherapy and immunoprophylaxis. In a more recent Point of View in Critical Care Medicine, entitled "Sepsis research: We must change course," Dr. Nasraway has hit the nail on its head (2). Reviewing the disappointing results of no less than 29 prospective controlled studies of human sepsis performed in the last decade, he has questioned whether "it is rational to attempt to alter the inflammatory responses by administering a single immunomodulating agent while simultaneously failing to control for the many interventions that also alter cytokine expression?" He has also raised serious doubts about the morality of any future trials of sepsis if conducted in the present manner. Baue (3), Opal and Yu (4), Cross et al. (5), Teplick and Ruben (6) and Abraham (7), have recently assessed the state of the art in sepsis research prevention and treatment, the reasons why the trials of sepsis have invariably failed to prolong the lives of septic patients, the hazards involved in the future use of multidrug strategies in sepsis, and the contributions of animal models to the development effective therapeutic regimens in humans. Reading through the extensive literature on sepsis research and treatment, it was surprising to realize that no less than 35 different anti-inflammatory agents and strategies have been recommended, usually singly, to cope with post-infectious sequelae (in 1–13). It is however important to stress that, at the bedside, anti-inflammatory agents are too often administered to patients when the deleterious pathophysiological cascades leading to septic shock and organ failure have already been irreversibly initiated. Therefore, one cannot avoid assuming that the recommendations to test only one antagonist, at time, to suppress the pathophysiological cascades in sepsis and septic shock, might have been unrealistic to begin with and also erroneous. Presumably, these have been based on the concept that there might exist a single "omnipotent" pro-inflammatory agonist generated following microbial invasions of the blood stream, which is efficiently neutralized, on time, might inhibit the multiple pathophysiological cascades responsible for the sepsis syndrome. Also, the use of multidrug strategies (4, 5, 8, 13) has been hampered by reports warning against the hazards of combination therapies in sepsis (4, 5, 16). Is it possible that,

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today, sepsis research has reached a dead end because of "flawed concept or faulty implementation?" (5).

Results from animal models have clearly indicated that the inhibition of septic shock induced either by endotoxin (LPS), lipoteichoic acid (LTA), peptidoglycan (PPG) or by viable microbial cells, has been mostly successful only if the anti-inflammatory agent has been administered prior to microbial challenge. This strongly suggests that the main obstacle facing clinicians at the bedside is that once sepsis symptoms have appeared, it might already be too late to effectively prevent the pathophysiological cascades leading to tissue damage and organ failure. Therefore, strategies to prevent septic shock and of additional post-infectious sequelae in humans should inonvolve distinct preventive measures especially in defined groups of high-risk patients (3–13).

Which Strategies Might Be Effective to Prevent Post-Infectious Sequelae?

The following clinical steps might prove effective if used early in patients suspected of developing bacteremia: 1) the use of early detection systems to herald the invasion of the blood stream by microorganisms, 2) the employment of therapeutic agents capable of inhibiting the activation of autolytic wall enzymes (muramidases) which induce bacteriolysis and the release of LPS, LTA and PPG, 3) the formulation of combinations among agents capable of disrupting the deleterious "cross-talks" (synergism) among microbial products and the host-derived proinflammatory agonists (14–16) and 4) a more aggressive use of preventive measures in selected groups of high risk patients.

The aim of the present point of view is to argue that two major aspects related to the pathophysiology of sepsis, septic shock and the "flesh-eating" post-microbial syndromes have not been adequately considered and also insufficiently researched, clinically: 1) the pivotal roles of synergistic interactions among microbial and host-derived agonists as the major mechanisms of tissue destruction in post-infectious sequelae and 2) the pivotal role of bacteriolysis in sepsis and the necessity to use drugs capable of attenuating it already at the very early phases following the invasion of the blood stream by microorganisms. Neither issues have been discussed to any extent in the clinical literature dealing with Critical Care Medicine. Therefore, it will be strongly recommended that a reassessment of some of the current concepts and dogams on which sepsis treatment and prevention have been based, be made.

A. The "Synergism Concept" of Cellular Injury: A Plausible Explanation for the Pathogenesis of Post-Infectious Sequelae

The most compelling evidence which might support the central role of synergistic interactions among a multiplicity of agonists in tissue damage in inflammation and infection had originated from the evaluation the life histories and the pathogentic strategies of the catalase-negative, highly toxigenic and invasive group A hemolytic streptococci and of the gas-gangrene-inducing clostridial species. Paradoxically, perhaps, these microorganisms share with activated mammalian phagocytes the ability to utilize synergism among their secreted agonists to spread in tissues, injure host cells and tissues and also to depolymerize the extracellular matrix (14, 15, 17). Therefore, lessons learnt from the pathophysiology of the disorders caused by toxigenic bacteria might shed light on the mechanisms of tissue damage and its possible prevention in a variety of post-infectious sequelae.

Already in 1959, it had been demonstrated that tumor cells which had been exposed to the non-immunogenic cytolysin, streptolysin S (SLS), were totally disintegrated upon the addition of non-toxic amounts of a streptococcus-derived cysteine proteinases (18). Also, while viable streptococci producing both H_2O_2 and the cell-bound SLS, readily killed mammalian cells, mutants lacking SLS were practically non-cytolytic (18, 19). Also, streptococcal cysteine proteinase acted in concert with additional exo products, mainly streptolysin O (SLO), to augment lung injury (20) and streptococcal mutants deficient in cysteine proteinase were much less invasive (21). These studies clearly indicated that combinations among several agents might be necessary to initiate spreading of streptococci in tissues and cell destruction (15). Extensive studies (14–16) have substantiated this hypothesis and further described how a synergism among subtoxic concentrations of membrane-perforators, oxidants and proteinases synergized to rapidly kill mammalian cells and also to release large amounts of arachidonic acid and some of its metabolites. The synergizing agents tested included: 1) the membrane-perforating agents, SLS, SLO, phospholipases A_2 and C, fatty acids, cationic proteins, the attack complex of complement, certain cytotoxic xenobiotics, 2) the oxidants H_2O_2, OH, ROO, HOCl, NO, and oxidants generated by xanthine-xanthine-oxidase, 3) the proteinases, elastase, cathepsin G, trypsin and plasmin. Synergism between oxidants and proteinases also induced destruction of extra cellular matrix (14, 22) and injured lungs (14, 23).

Synergism between cytotoxic antibodies, complement and plasmin (14), between H_2O_2 and cytotoxic antibodies, oxidants and lysophosphatides and between oxidants and free fatty acids (14), has also been described. Thus, irrespective of the sources of agonists used, whether of microbial or of host origins, a triad comprised of a membrane perforator, an oxidant and a proteinase constituted a most powerful cell injuring cocktail. Such agents are generated in large amounts during infection and inflammation. Since the synergistic cell damage could be inhibited to a large extent either by inhibitors of the perforators, by scavengers of the oxidants or by proteinases inhibitors, it was assumed that the simultaneous presence of all three types of agents was necessary to induce maximal synergistic cell damage (14, 15). However, since it is unrealistic to expect that even the administration of large, tolerable amounts of anti-inflammatory agents, might totally eliminate the bulk of toxic agents generated in tissues, even small amounts of agents, remaining, might still synergize to injure cells (14). Therefore, it is speculated that only cocktails of appropriate antagonists might be capable of disrupting the synergism among the pro inflammatory agents responsible for the initiation of septic shock, organ failure and the "flesh-eating syndromes" (16, 24).

B. Is a Failure to Suppress Bacteriolysis in vivo the Achilles Heel of Treatment of Post-Infectious Sequelae?

While phagocytosis might kill internalized bacteria either by oxidative or by non-oxidative pathways, it is also accompanied by exocytosis of lysosomal hydrolases, neutral and cationic proteinases, highly cationic proteins and enzymes (PLA_2) and also the generation of reactive oxygen and nitrogen species. As suggested, these secreted agents might act in synergy to injure cells and tissues (14, 15, 18). However, the highly cationic agents secreted by activated phagocytes (25–27) also share an important common property in their ability to activate nascent autolytic wall enzymes (muramidases) in bacteria which results in bacteriolysis (27, 28) and the massive release of endotoxin lipoprotein, (LPS), lipopteichoic acid (LTA), and peptidoglycan (PPG). Paradoxically, perhaps, beta-lactam antibiotics are also potent activators of bacteriolysis and their administration during sepsis might adversly affect patient's lives (29, 30), (see further). However, microbial cell wall components released by bacteriolysis can activate the complement and the coagulation cascades but most importantly, also act on mononuclear cells to induce the generation of reactive oxygen species (ROS), NO, OONO, a large variety of hydrolases, including PLA_2, TNF- and additional cytotoxic cytokines. Many of these might act in synergy to injure cells, to cause circulatory failure and probably also to enhance translocation of bacteria from the gut into the blood stream. Therefore, it is highly plausible that combinations among anti-bacteriolytic agents and anti-inflammatory strategies might prove more beneficial than the use of single antagonists to inhibit the deleterious consequences of sepsis (16).

C. Therapeutic Strategies to be Used at the Bedside

At the bedside, the following strategies might be found beneficial to control sepsis, septic shock myositis and faciitis:

Early detection systems. The presence of microbial cells and their secreted toxins (LPS, LTA, PPG) in the blood stream, might be detected by sophisticated immunotechniques. Also the measurement of the levels of the sensitive predictive markers of sepsis, LPS, CRP, IL-1, IL-8, PLA_2 and procalcitonin, have proven predictive. However, insufficient awareness of the problem, but mostly economic constraints still do not allow a widespread use of such tests in general hospitals.

The potential benefits of anti-bacteriolytic agents. Although the potential role of bacteriolysis-inducing antibiotics which result in LPS and LTA release, is well recognized but still hotly debated (29, 30), there are no published reports on strategies to prevent early bacteriolysis in sepsis by selective drugs. It is encouraging, therefore, that, in vitro, the polyanions (e.g. polyanethole sulfonate, heparin, dextran sulfate, suramin and Evan's blue and certain D-amino acids) were found to strongly inhibit polycation and beta-lactam-induced bacteriolysis (27, 28). In gram-positives, the sulfated polyanions are believed to interact and bind to LTA, the presumed regulator of the autolytic wall enzymes (28). Preliminary studies (to be published) have also shown that polysulfates also strongly inhibited penicillin-induced lysis of *E. coli*. It is enigmatic that publications in reputed basic science journals which had described the role of polycations in bacteriolysis and the potential inhibitory effects of polysulfates on bacteriolysis, are never cited in the clinical literature. The potential value of certain antibiotics as bacteriolysis inhibitors has also been described. Vancomycin, has been shown to depress cell wall turnover in staphylococci (31), and clindamycin (32) was found to depress LPS release from *E. coli* and the subsequent

production by mononuclear cells of TNF- and IL-1 beta. Also, chloramphenicol was shown to depress the biosynthesis of autolysins in staphylococci and also to induce a significant cell wall thickening contributing to bactriolysis inhibition. Although tetracycline is not considered an anti-bacteriolytic agent, it was recently shown to depress cytokine production and septic shock induced either by LPS or by Gram-negative rods (33). Therefore, the attenuation of bacteriolysis, at the very early phases of blood invasion, might be essential to prevent the synergy among pro-inflammatory agonists generated by microorganisms and the host's own immune system (14–16).

Additional strategies might prove effective to inhibit synergistic interactions causing tissue damage and post-infectious sequelae. In addition to their potential anti-bacteriolytic properties (27, 28), polysulfates might also neutralize the direct toxic effects exerted by leukocyte-derived cationic proteins, including lysozyme, elastase, cathepsin G and PLA_2 (14, 27), the synergism between polycations and ROS (see previously), the attack complex of complement, intravascular coagulopathy, and also several of additional injurious effects of neutrophils (14, 15, 27). Polyanions might perhaps also act to inhibit LPS-binding proteins (LBP) (34) shown to transfer LPS and LTA to CD14 present on cells of the myeloid lineage (35). The following strategies and agents have already been tried, mostly singly, in clinical trials of sepsis, but only with a limited success (1–12, 16, 41): Anti-endotoxin strategies (4, 10), IL-10 (36), IL-12 (37), inhibitors of chemokine receptors (38), glucans and additional non-metabolizable sugars, to lower the translocation of the microbial flora from the gut (16), hemodialysis to eliminate excessive amounts of LPS, LTA, PPG and cytotoxic cytokines, intravenous hyperimmune gamma globulin to neutralize exotoxins (39), LPS, LTA and superantigens, GMCSF (40), corticosteroids, NSAID, pentoxyphiline (an anti-TNF-agent), NO synthase inhibitors, a variety of anti-oxidants, anti-bradykinin, anti-PAF, and anti-prostaglandins. Ongoing trials of sepsis (Dr. Steven Opal, personal communication), also test the potential therapeutic efficacy of tissue factor pathways inhibitor, antithrombin III, activated protein C, PAF acyl hydrolase, polymyxin dextran conjugates, bacterial permeability increasing proteins (BPI), FAF-acetyl hydrolase, soluble PLA_2 inhibitor and TNF Fab antibody. However, it seems that as in previous clinical trials of sepsis, only single antidotes in selected groups of patients, are being tested. Today, no trials in humans have been reported which test the potential efficacy of combination therapies using any of the above listed agents. The main clinical frustration and dilemma is still that therapeutic agents are administered late when the deleterious inflammatory cascades have already been irreversibly activated. It is encouraging, therefore, that three recent publications have reported that animals could survive lethal injections either of LPS or of viable Gram-negative bacteria if either, 1) tyrfostin, a tyrosine kinase inhibitor (42), 2) dexabinol, a non psycho tropic cannabinoid but also an inhibitor of TNF- and NO production (43), or 3) the ROS scavenger, 21-amino steroid U-74389G (44), had been administered even a short period after LPS or bacteria. Another promising agent which merits clinical testing in sepsis is the non-toxic Tibetan plant preparation (PADMA-28) used for centuries as a remedy against inflammatory manifestations. Aqueous extracts of PADMA-28 were found to strongly inhibit neutrophil chemotaxis, ROS production by activated neutrophils, peroxidation of lipids, neutrophil elastase and cathepsin G, and the killing of epithelial cells induced by synergism among oxidants, proteinases and membrane-perforating agents. PADMA-28 also significantly inhibited the generation of TNF- and IL-8 by LPS-stimulated human mononuclear cells and also prolonged the survival of mice injected with LPS (Ginsburg and Barak, in press).

Today, the use of multidrug strategies in post-infectious sequelae might seem a "missions impossible" because both pro-inflammatory and anti-inflammatory processes occur side by side (distinct "double-edged sword" phenomena) (1–12). Nevertheless, the more extensive use of rapid, reliable, and inexpensive predictive markers of sepsis, which if followed by an early administration of anti-bacteriolytic agents combined with "cocktails" of appropriate antagonists, might significantly lower the load of those key pro-inflammatory agonists which otherwise might continue to synergize among themselves to injure tissues and also to activate the deleterious cascades responsible for organ failure. Obviously, the employment of "cocktail strategies" might be more effective if administered as prophylactics in certain high risk groups of patients.

However, any future development of novel multidrug strategies should be based on careful assays in animal models. In this respect the question whether a successful sepsis control in small laboratory animals resulting from any current strategy has any relevance to the human disease, is still controversial and hotly debated. Undoubtedly, this is still the main obstacle to the development of any novel anti-sepsis strategies in humans.

We should change some of the current concepts

and dogmas of sepsis research. It is surprising that the numerous publications in basic science journals which have described the potential role of cationic proteins and enzymes in bacteriolysis, its possible inhibition by polysulfates, and the possible role which might be played by synergistic cross-talks among microbial and host-derived agonists in the initiation of tissue injury in post-infectious sequelae, are never cited in the extensive clinical literature dealing with post-infectious manifestations. This is how pioneering observations and "novel" view points and ideas which might be so crucial to the elucidation of the pathophysiology, prevention and treatment of post-infectious complications, in humans, are "buried" for good.

Finally, the arguments presented further strengthen and also justify the calls by eminent specialists in Critical Care Medicine (1–4, 7–11) "to go back to the drawing board" (1), to reassess, but mainly to change what seems to be the "flawed concepts" (5) and some of current dogmas on which prevention and therapy of post-infectious sequelae have been based.

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