Study of the incidence of bacteremia in chronic hemodialysis patients.

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By

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Introduction:

Bacteremic infections are a major cause of morbidity and mortality in chronic hemodialysis patients **(Hoen, et al.,1998)**, infection arising from the percutanous vascular access necessary to accomplish hemodialysis is the most common source of infection occurring in these patients, previous studies have established that infection risk is lowest when vascular access occurs through arteriovascular fistula and highest when through central venous catheter **(Pasten et al., 2002).** Bacteremia is now the second most common cause of death in the hemodialysis population **(Lentino et al ., 2000).**

Staphylococcal bacteremia in chronic hemodialysis patients is the most frequent one and associated with the highest risk of complications especially infective endocarditis ***(*** **Dulton T., et al., 2003** ***).*** with mortality rates approaching 25% **(D-Agata EMC., 2002).**

Despite improvements in aseptic techniques and measures taken to decrease staphylococuss aureus carriage colonization, S taph aureus bacteremia remains a serous and frequent complication of hemodialysis **(Kiern et al., 1998).**

The emergence and rapid spread of S.aureus strains that are resistant to multiple antibiotics has limited the therapeutic options available to treat these infections.In the year 2000, 71%of dialysis units reported having>1 patient with an infection

caused by a methicillin-resistant S.aureus (MRSA) isolates.Of even more concern are the recent reports of recovery of S.aeureus isolates that are resistant to vancomycin and linezolid from patients undergoing long term hemodialysis.Therefore ,prevention of S. aureus infection is of paramount importance in this patient population **(Tokars et al., 2002).**

Many risk factors are implicated in occurance of bacteremia in chronic hemodialysis patients include: vascular access infection,diabetes, s.aureus nasal carriage, bad hygiene,iron overload,malnutrition, anemia and use of bioincompatible membranes **(Hoen B ., et al., 1998)**.

New developments in managing these patients(erythropoietin therapy, nasal mupirocin ,long term implanted catheters and synthetic membranes) may have alterd the epidemiologic patterns of bacteremia in chronic hemodialysis patients **(Lok ., et al., 2003 and Peacock et al., 2002).**

Mupirocin is a topical antimicrobial ointement with demonstrated benefit in eradicating colonization with S. aureus. Its efficacy for preventing S.aureus infection , however, remains controversial, especially for prevention of postoperative S.aureus infection **(Perl et al ., 2002).**

Aim of the work:

A Survey study to detect the incidence of bacteremia in chronic hemodialysis patients as an important risk factor for metastatic complications especially infective endocarditis in these patients.The study will involve those patients using arteriovenous fistulas and grafts for hemodialysis access.

IMMUNE DYSFUNCTION IN UREMIA

Introruction:

Uremia is associated with a state of immune dysfunction with increased susceptibility to infection and malignancy possibly related to dysregulation of immune system cell apoptosis. Apoptosis rates correlate with phagocytic function highlighting the benefit of efficient toxin clearance **(D'Intini et al.,2003).**

The pathogenesis underlying this increased susceptibility to infection has not been clearly identified, but it is believed to be attributable to impaired host defense mechanisms **(cohen et al., 1997).**

Both cellular and humoral immunity have been shown to be affected. Defects in cellular immunity appear to be more significant clinically. Most infections in ESRD patients are caused by common pathogens rather than opportunistic organisms, although patients with renal failure are considered to be immunocompromised **(Lew and Kaveh, 2000).** (Professional) phagocytes such as neutrophils exhibit impaired chemotaxis, adherence, reactive oxygen species (Ros) production, and phagocytosis. The mechanisms responsible for altered neutrophil functions are only partially understood and have been attributed to uremic toxins, malnutrition, iron

overload, increased intracellular ionized calcium, and dialysis therapy perse **(Cohen et al., 1997).**

Host Defense Dysfunction :

No aspect of host defenses is unaffected by uremia or its metabolic consequences. In addition to the accumulation of waste products which appear capable of directly inhibiting a wide variety of functions, the additional impact of chronic malnutrition **(Horl, 1999)** and anemia **(Besarab et al., 1999)** on resistance to infection play a major role in the appropriate responses to infection in these patients. Iron overload, an iatrogenic complication of transfusion therapy of anemia of chronic disease, contributed to impaired host defenses in uremic patients **(Walker and walker, 2000).**

Pathogenesis :

The defective host defenses in chronic renal failure patients, can be related to abnormal function of two cell types; the phagocytic cells and lymphocytes. Defective function of these cells, due to accumulation of a variety of substances as a result of impaired kidneys clearance **(Hirayama et al., 2000)** can be incriminated in most of the host defence impairment in chronic renal failure. Impaired responss to vaccines as well as delayed skin graft rejection in chronic hemodialysis patients is likely attributable to functional impairment of lymphocytes and antigen presenting cells.

Pathogenesis of neutrophil dysfunction in uremia:

Neutrophil impairment in uremia may be attributed to decreased cell survival as well as decreased functional response of cells; neutrophils from uremic patients have repeatedly been shown to express accelerated apoptosis **(Cendoroglo et al., 1999).** All aspects of neutrophil functions are, to a greater or lesser extent, impaired; in order to defend the host from foreign invaders, neutrophils must respond to signals that the particle is present(chemotactic signals), then migrate through the vascular endothelium and through the involved tissues.

Neutophils from uremic patients exhibit impaired chemotaxis and mobility **(Cohen et al., 1998).** Upon contact with the particle,the neutrophil must interiorize it; however neutophils from uremic patients exhibit markedly defective ingestion **(Vanholder and Ringoir , 1993).** There are available data indicating that substances ,which accumulate in renal failure cause the dysfunctional membrane dynamics of phagocytic cells, with, modified ubiquitin **(Cohen et al., 1998)**, a calcitriol correctable anomaly **(Hannula et al., 2000)** and p-cresol **(Cohen et al., 1998)** being implicated in various studies . After ingestion by phagocytosis, the phagocytic vacuole must fuse with intracellular granules and trigger toxic oxygen derivatives to result in death of invading microbes ,neutophils

exhibit decreased phagocytosis **(Himmelfarb and Hakim., 1994)** and decreased intracellular killing **(Diecher et al., 2000).**

Uremic syndrome and macrophage dysfunction :

It has been observed that in uremic patients an immunodeficient state and signs of activation of the immune system often, paradoxically, coexist. Furthermore, in uremic patients lymphocyte abnormalities, depression of cell-mediated immunity, impaired phagocytosis, chemotaxis and lymphopenia have been reported **(Marzocco et al., 2005).**

Immune system dysregulation mechanisms could be related to a reduced bioavailability of IL-2 secondary to its over consumption by activated T cells, to a down regulation of phagocyte adhesion molecules, to an increased production of IL-1, TNF and IL-6 by activated monocytes and of soluble CD23 by B lymphocytes and lastly to the presence of uremic toxins. Le Meur and coworkers suggested the possibility that uremia-associated-immunodeficiency could be linked to multiple and complex alterations of cytokine network and to the impaired involvement of monocytes, T or B lymphocytes, fibroblasts and endothelial cells. Many reports indicated that, in addition to the effect of the uremic toxins, therapeutic interventions, like haemodialysis and peritoneal dialysis, are suspected to contribute to the immune dysfunctions observed in uremic patients **(Marzocco et al., 2005).**

Among the immune cells, macrophages constitute the first line of host defence in conferring immunity against infections in humans and their functions have been recognized as a key factor responsible for immunological disorders associated to uremia. Stimulated macrophages induce a cascade of events which involve overproduction of cytokines, such as TNF, IL-1 and NO that has an important role in mediating macrophage functions. High blood concentration of various endogenous nitrogen compounds, deriving from protein metabolism, was hypothesised to be responsible of uremic symptoms and immunodysfunctions. Indeed, it has been demonstrated that uremia is often accompanied by accumulation of L-arginine analogues, like NG-monomethyl-L-arginine, MG and its precursor creatinine.

NO and macrophages:

NO is a pleiotropic mediator which acts in a variety of physiological and pathophysiological processes. NO is released by different type of cells (dendritic cells, NK cells, mast cells and phagocytic cells including monocytes, macrophages, microglia, Kupffer cells, eosinophils and neutrophils) as well as other cells involved in immune reactions, such as endothelial cells, epithelial cells, vascular smooth muscle cells, fibroblasts, keratinocytes, chondrocytes, hepatocytes, mesangial cells and Schwan cells **(Bogdan et al., 2000).** NO is produced from the

oxidation of Larginine by the enzyme NO synthetase which occurs in two major isoforms one is constitutive (endothelial and neuronal) and another is inducible (macrophagic). The constitutively expressed enzyme (cNOS) is calcium-dependent, releases NO under physiological conditions in various cells, including endothelial cells and neurons, and NO released by this isoform is involved in the regulation of blood pressure, organ blood flow distribution and the inhibition of the adhesion and activation of platelets and polymorphonuclear granulocytes. The iNOS is calcium independent and can be induced by pro-inflammatory agents, such as endotoxins (bacterial lipopolysaccharide, LPS), interleukin-1, tumor necrosis factor (TNF) and interferon, in endothelial and smooth-muscle cells, in macrophages and in other cell types **(Marzocco et al., 2005).**

Enhanced formation NO following the induction of iNOS has been implicated in the pathogenesis of shock and inflammation. Indeed, NO per se has been shown to behave rather poorly as a free radical. It is its reactivity with molecular oxygen, transition metals and superoxide that results in the formation of compounds with potentially profound cytotoxic effects. These derivatives of NO include highly reactive intermediates such as its oxidation product nitrosonium ion (NO+), its reduction product nitroxyl radical (NO-), the product of its reaction with superoxide anion, peroxynitrite (ONOO-),

and the secondary products generated from these precursors **(Cuzzocrea et al., 2001).** The nitrosation of amines and the deamination of DNA basis could contribute to the toxicity of NO. The recognition of NO production by activated macrophages as part of the inflammatory process was an important milestone for assessing both the biological production of NO and phenomenon of induction of NOS activity **(Forman and Torres., 2001).** Low concentrations of NO produced by iNOS are likely to contribute much of the antimicrobial activity of macrophages, however high concentrations of NO and its derivatives, such as peroxinitrite and nitrogen dioxide, are found to be involved in inflammation and in the multistage processes of carcinogenesis **(Iuliano., 2001).**

Macrophage derived cytokines and mediators, alone or in combination with LPS, have been found to induce co-expression of inflammatory enzymes such as iNOS and COX-2 **(Surh et al., 2001).**

Many other reports discussed the NO synthesis inhibition as a consequence to retained endogenous factors in uremic conditions. More recently Prabhakar and coworkers showed that urea inhibits iNOS expression and NO production in LPS-stimulated macrophages. It is therefore conceivable that macrophage dysfunctions in uremia may indeed be due to the synergistic action of simultaneous presence of graded

concentrations of various uremic toxins such as urea, MG and other guanidine compounds that excreted in physiological condition,and are raised to very high concentrations in the blood of uremic patients **(Marzocco et al., 2005).**

Lymphocyte Dysfunction in Uremia:

Immunodeficiency explaines the very high frequency of bacterial infections in such patients, which can lead to high morbidity and mortality despite the improvement in renal transplants and medical therapy **(Fenton et al., 1997).** Infections in these patients are mostly due to commonly occurring and non opportunistic organisms. In addition, there is an increased incidence of infections due to intracellular pathogens such as Mycobacterium, which are more frequent in patients with end stage renal disease than in the normal population. It is the presence of these infections which is indicative, in these patients, not only of abnormal phagocytosis but also abnormal antibody responses, and major T cell defects **(Cohen et al., 1997).** Other important clinical observations also point to the crucial role of a T cell defect in the end stage renal disease immunodeficiency syndrome, for example, the presence of cutaneous anergy indicating an abnormal, T cell-mediated delayed type hypersensitivity response, a defective capacity of renal patients to reject skin homografts, and the incapacity of end stage renal disease patients to mount an adequate T cell

response against different viruses and, in particular, hepatitis viruses. A large body of evidence has accumulated to suggest the existence of functionally polarised human T cell responses, based on the profile of cytokine secretion by CD4+ T helper cells (TH). Type1 cells produce interferon (IFN-gamma) and interleukin-2 (IL-2), these mediate pro-inflammatory reactions and help B cells produce igG2a. In contrast, type2 cells produce IL-4, IL-5, IL-10 and IL-13 and help B cells in the production of antibody IgG1 and IgE and inhibit several macrophages and T -cells functions. Although these functionally distinct T cell subsets were originally described in the mouse, human T cell clones have subsequently been shown to have a similar, although not identical, restricted cytokine profile **(cohen et al., 1995).**

B-lymphopenia in uremia :

Lymphoid homeostasis is based on a tight equilibrium between cell growth and cell death. Control mechanisms exist which serve to select fully functional lymphocytes and to discharge either incompetent or potentially autoreactive lymphocytes. This elimination is mostly accomplished by a particular type of cell death known as apoptosis that plays a central role in the development and shape of a functional peripheral lymphoid receptoire **(Lopez et al., 1998).** Thus, the dysregulation of apoptotic lymphoid death can lead to an ever –