

# A Gut Feeling on Endotoxemia: Causes and Consequences in Chronic Kidney Disease

Aline B. Hauser<sup>a</sup> Andréa E.M. Stinghen<sup>a, b</sup> Simone M. Gonçalves<sup>a</sup>  
Sergio Bucharles<sup>a</sup> Roberto Pecoits-Filho<sup>a</sup>

<sup>a</sup>Center for Health and Biological Sciences, Pontifícia Universidade Católica do Paraná, and <sup>b</sup>Basic Pathology Department, Universidade Federal do Paraná, Curitiba, Brazil

## Key Words

Chronic inflammation · Chronic kidney disease · Endotoxemia · Endotoxin · End-stage renal disease · Inflammation

## Abstract

Chronic inflammation is closely linked to several complications of chronic kidney disease (CKD), such as vascular calcification, accelerated atherosclerosis, loss of appetite, insulin resistance, increased muscle catabolism and anemia. As a consequence, inflammation is a predictor of mortality in this group of patients. Specific causes of the activation of the immune system in CKD are largely unknown. Endotoxin (ET) release to the circulation represents a potentially important target for interventions aiming to reduce mortality in CKD patients. In this minireview, we propose that there are several potential sources of endotoxemia in CKD and that gut translocation, leading to the generation of ligands of the innate immune response, represents a potentially reversible cause. Prevention of endotoxemia, through treating foci of ET (periodontal disease, catheters, vascular access) or reducing translocation from the gut, will potentially reduce the inflammatory response.

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## Introduction

Signs of an activated immune system and elevated levels of inflammatory mediators can be observed in the early stages of chronic kidney disease (CKD), and increase with the progression of renal dysfunction. This chronic inflammatory state is closely linked to several complications of CKD, such as vascular calcification, accelerated atherosclerosis, loss of appetite, insulin resistance, increased muscle catabolism and anemia. As a consequence, inflammation is a major predictor of mortality in this group of patients. From the immunologic viewpoint, CKD is characterized by disorders of both the innate and adaptive systems, generating a complex and still not fully understood immune dysfunction. Accelerated tissue degeneration that occurs as a consequence of chronic inflammation, and increased rate of sepsis because of a loss of the orchestrated immune response, represent the most important targets for interventions aiming to reduce mortality in CKD patients. It is important to understand the mechanisms behind the immune dysfunction in CKD patients to generate a perspective to improve outcomes [1].

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Roberto Pecoits-Filho, MD, PhD  
Centro de Ciências Biológicas e da Saúde  
Rua Imaculada Conceição, 1155  
Curitiba, PR 80215-901 (Brazil)  
Tel./Fax +55 41 32 11657, E-Mail [r.pecoits@pucpr.br](mailto:r.pecoits@pucpr.br)

## Endotoxin Structure and Localization in the Body

Richard Pfeiffer (1858–1910) discovered a heat-stable toxic localized inside the bacterial cell and thus named it endotoxin (ET) to distinguish it from the already known exotoxins. Several important commensal or human pathogenic bacteria species are important fonts of ET [2]. The cell envelope of Gram-negative bacteria consists of two membranes, the inner membrane that is a phospholipid bilayer and the outer membrane asymmetrical bilayer, consisting of phospholipids and lipopolysaccharides (LPS) in the inner and outer leaflet, respectively [3]. The LPS presents 200,000–1,000,000 kDa and it is composed of glycerophospholipids and a region called lipid A known as ET, that is recognized as a primary immunostimulatory center [4]. While the terms ET and LPS are used interchangeably, ET is used to emphasize the biological activity and LPS to refer particularly to the chemical structure and composition of the molecule [4]. Circulating ET can be derived from many sources (as will be discussed in detail bellow), such as foci of infection and contamination of tissue or foreign bodies. On the other hand, the human intestinal microflora is estimated to contain 500–1,000 bacterial species and LPS are continuously released in small amounts during cell proliferation and cell death, although during severe bacterial infections, larger amounts of LPS may be translocated into the bloodstream [5].

## Sources of Endotoxemia in Patients with CKD

### *Contamination of Tissues, Fluids or Foreign Bodies*

Several studies have clarified that very slight amounts of contamination can lead to inflammatory response, and we could not confirm biological dialysate quality only by measuring ET levels despite measuring viable cell counts or biofilms. To achieve this, there are published standards for dialysate in which very strict control levels were recommended with regard to viable bacterial cell counts [6]. The potential for clinically significant transfer of pyrogen-inducing material in dialysate and substitution fluids is well recognized in the setting of chronic hemodialysis and hemodiafiltration, and has led to the establishment of strict standards for microbiological purity. Preliminary evidence has indicated the potential for fluid contamination in continuous renal replacement therapy, although the scale of the problem in contemporary, industry-standard equipment is unclear [7].

The rate of infectious morbidity and mortality is much higher when catheters are used than when patients are dialyzed through grafts or native fistulas, and it is generally agreed that implementing appropriate preventive measures would do more to lower its incidence. Almost 30% of prevalent hemodialysis patients use catheters for vascular access although outcomes are superior with the use of either an arteriovenous fistula or a synthetic graft. Surface-treated catheters have been developed to combat the three most common causes of catheter failure: infection, fibrin sheath formation, and thrombus formation. At the present time, it is difficult to justify the increased cost of surface-treated catheters for chronic hemodialysis in the absence of clinical data demonstrating that they reduce catheter-related complications in this population [8]. Kato et al. [9], based on the emerging links between the alterations of immune system, cardiovascular disease (CVD), and infections in end-stage renal disease (ESRD) patients, emphasized the potential role of the immune dysfunction in ESRD as an underlying cause for the high mortality in this patient population and the need for more studies in this area.

Bacteria attach to surfaces and aggregate in a biopolymer matrix to form biofilm. Studies on biofilm have shown its presence in many prosthetic devices used in nephrology as well as in fluid pathways of hemodialysis plants and monitors. As more and more data link final dialysate microbial contamination to clinical effects of bioincompatibility from chronic inflammation in dialysis patients, attention has to be focused on possibilities of biofilm avoidance [10]. Dialysis fluid produced by state-of-the-art water preparation and distribution is contaminated with Gram-negative bacteria and cytokine-inducing substances derived from these microorganisms. The presence of a biofilm increases the risk of continuous contamination of dialysis fluid. Depending on the type of dialyzer membrane (cellulosic vs. synthetic) and the mode of dialysis (low flux vs. high flux with backfiltration), cytokine-inducing substances may penetrate intact dialyzer membranes, induce cytokine production and contribute to chronic inflammation associated with long-term hemodialysis therapy. Measures to improve the microbiological quality of dialysis fluid are regular testing of dialysate samples, disinfection of the entire water preparation and installation of ultrafilters in the dialysate circuit [11]. Hemodiafiltration and high-flux dialysis are the procedures of choice when one considers significant removal of solutes and substances beyond the traditional range of small molecules. These modalities are now becoming more popular and high-flux dialysis are now

used for two thirds of HD patients around the world. With respect to safer procedures, hemodiafiltration and high-flux dialysis patients must receive a treatment with ultrapure dialysis fluid and even a sterile fluid (online or in bags prepared) for a maximum ET exposure of 5 IU/kg body weight and hour of treatment, along with a sterilizing filter. These procedures, now becoming available in most dialysis centers, warrant safer dialysis sessions and provide good protection against bacterial products [12].

One study by Buhlin et al. [13] indicates that a substantial number of patients who suffer from advanced CKD, close to the start of dialysis treatment, have dental problems that require attention. Periodontitis is a bacterially induced chronic inflammatory disease and a major cause of tooth loss in the world. The tissue damage and alveolar bone resorption characteristic of the disease are believed to be due to a destructive innate host response to a pathogenic subgingival biofilm. *Porphyromonas gingivalis* has been designated an etiologic agent of periodontitis. Bainbridge et al. [14] examined highly purified preparations of *P. gingivalis* LPS and they concluded that *P. gingivalis* lipid A structural heterogeneity contributes to the unusual innate host response to this LPS and its ability to interact with different TLR molecules. Severe periodontitis are associated with increased serum hs-CRP concentration in patients after kidney transplantation and it seems to be correlated with the increase the risk of patients' death after kidney transplantation [15].

#### *Translocation from the Intestinal Lumen*

Bacterial translocation means the migration of intact bacteria or bacterial bioproducts as ET across the intestinal mucosal barrier into the circulating. The intestinal barrier is formed by enterocyte membranes, tight junctions, secreted mucus, and immunologic factors, such as tissue macrophages. There are two pathways from this mechanism: a paracellular route controlled by tight junctions and a transcellular route controlled by membrane pumps and channels [16]. Dysfunction of this barrier can be caused by different types of disease states and clinical conditions associated with impaired intestinal barrier function.

Some situations are observed in CKD patients that could be important sources of endotoxemia and should be targets of studies as: uremia [17], malnutrition leading to atrophy of intestinal mucosa [18], heart failure and edema leading to impaired intestinal barrier [19], physiological, pathological, psychological or pharmacological stress could reduce the intestinal blood flow that could

cause disruption and endotoxemia [20]. Many diseases and insults are related to impaired intestinal barrier function such as infections in intestinal tract or other sites, inflammatory bowel disease, parenteral nutrition, malnutrition, surgical stress, burns, shock, obstructive jaundice, thermal injury, stress circulatory compromise, congestion, heart failure and hypoxia, bacterial overgrowth and reduced intestinal motility [21]. However, the gastrointestinal tract has received little attention as a possible source contributing to the chronic inflammation state in CKD patients.

Uremia per se can be a cause of ET translocation; concentration of urea, creatinine and other nitrogenous metabolites reach the gut and become subject to microbial metabolism. The bacterial population in small intestine (duodenum and jejunum) in uremia is increased [22]. Constipation, a frequent problem in CKD patients, is another mechanism that promotes bacterial translocation through the bacterial overgrowth, which increases intestinal barrier permeability. In CKD patients the causes of ET translocation are not well understood. There is a hypothesis about ET releasing into the circulation during the portal path that occurs as reabsorption from gut. It was recently shown that circulating microbial products, probably derived from the gastrointestinal tract [23], are a cause of HIV-related systemic immune activation. There is also early evidence that circulating microbial products, probably derived from the gastrointestinal tract, are not uncommon in CKD patients. The intestinal mucosa barrier is impaired and bacterial translocation occurs in experimental uremia [24]. Indeed, translocation of bowel flora is a cause of Gram-negative peritonitis in PD patients [25]. In incident Chinese peritoneal dialysis patients, higher circulating LPS levels were inversely related to all-cause mortality and cardiovascular mortality in a group of peritoneal dialysis patients [26] presenting ET levels different to those in a hemodialysis population series [27].

There is increasing evidence that patients with CKD develop signs of fluid overload in the early phases of the disease, and this may be a stimulus for inflammatory activation that may lead to both accelerated CVD and rapid progression to renal failure [28]. Patients with fluid overload, such as patients with congestive heart failure (CHF), present signs of systemic inflammation that reduce when the disease is compensated [29]. This inflammatory state appears to be associated with an altered gut barrier permeability that occurs as a consequence of the edema, allowing the translocation of macromolecules including ET into the circulation.

Sharma et al. [30] demonstrated that adults with congenital heart disease and CHF have elevated levels of inflammatory cytokines and bacterial ET, which were directly related to cardiac functional status, suggesting that congestive phenomena could be implicated in ET levels of volume overload. Although the study was not made in CKD patients, it included some CHF patients with a severe grade of myocardial impairment, a clinical set where we frequently find non-dialysis CKD. Indeed, Sandek et al. [31] demonstrated that morphology and function of gut are abnormal in CHF patients. They observed increased wall thickness of both small and large gut, as well increased permeability of ileum and colon, and higher concentrations of adherent bacteria within mucus of CHF patients compared with control subjects. Furthermore, regression of volume overload in CHF patients treated with diuretics resulted in parallel reduction of ET mean levels [32]. These observations help us to explain that intestinal bacterial translocation really happens in CHF patients, this phenomenon is related to elevated ET levels and inflammation in patients with volume overload, and that interventions to reduce peripheral edema could result in improvement in ET levels, potentially attenuating immune activation.

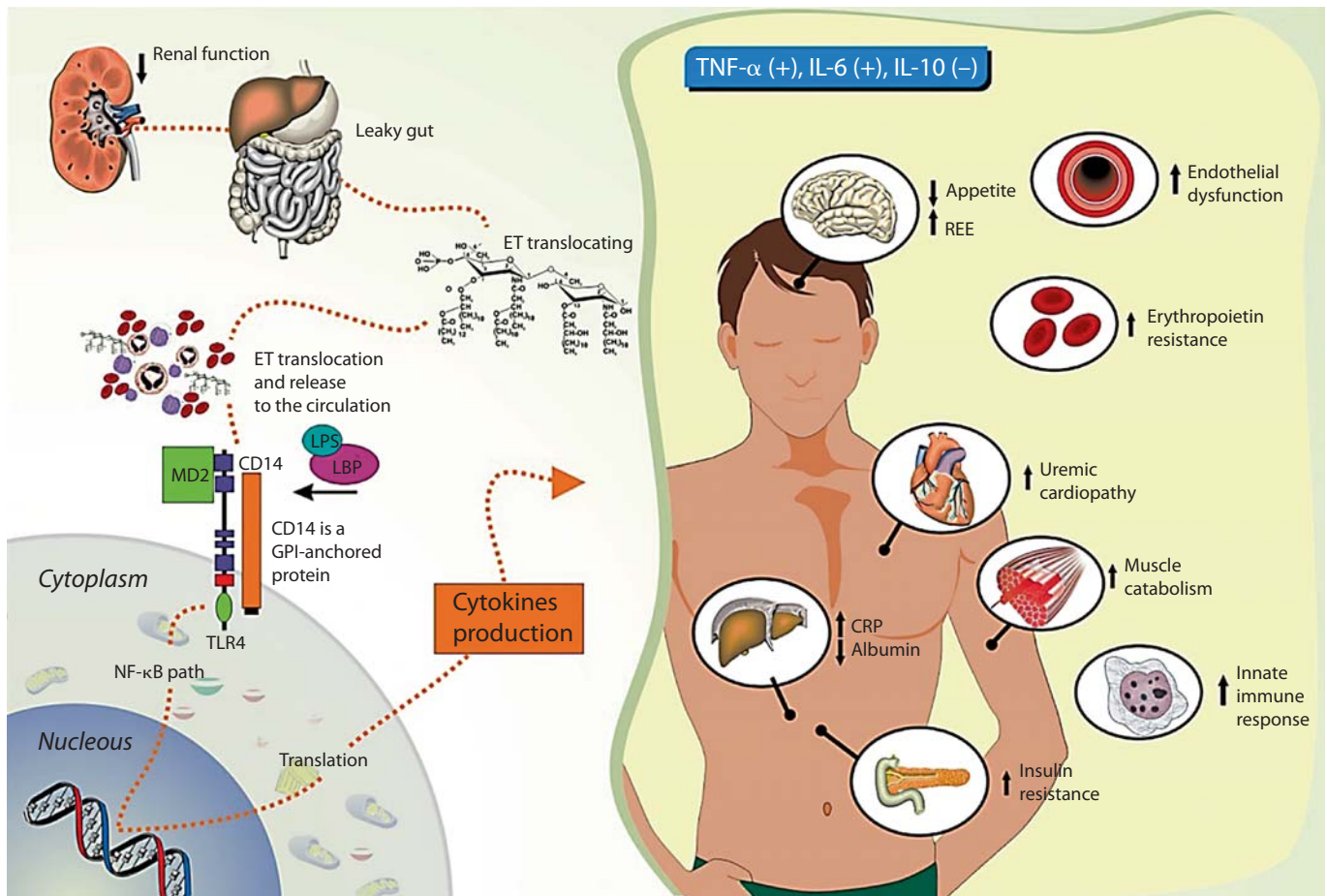
As a consequence of the presence of circulating ET, the immune system may be activated, generating a chronic inflammatory status. Dialysis patients with history of heart failure had higher CRP levels confirming this hypothesis [33]. In an animal study, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and ET levels were measured in serum of CKD and sham rats. TNF- $\alpha$  level was undetectable in all control animals in contrast to the CKD group. Similarly, CKD promoted an increase in ET levels suggesting that endotoxemia is induced in the CKD animals [55]. ET concentrations are shown to be higher in CKD patients in stages 1–5 with signs of fluid overload, but no correlation was observed between circulation ET and systemic inflammation [34]; thus, this study provides a plausible mechanism involved for the causes of ET translocation in CKD: bowel wall edema that is a very common condition in this patient with fluid overload. Finally, it suggests that the reduction of the renal function leads an ET translocation, by leaky gut or biliary recirculation, as showed in the figure 1. In the circulation, ET binds a protein (LBP) forming a complex LPS-LBP that interacts with the MD-2 part of the TLR4/MD-2 receptor, anchored by CD14. It stimulates via transcriptional nuclear factor  $\kappa$ -light chain enhancer of activated B cells (NF- $\kappa$ B) to translation and production of cytokines.

### **Cellular and Molecular Mechanisms of Inflammatory Activation by Endotoxemia**

One of the main biological systems responsible for triggering inflammation is related to the activation of NF- $\kappa$ B, which is a protein complex that acts as a transcription factor. NF- $\kappa$ B is found in almost all animal cell types and is involved in cellular responses to stimuli such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL, bacterial or viral antigens, and fragment of bacteria like LPS or ET.

It was demonstrated some years ago that an evolutionarily conserved signaling pathway employing specific members of the TLR family of non-clonal innate immunity receptors has been shown to be activated by LPS in numerous eukaryotic cells including the group of mammalian phagocytes. TLR4 in association with its co-receptor, MD-2, is responsible for responses to the LPS as well as CD14 antigen (mCD14), a membrane bound and expressed by peripheral monocytes, tissue macrophages and neutrophils [35]. ET is solely responsible for the initiation of immune responses, which interacts with the MD-2 part of the TLR4/MD-2 receptor complex in phagocytes and other ET-responsive cells [36]. Taken together, TLR4 forms a large complex with several associated proteins to achieve efficient LPS-induced cell activation [37]. TLR4 expression was highest in the spleen, followed by the lung and kidney, while it was not detectable in the liver and brain.

In macrophages, investigation of the LPS-induced cytokine (IL-6) response revealed a linear relationship between the response and the logarithm of TLR4/MD-2 levels, indicating a direct correlation between TLR4 expression and LPS sensitivity [38]. Interestingly, a recent study showed that an increased sCD14 level is related positively to markers of inflammation and negatively to nutritional status and is an independent predictor of mortality in long-term hemodialysis patients, and an additional study associated soluble CD14 (sCD14) as a marker of activation of the ET/TLR4 system to mortality in a large number in this group of patients [39]. IFN- $\gamma$  is a key mediator of the LPS hypersensitivity induced, which is dependent of IL-12 and IL-18 [40]. IFN- $\gamma$  may contribute to the enhancement of ET sensitivity by the primary pro-inflammatory cytokine. In addition, LPS may cause an intense and rapid activation of the mammalian complement system, in addition CRP has been shown to be involved in LPS- or lipid A-induced complement activation [41].



**Fig. 1.** Potential pathway linking endotoxemia and immune-mediated consequences in CKD.

### Consequences of Inflammation Particularly in CKD

ESRD is associated with significantly increased morbidity and mortality resulting from CVD and infections, accounting for 50 and 20%, respectively, of the total mortality in ESRD patients, because of alterations in the immune system in ESRD. Uremia is associated with a state of immune dysfunction characterized by immunodepression that contributes to the high prevalence of infections among these patients, as well as by immunoactivation, resulting in inflammation that may contribute to CVD. The disorders of the innate and adaptive immune systems in ESRD underline the specific role of ESRD-associated disturbances of Toll-like receptors [9].

TNF- $\alpha$  was demonstrated to mediate endothelial dysfunction [42] and CRP has been revealed as having direct pro-inflammatory effects on human endothelial

cells [43]. Furthermore, other acute-phase reactants, such as lipoprotein(a) [44] and fibrinogen [45], have been implicated in CKD-accelerated atherogenesis. Cardiodepressant effects of TNF- $\alpha$  have been documented in numerous in vitro and in vivo studies [46, 47]. The origin and trigger mechanisms for the release of TNF- $\alpha$  in heart failure are a matter of debate, ET (LPS) from an intestinal translocation in venous congestion being one possibility [46]. The negative inotropic impact of TNF- $\alpha$  is frequently ascribed to the induction of inducible nitric oxide (NO) synthase (iNOS), but, although ET and TNF- $\alpha$  may exert a depressant effect in cardiomyocytes, they appear to work by different cardiodepressant profiles [46].

Although many efforts in the investigation of the mechanisms behind the uremic inflammatory status have focused on monocytes and macrophages, recent evidence indicates that vascular inflammation mediated by

cytokines and adhesion molecules is an important fact in the regulation of inflammation [48]. This results in plaque formation and cardiovascular events, which are initiated and perpetuated by the interaction of immune cells mainly with the endothelium. Leukocyte interactions with vascular endothelium during inflammation occur through steps involving selectin-mediated leukocyte rolling, mild adhesion mediated by adhesion molecules such as vascular adhesion molecule-1 and intercellular adhesion molecule-1, and subsequent firm adhesion mediated by chemokines such as monocyte chemoattractant protein and IL-8. Thus, concentrations of circulating adhesion molecules are found in CKD patients and are associated with inflammation, dyslipidemia, and cardiovascular events in hemodialysis patients [49].

Inadequate immunization against hepatitis B, diphtheria, tetanus, and various other agents are also observed in CKD patients. In contrast, vaccines based at polysaccharide antigens generally result in efficient responses, suggesting that the T-helper cells are particularly affected during renal failure [50]. Many mechanisms have been proposed to explain the altered adaptive immune response in CKD patients. In particular, uremic toxin accumulation, chronic inflammation and altered cytokine expression could result in a Th1/Th2 imbalance, leading to a paradoxically suppressed immune system in these patients.

### **New Strategies and Therapeutic Perspectives for the Reduction of the Inflammation through ET Reduction**

One therapeutic strategy which could be tested in CKD would be the use of drugs that could bind ET in the intestine, leading to the decrease in ET translocation, due to the formation of a large (and non-absorbable) drug-ET complex. Cholestyramine, a sorbent that binds biliary acids, has been used for removal of ET as shown in bile duct-ligated rats where the gut ET restriction improves post-operative hemodynamics [51]. Prophylactic treatment with enteral cholestyramine preserved cellular immune functions after partial hepatectomy in the rat on the post-operative course. The results showed that proliferative responses of splenic B and T lymphocytes and LPS-stimulated production of TNF- $\alpha$  and IL-1 by splenocytes were lower in rats after partial hepatectomy than in sham-operated animals [52].

Sevelamer carbonate is a cross-linked polymeric amine that has been extensively used as a phosphate

binder. Although its clinical use has been as a phosphate binder, sevelamer binds in an unspecific way to trivalent anions, biliary acids and conjugated amino acids that are negatively charged. The binding of sevelamer to these compounds leads to the increase of the fecal excretion and reduction in intestinal absorption to circulation. Sevelamer leads to favorable changes in lipids and inflammatory markers with potentially useful antiatherogenic effects in hemodialysis patients [53] and delays not only vascular calcification, but also atherosclerotic lesion progression in uremic apolipoprotein E-deficient mice. It opens the possibility of a cholesterol-independent action of sevelamer on atheroma formation via effects on mineral metabolism, inflammation, and oxidative stress [54].

Our group used an animal model that compared CKD rats using Sevelamer (CKD+Sev) with CKD rats not using Sevelamer (CKD-Sev), and concluded that there was a positive impact of sevelamer on the reduction of inflammation through TNF- $\alpha$  levels, in parallel to a decrease of endotoxemia shown by ET levels. Additionally, we observed in a clinical study that sevelamer treatment leads to a decrease in hs-CRP levels which was accompanied by a parallel decrease in endotoxemia, suggesting that endotoxemia may contribute to the systemic inflammation in HD patients which was partially reduced by the use of sevelamer [27]. Therefore, this background information stimulates the investigation of the potential use of sevelamer as an ET binder in CKD, a strategy that could potentially lead to the reduction of signs of inflammation through anti-inflammatory properties.

### **Conclusions**

To conclude, we propose that there are several potential sources of endotoxemia in CKD and that gut translocation, leading to the generation of ligands of the innate immune response, represent a potentially reversible cause. Prevention of endotoxemia, through treating foci of ET (periodontal disease, catheters, vascular access) or reducing translocation from the gut will potentially reduce the inflammatory response. These anti-inflammatory strategies may be efficient in reducing complications related to inflammation in CKD patients.

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## Editorial Comment

M. El Nahas, Sheffield

This review, on the impact of endotoxemia and inflammation on ESRD outcomes, is of major importance to emerging countries where dialysis outcomes are poor. The latter is due to a number of factors including poverty, limited resources and infrastructure, poor access to healthcare and lack of compliance. In many of these emerging economies, ESRD is a triple hit resulting from the combined effect of poverty, infectious disease as well as westernization with the rising tide of non-communicable diseases such as diabetes and hypertension. In ESRD patients from these countries, chronic inflammation due to a variety of causes also has a major impact on their outcomes and survival. This is the case in those suffering from chronic hepatitis, mostly HCV, malaria and tuberculosis.

Poverty and social deprivation are also associated with chronic inflammation due to conditions such as chronic dermatitis, including scabies, as well as poor oral hygiene causing gingivitis and periodontitis. These are all associated with endotoxemia and poor cardiovascular outcomes. As highlighted in the review they are also associated with malnutrition – the MIA syndrome combining malnutrition, inflammation and atherosclerosis. Finally, a compounding factor and endotoxemia load in dialysis units from emerging countries is often provided by the dialysate poor quality control and high bacterial and endotoxin levels. Survival on renal replacement therapy may improve by better infection control in patients as well as facilities used to deliver healthcare.