Infectious Gram-positive Bacteria Recovered From Diabetic Patients Under Dyalisis Treatments

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1 Introduction

Chronic kidney disease (CKD) has been recognized as a major health problem in the industrialized world. In fact, a great prevalence of earlier stages of CKD has been inferred (Eknoyan *et al*., 2003). Based on data from the Third National Health and Nutrition Examination Survey, an awesome number of individuals in the United States have significantly decreased kidney function. There are even more individuals with manifestations of kidney damage (particularly albuminuria) without a significant decrease in kidney function. It is evident that most patients with CKD do not progress to End-Stage Renal Disease (ESRD; this term is the same as stage 5 CKD), but likely succumb to cardiovascular disease (CVD), which also is the leading cause of death for patients. In this setting the presence of infections and septicaemia has also contributed to an increase in morbidity and mortality. Stated otherwise, patients with CKD should have their disease detected and treated well before the onset of kidney failure and the need for dialysis or transplantation.

Existing epidemiological data suggest that infection in dialysis populations is associated with a marked increase in the use of health-care resources, as well as excess morbidity and mortality. For instance, patients undergoing peritoneal dialysis (PD) or hemodialysis (HD) have a notably increased risk of infection, particularly peritonitis in the former group and catheter-related bloodstream infection in the latter group. Moreover, infection in those patients on either form of dialysis is also associated with an increased risk of subsequent cardiovascular (CV) events; this increase in risk is only partially explained by underlying conditions, such as frailty. Thus, the presence of infection in a patient on dialysis has a substantial effect on CV mortality and morbidity, and should influence decisions regarding the use of therapies intended to minimize that risk.

2 Type 2 Diabetes as Leading Cause of CKD: Diabetic Nephropathy

The 21st century has the most diabetogenic environment in human history (Zimmet *et al*., 2001; King *et al*., 1998). Over the past 25 years, the prevalence of type 2 diabetes in the United States has almost doubled, with three to fivefold increase in India, Indonesia, China, Korea, and Thailand (Yoon *et al*., 2006). In 2007, there were 246 million people with diabetes in the world, but by 2025, that number is estimated to reach 380 million. People with impaired glucose tolerance, a 'prediabetic state,' numbered 308 million in 2007, and this will increase to 418 million by 2025 (Sicree *et al*., 2006). The increase in prevalence of diabetes will be greater in developing countries.

Diabetes is now the major cause of ESRD throughout the world in both developed and emerging nations (Reutens *et al*., 2008). It is the primary diagnosis causing kidney disease in 20%–40% of people starting treatment for end-stage renal disease worldwide. In Australia, the number of new type 2 diabetes patients starting dialysis increased fivefold between 1993 and 2007 (ANZDATA Registry Report. 2008.). Between 1983 and 2005, there was a sevenfold increase in the number of new patients starting renal replacement therapy in Japan because of diabetes, accounting for 40% of all new-incidence patients (Yamagata *et al*., 2008). In the United Kingdom Prospective Diabetes Study (UKPDS), the rates of progression of newly diagnosed type 2 diabetics between the different stages of diabetic nephropathy (normoalbuminuria, microalbuminuria, macroalbuminuria) and renal

failure were 2%–3% per year (Adler *et al*., 2003). Over a median of 15 years of follow-up for 4000 participants, almost 40% developed microalbuminuria, which represent the initial stage of kidney damage in patients suffering of diabetes (Retnakaran *et al*., 2006). About 30% of the UKPDS (United Kingdom Prospective Diabetes Study) cohort developed renal impairment, of which almost 50% did not have preceding albuminuria (Retnakaran *et al*., 2006). Reduced glomerular filtration rate and albuminuria caused by diabetic nephropathy are independent risk factors for CV events and death (Ninomiya *et al*., 2009).

According to the WHO (World Health Organization), China and India will have about 130 million diabetics by 2025; they will consume about 40% of their countries healthcare budget in addition to reducing productivity and hindering economic growth. It was against this background that on December 21, 2006, the United Nations General Assembly unanimously passed Resolution 61/225 declaring diabetes an international public-health issue and identifying World Diabetes Day as a United Nations Day —only the second disease (after HIV/AIDS) to attain that status—. For the first time, governments have acknowledged that a noninfectious disease poses as serious a threat to world health as infectious diseases such as HIV/AIDS, tuberculosis, and malaria. The problems of diabetes are now seen as a major global public-health concern, especially in the developing world, which least can afford it. The first step to acting on diabetic kidney disease must encompass public-health campaigns aimed at preventing the development of type 2 diabetes. Medicare spending on the US ESRD program reached $26.8 billion in 2008. Furthermore, some 30% of the predicted US$1.1 trillion medical costs of dialysis worldwide during this decade will result from diabetic nephropathy (Lysaght 2002). Therefore, prevention of Diabetic Kidney Disease is important to improve health outcomes of persons with diabetes and to reduce the societal burden of chronic kidney disease (US Renal Data System, 2010).

3 Chronic Kidney Disease and Suceptibility to Infection

CKD and uremia milieu are associated with an increased susceptibility to infections and until recently the pathophysiology has been poorly understood. Infections remain a major cause of morbidity and mortality in patients with uremia and ESRD. Most of these infections are of bacterial origin and account for the majority of hospitalizations in this patient population. Infections were responsible for 12 to 22% of deaths among dialysis patients in the United States and Canada. Infections are the second most common cause of mortality in patients on dialysis, after coronary artery disease (US Renal Data System, 2006).

The presence of a substantial impairment of immunity in patients with uremia has been well documented (Descamps-Latscha *et al*., 1994). Vascular access (VA) sites and PD catheters serve as ready portals of entry for pathogens. CKD and the subsequent need for maintenance HD can alter neutrophil function, reduce the ability for phagocytosis, depress natural killer cell activity, and can alter T and B cell function. These functional and quantitative abnormalities of cellular function account for the increased susceptibility to infection, and are independent of the cause of uremia. Various factors contribute to the altered cellular function in uremia. These include low albumin from malnutrition, metabolic acidosis, increased intracellular calcium, low molecular weight uremic

toxins, and the presence of circulating inhibitors to chemotactic factors (Vanholder *et al*, 1996). Iron overload can impair immune function, enhances bacterial growth and virulence and thereby predisposes to an increased risk of infection in uremic patients (Sunder-Plassmann *et al*., 1999). Besides that, a decreased production of endogenous pyroxenes may cause a delay in recognition of infection (Lewis 1992). Skin test responses to standard antigens are impaired markedly in uremic patients. With the advent of dialysis for uremia, patients are subject to invasive procedures such as placement of intravenous catheters for temporary and permanent dialysis, what poses an increased risk of infections and for the same reasons dialysis patients are at increased risk of infections by resistant organisms.

In more recent years, convincing evidence has accumulated signaling that the immune system is chronically activated in clinically relevant uremic states (Foley 2007) (Table 1). As a result, many investigators believe that chronic activation with hypo-responsiveness may be the most accurate description of the immune dysfunction in clinical uremia. Some recent insights show several immune dysfunctions of advanced kidney disease. Thus one well-characterized observation in dialysis patients is that response rates to Hepatitis B vaccination are inexplicably low, and similar findings have been seen with other vaccines, such as tetanus or diphtheria; in contrast, vaccination responses to *Pneumococcus* are usually normal (Kohler *et al*., 1984). This hypo-responsiveness to hepatitis B vaccination seems to reflect impaired proliferation of T cells and decreased rates of production of T-cell growth factors, such as interleukin-2 (Girndt *et al*., 1993). Comparatively few antigens stimulate antibody production by B lymphocytes in complete independence of T cells; highly polymeric bacterial antigens, however, can elicit this response, among them the *Pneumococcus* vaccine. For most antigens, activation of helper T cells is required for both cellular and humoral immune responses. These findings suggest that defects in T-cell activation pathways may be an important component of the immune deficits of advanced CKD. Experimental studies suggest that the following may occur with uremia: defective co-stimulatory function of antigen-presenting cells, inflammatory activation of monocytes, and high levels of interleukin-12, leading to a reduced CD4þ/CD8þ T-lymphocyte ratio (Girndt *et al*., 1999). Finally, in HD patients the use of flow cytometry showed increased rates of apoptosis and smaller populations of naive and central memory T lymphocytes (Yoon *et al*., 2006).

Depressed neutrophil function.
Leukopenia secondary to complement activation.
Impaired phagocytosis.
Reduced natural killer cell activity.
Decreased T and B lymphocyte function.
Decreased T lymphocyte response to standar antigens.

Table 1: Host defense defects in uremia

4 Infections in Dialysis Modalities: Hemodialysis and Peritoneal Dialysis

Dialysis is a process by which waste products are removed from the body by diffusion from one fluid compartment to another across a semipermeable membrane. There are two different types of renal dialysis in common clinical usage: HD and DP. Both are acceptable modes of treatment of chronic renal disease. Over the past half century, the widespread use of dialysis to prolong life for people without kidney function has been a remarkable achievement (Himmelfarb *et al*., 2010). As a result of its growth and evolution, the U.S. ESRD Program has often provided an early window into social, political, and economic developments in health care, and these changes have later been reflected throughout the U.S. health care system. Despite such successes, the use of dialysis in the treatment of ESRD is problematic in some respects. The number of patients treated, especially in the United States, has escalated and is far beyond early estimates. Aggregate dialysis-associated costs have increased accordingly, and morbidity and mortality among treated patients remain high despite considerable technical and scientific improvements. Our knowledge of which uremic toxins confer injury and of how they can be optimally removed during dialysis therapy remains incomplete. The limited numbers of clinical trials that have attempted to improve outcomes have had disappointing results, so well-designed and adequately powered clinical trials are needed. Ongoing studies are assessing whether longer or more frequent dialysis treatments, or both, can improve outcomes and whether these changes would be acceptable to most patients. However, substantive improvements for patients receiving dialysis will probably require major technological breakthroughs that will be predicated on an improved understanding of uremic toxins and uremic complications. Among these complications, infections represent the second leading cause in patient mortality and morbidity in the existing types of dialysis modalities.

The demographics of the dialysis population have changed dramatically over time. Less stringent selection of patients has led to treatment of an increasing proportion of elderly patients, patients with diabetes, and patients who are frail and have complex coexisting conditions (Moss 2001). The initiation of dialysis in patients with higher levels of residual kidney function has occurred concomitantly, particularly among patients older than 75 years of age. Among elderly nursing-home residents, the initiation of dialysis is associated with a substantial decline in functional status and high mortality. The factors driving these clinical practices, and their societal implications, are only beginning to be studied but may well lead to increased consideration of conservative management and palliative-care options for some patients (Murtagh *et al*., 2007).

Dialysis patients have a strongly increased absolute risk and relative risk (RR) for morbidity and mortality from infectious diseases (Table 2). Infection accounts for 12 to 36% of the mortality in patients with ESRD and is second only to CVD as a cause of death (Nassar & Ayus, 2001) and septicemia is responsible for approximately three quarters of the infectious mortality. Infectious mortality is 1.66 times more frequent in PD than in HD. The annual mortality rate caused by sepsis is 100 to 300 times higher in patients with ESRD than in the general population (Laupland et al., 2004). A large cohort study reported that the increase in risk is not significantly altered by age, gender, or the presence of diabetes (Sarnak *et al*., 2000). Other studies indicated that the risk for infection is linked to age, low Karnovsky index, type of VA, frequency of hospitalization,

immunosuppressive therapy, use of a mistreatment heparin bolus, iron overload, and poor hygiene (Hoen *et al*., 1998; Diskin *et al*., 2007; Teehan *et al*., 2004).

Malnutrition (Low albumin and low Karnovsky index).
Age.
Increased intracellular calcium.
Iron overload.
Low molecular weights toxins.
Decreased T lymphocyte response to standar antigens.
Invasive vascular and peritoneal procedures for dialisys access.
Poor hygiene

Table 2: Predisposing factors to infection in dialysis patients.

5 Hemodialysis

HD represents the most extended dialysis therapy worldwide. In this modality of dialysis blood is passed through an artificial kidney machine and the waste products diffuse across a man-made membrane into a bath solution known as dialysate, after which the cleansed blood is returned to the patient's body. In standard basis HD is accomplished usually in three- or four-hour sessions three times a week.

Infection as a cause of hospitalization for HD patients in the U.S. has increased in recent years. Between 1993 and 2006, hospitalization rates for infection rose 34%, and the rate of hospitalization for VA infections in HD patients more than doubled (US Renal Data System, 2008). The admission rate for pneumonia rose 7.3%, for bacteremia /septicemia 31%, and for cellulitis 20.3%. In 2006, there were 103 admissions per 1000 patient years with the diagnosis of bacteremia / septicemia and 129 per 1000 patient years with the diagnosis of VA-associated infection. Infection is reported as the second most common cause of death in HD patients (20.2% in 2006), after CVD (US Renal Data System, 2008). As previously referred patients on maintenance HD are strikingly vulnerable to infection for many reasons, including the immunodepressed state intrinsic to ESRD, the high prevalence of diabetes, exposure to other patients in the HD facility three times per week, frequent hospitalization, and the invasiveness of the HD procedure.

Many of the acute bacterial infections in HD patients are caused by *Staphylococcus aureus*, and are mainly related to temporary central venous catheters (CVCs). Also these infections can lead to sepsis and result in bacterial seeding/ infection of implants such as total hip/knee and cardiac valves. This is a serious complication that can result in significant additional morbidity and may require removal/ replacement of implants. Bacterial seeding/infection of compression spine fractures have also been reported resulting in long-term antibiotic therapy. Other infection-associated risks include pneumococcal pneumonia, which also remains common in the HD population. Pneumonia is one of many reasons that antibiotics are prescribed for HD patients which in turn increases the risk

of developing colonization or infection with multidrug-resistant organisms (MDROs) such as methicillin-resistant *S. aureus* (MRSA).

6 Vascular Access and Infections

The necessity for vascular access in patients with renal failure can be temporary or permanent. The necessity for temporary access may vary from several hours (single dialysis) to months [if used to dialyze while waiting for an arteriovenous (AV) fistula to mature]. Temporary access is established by the percutaneous insertion of a catheter into a large vein (internal jugular, femoral, or, less desirably, subclavian). Construction of a permanent VA permits repeated angioaccess for months to years. An ideal permanent access delivers a flow adequate for the dialysis prescription, lasts a long time, and has a low complication rate. The autonomous AV fistula comes closest to satisfying these criteria because it has the best 5-year patency rate and during this period requires many fewer interventions than other access methods. Prosthetic accesses (AV grafts) are constructed by the insertion of a subcutaneous tube in a straight, curved, or loop configuration between an extremity artery and vein. Placement of a cuffed double-lumen silicone elastomer catheter (e.g., Perm-Cath device) or a pair of cuffed single-lumen catheters (e.g., Tesio catheter) into an internal jugular vein for permanent access is also done in selected circumstances. Although the autologous AV fistula is clearly the desired access for patients initiating HD, there is disproportionate use of AV grafts in the U. S. and an increasing dependence on cuffed indwelling central venous catheters. Guidelines developed by the National Kidney Foundation Dialysis Outcomes Quality Improvement initiative promote the increased construction of AV fistulas and earlier referral of patients to nephrologists, permitting early-access evaluation and early construction of an AV fistula or graft, thereby minimizing the use of venous catheter access. A second goal of the guidelines is to promote detection of access dysfunction prior to access thrombosis.

Infection is the leading cause of catheter loss and increases morbidity and mortality. Infection usually arises from the migration of the patient's own skin flora through the puncture site and onto the outer catheter surface, although it can also result from contamination of the catheter connectors, lumen contamination during dialysis, or from infused solutions. Catheters can also become colonized from more remote sites during bacteremia. Gram-positive bacteria (usually *Staphylococcus* species) are the most common culprits. In these setting access remains the Achilles heel of dialysis treatment, especially with regard to VA for HD due to its association with bacteremia, infections and sepsis that contributed to a great extent in the high rates of morbidity and mortality of HD patients. The incidence of VA-related bloodstream infection varies between medical facilities and can be influenced by the percentage of patients who receive dialysis via a central venous catheter (Marr *et al*., 1998). As already mentioned several types of VA used in hemodialysis, listed in order of increasing risk of infection, are as follows: arteriovenous fistulas created from the patient’s own blood vessels; arteriovenous grafts constructed from synthetic materials; tunneled CVCs; and non-tunneled CVCs (Marr *et al*., 1998).

Several studies show that 48 to 89% of bacteremias in HD patients are related to a VA infection (Hoen *et al*., 1998; Marr *et al*., 1998; Nassar *et al*., 2001). The type of VA is the most

important predictor of the infection risk, with native fistulas being safer than grafts (RR 1.47), cuffed catheters (RR 8.49), and no cuffed catheters (RR 9.87) (Taylor *et al*., 2002). Other studies reported a 10 to 30 times higher risk associated with noncuffed catheters than with native fistulas (Stevenson *et al*., 2002). The incidence of bacteremia in HD patients varies from 7.6 to 14.4 episodes per 100 patient-years (Hoen *et al*., 1998; Marr *et al*., 1998). Although the type of VA has a major impact on the risk of bloodstream infections, it hardly affects the outcome of the subsequent infection (Inrig *et al*., 2006). Major complications from VA related infections in dialysis are severe sepsis, metastatic mainly osteoarticular infections, and infective endocarditis. The risk for infective endocarditis in HD patients is 17.8 times higher than in the general population, mounting to 5.6 per 1000 patient-years (Abbott & Agodoa, 2002). Up to 57.9% of these episodes are caused by *S. aureus*, with an in-hospital mortality of approximately 50% (Kamalakannan *et al*., 2007).

As previously mentioned Gram positive bacteria *S. aureus* is the most common microorganism implicated in vascular-access-related bloodstream infections, accounting for over half of HD catheter related infection (Nsouli *et al*., 1979), followed by coagulase-negative staphylococci and has been associated with high morbi-mortality in these patients.

Of special interest is the control of MRSA. These species was first described in 1961 and has become a worldwide problem (Jevons, 1961), currently constituting the most commonly identified antibiotic resistant pathogen in many hospitals and contributing significantly to patient morbidity and mortality (Cosgrove *et al*., 2003; Diekema *et al*., 2004; Melzer *et al*., 2003; Whitby *et al*., 2003). Humans are the main natural reservoir of *S. aureus*. Although multiple body sites can be colonized by *S. aureus*, the rate of colonization is highest in the anterior nares (Wertheim *et al*., 2005). In crosssectional population-based surveys, 10 to 50% of adults were colonized with *S. aureus* (Graham, 2006; von Eiff *et al*., 2001). Longitudinal studies revealed three patterns of *S. aureus* nasal carriage (Wertheim *et al*,, 2005). Approximately 20% of healthy adults (range 12 to 30%) are persistent carriers and are colonized by a single strain over prolonged periods. Thirty percent (range 16 to 70%) are intermittent carriers that may harbor different strains in their nose over time. Fifty percent (range 16 to 69%) are persistent non carriers (von Eiff *et al*., 2001). The large variation in the number of persistent and intermittent carriers between the available studies is the consequence of non-uniform definitions and methodological issues (Wertheim *et al*., 2005). In addition to the anterior nares, *S. aureus* frequently colonizes the skin, the perineum, and the pharynx and, to a lesser extent, the gastrointestinal tract, the vagina, and the axillae *Staphylococci* can also survive for months on many types of surfaces and in environmental dust (Dancer *et al*., 2008; Wertheim *et al*., 2005). Airborne transmission is important in the maintenance of environmental reservoirs, but hands are the main vectors that transmit *S. aureus* from the environment to the nasal niche and from the nasal niche to several body sites, respectively. Although the presence of *S. aureus* in the nose elicits a subclinical immune response, this host response is ineffective to prevent further colonization once the germ has reached the anterior nares (Wertheim *et al*., 2005). This may indicate that although the subclinical immune response provoked by nasal carriership is inadequate to prevent tissue invasion, it may decrease the devastating consequences of invasive *S. aureus* infection.

HD-patients as are patients with diabetes are at increased risk for intermittent or persistent carriership from the onset of dialysis (Wertheim *et al*., 2005; Vandecasteele *et al*., 2009). Importantly, incidence of invasive MRSA infection among dialysis patients is 100-fold higher than

for the general population (Centers for Disease Control and Prevention (CDC), 2007). Moreover, *S. aureus* carriers who are on HD have a 1.8- to 4.7-fold increase of vascular VA infections and bacteremia compared with noncarriers (Wertheim *et al*., 2005). The majority of dialysis patients carry the same strain on the hands and in the nose and also these strains are frequently the same as those recovered from subsequent infections (Ena *et al*. 1994). Similar to those in the general population (Wertheim *et al*., 1994), the majority of *S. aureus* infections in HD patients therefore have to be considered autoinfections (Boelaert *et al*., 2009). In summary, patients on dialysis have an increased rate of *S. aureus* nasal colonization which increases the risk of subsequent infection; eradication of nasal carriage would be beneficial (Golper *et al*., 2000).Elimination of staphylococcal nasal carriage by topical nasal mupirocin application has been found to reduce the incidence of infection in patients on dialysis (Kluytmans *et al*., 1997).

The Enterococci are the third group of microorganims responsible for bacteremia in HD patients. Particularly vancomycin-resistant enterococci (VRE) have emerged as an important nosocomial pathogen in these patients. A systematic literature review analysing the impact of vancomycin resistance on mortality by bacteremias showed that patients infected with VRE were more likely to die than those with vancomycin susceptible enterococci (Diaz-Granados *et al*., 2005). Two species are especially important in enterococcal infections: *Enterococcus faecalis* and *Enterococcus faecium* although vancomycine resistance seems to be more extended in the last (Minnaganti *et al*., 2001). Widespread and incorrect dosing of vancomycin in HD patients has probably led to the emergence of VRE.

Aerobic Gram-negative bacilli are responsible for the remainder HD infections. When these infective agents appear, inadequate disinfection of water treatment or distribution systems errors in dialyser reprocessing are usually involved. Among chronic hemodialysis patients, approximately 25% of blood stream infections are caused these bacteria (Marr *et al*., 1998), and this percentage is increasing steadily.

7 Peritoneal Dialysis

In this type of dialysis therapy the waste products pass from the patient's body through the peritoneal membrane into the peritoneal (abdominal) cavity where the bath solution (dialysate) is introduced and removed periodically. Schematically there two standard modalities of PD: Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated PD (APD). CAPD represents a variation of PD that was developed as an alternative mode of dialysis for home dialysis patients, is a continuous dialysis process using the patient's peritoneal membrane as a dialyzer. The patient connects a two-liter plastic bag of dialysate to a surgically implanted indwelling catheter and allows the dialysate to pour into the peritoneal cavity. Four to six hours later, the patient drains the fluid out into the same bag and replaces the old bag with a new bag of fresh dialysate. This is done three to five times a day with the first exchange being made when the patient wakes up in the morning and the last exchange being made at bedtime. Because no machine is used, CAPD frees patients from the dietary restrictions associated with intermittent HD or intermittent PD. APD is a treatment modality that combines the advantages of the long-dwell, continuous steady state dialysis of CAPD, with the

advantages of automation inherent in intermittent peritoneal dialysis. The major difference between APD and CAPD is that the solution exchanges, which are performed manually during the day by the patient on CAPD, are moved to nighttime with CCPD and are performed automatically with a peritoneal dialysis cycler. The long nighttime dwell of APD is moved to the daytime with CAPD. At night, the patient connects the catheter to the cycler system, which has several (two to four) five-liter containers of dialysate suspended. The cycler automatically empties the patient's peritoneal cavity of the all-day dwell. The cycler then cycles the nocturnal exchanges automatically while the patient sleeps; the number of nocturnal exchanges occurring at intervals of one to three hours (depending on the dialysis schedule) and the last exchange being instilled in the morning upon awakening. The patient then disconnects form the cycler and leaves the last two-liter inside the peritoneum to continue the daytime long-dwell dialysis.

The utilization of PD as an effective and feasible dialysis therapy CKD patients was extend world wide since the seventies and at present represent an attractive and first line dialysis option for patients with ESRD because it offers a very different lifestyle that enables people to work, travel, and avoid the rigid schedule of in-center HD. PD was utilized in about 14%-15% of dialysis patients from the early 1980s through the early 1990s and was an attractive option during those years when physicians faced multiple barriers to start outpatient HD programs. For many reasons, some of which remain enigmatic, PD use subsequently declined to about 6% of all dialysis patients in 2008 (US Renal Data System, 2010).

As in HD patients infections also represents a serious complication for PD patients. Reducing the risk of PD-related infections should be a primary goal of every PD program. Quality improvement programs with continuous monitoring of infections and root-cause analysis of each infectious episode are critical to decrease PD-related infections (Borg *et al*., 2003). Very low rates of infection can be achieved if close attention is continuously paid to training and retraining, equipment, and protocols to prevent infections.

8 Peritonitis

Peritonitis, infection of the peritoneal cavity, remains the Achilles' heel of PD. In these patients, peritonitis is the most common reason for hospitalisation and for discontinuation of PD (Bloembergen & Port, 1996). A major route of spread of infection is as a consequence of intraluminal contamination associated with frequent manipulations of the catheter (Nolph, 1988). The overall incidence of peritonitis in CAPD patients during the 1980s and early 1990s had averaged 1.1–1.3 episodes per year in the United States, but the introduction of Y-set and double-bag systems has reduced this to approximately one episode every 24 months (Monteon *et al*., 1998). The incidence rate in CAPD patients in the U. S. is now comparable to that seen in APD patients. The same flush-before-fill methodology used in CAPD Y sets may also be used effectively in APD (Leehey & Lentino, 2003).

Peritonitis etiology is determine by using appropriate culture techniques, an organism can be isolated from the peritoneal fluid in over 90% of cases in which symptoms and signs of peritonitis and an elevated peritoneal fluid neutrophil count are present. The responsible pathogen is almost

always a bacterium, usually of the Gram-positive variety (Table 3). Gram-positive organisms account for two thirds of all episodes of peritonitis (Band, 1999). However, unlike to HD-related infections, coagulase-negative staphylococci, especially *S. epidermidis*, are more common that *S. aureus* in PD-related peritonitis. Moreover, peritonitis caused by *S. aureus* are more severe. It has been well documented that patients who are nasal carriers of *S. aureus* are at increased risk of infection and are prone to recurrent infection (Lazar *et al*., 1990; Swartz *et al*., 1991). Like occurs in HD patients, elimination of nasal carriage in patients on PD decreased the ESI rate, but the effect on the incidence of peritonitis is unclear. Other less common, but accounting significant number of episodes Gram-positive infective agents, are non-enterococcal streptococci and enterococci. Patients receiving outpatient PD are at a low risk for acquiring VRE because these patients receive less intravenous vancomycin than HD patients (Ng *et al*., 1999). Among all the Gram-negative organisms, the genus *Pseudomonas* and the *Enterobacteriaceae*, have become an increasingly recognized cause of infective peritoneal complications. Within the Enterobacteriaceae group, *E. coli*, *Klebsiella spp.*, and *Enterobacter* sp. are the most prevalent PD-infection-related organisms. At this point, the production of extended-spectrum β-lactamases (ES βLs) in Enterobacteriaceae must be commented. There are few reports on ESβLs-producing Enterobacteriaceae in haemodialysis patients. However, the presence of ESβLs-producing *Escherichia coli* infections in PD-patients has been associated with a higher risk of dialysis failure (Yip *et al*., 2006). In addition, *Pseudomonas* species isolates account for a few episodes of and anaerobes are rarely if ever isolated. Probably, *Pseudomonas aeruginosa* is the most important peritonitis-causal agent of this genus (Krothapalli *et al*., 1982). The infection is severe and frequently associated with exit site or tunnel infection (Bernardini *et al*., 1987), loss of peritoneal space, and abscess formation (Kaczmarski *et al*., 1988), and is the main reason for the excess catheter removal rate in *P. aeruginosa*-caused peritonitis compared with rates in peritonitis of other etiology (Bernardini *et al*., 1987). Less common are reported infections by *Acinetobacter* spp. (Ruiz *et al*., 1988). The occurrence of fungal peritonitis (e.g., *Candida*) is uncommon but by no means rare. Infection with *Mycobacterium tuberculosis* or other type of mycobacteria has been reported but is unusual.

Common	Uncommon
Staphylococcus aureus	Aerobic gram-negative bacilli
Coagulase-negative staphylococci	- *Acinetobacter*
- *Staphylococcus epidermidis*	- *Alcaligenes*
Enterococcus faecium	- *Aeromonas*
Enterococcus faecalis	- *Achromobacter*
Klebsiella pneumoniae	- *Flavobacterium*
Escherichia coli	- *Proteus*
Nonenterococcal streptococci	- *Pseudomonas aeruginosa*

Table 3: Bacterial pathogens causing infections in Dialysis Patients

9 Exit Site Infections

Proportionally to the decline in the incidence of peritonitis because of improvements in PD, there has been an increase in the incidence of exit site infections (ESIs). Habitually, the incidence of ESI is directly proportional to the size of the exit wound. Approximately one-fifth of peritonitis episodes are temporally associated with exit site and tunnel infections (Piraino *et al*., 1987). The incidence of exit site infections is approximately one episode every 24–48 patient-months. Patients with previous infections tend to have a higher frequency of occurrence.

Exit site infections are predominantly due to *S. aureus* or Gram-negative organisms. In contrast to peritonitis, *S. epidermidis* is the causative organism in less than 20% of patients. *S. aureus* infections appear to have a distinct pathogenesis as they are associated with nasal and or skin carriage of the organism (Luzar, 1990). Therefore, eradication of the carrier state is very helpful to effective management. Exit site infections due to Gram-negative bacilli (enteric and pseudomonal organisms are most common) are also a source of considerable morbidity.

10 Staphyloccoci Resistance to Antibiotics in Dialysis

10.1 Methicillin

Methicillin resistance in staphylococci is conferred by the *mecA* gene, which is easily transferred horizontally and encodes for an altered penicillin-binding protein (PBP2a) that has a low binding affinity for all lactam-β antibiotics. The progressive spread of methicillin-resistant *S. aureus* (MRSA) is daunting. Twelve to 30% (2006 through 2007 European data), 33% (1994 through 2001 U.S. data), and up to 65% (most recent U.S. data) of patients on hemodialysis are colonized with MRSA (Lederer *et al*., 2007). The proportion of infections that are caused by MRSA varies strongly with local epidemiology and according to the year of surveillance. A recent report from Taiwan demonstrated a colonization rate with MRSA as low as 2.4% (Lu *et al*., 2008). In North America, conversely, community-acquired MRSA infections are rapidly emerging, accounting for 60 to 75% of all isolates in the community (Moellering *et al*., 2008). The risk for invasive MRSA infections is 100-fold higher in dialysis patients than in the general population (45.2/1000 *versus* 0.2 to 0.4/1000) (Centers for Disease Control and Prevention, 2007). Dialysis patients currently account for up to 15.4% of all invasive MRSA infections (Centers for Disease Control and Prevention, 2007). As for methicillin-sensitive *S. aureus* (MSSA) infections, molecular typing suggests that colonization of MRSA strains precedes clinical infection (Lu *et al*., 2008). Data regarding the role of methicillin resistance in outcome are conflicting, although most data suggest a higher mortality and recurrence rate. A small, single-center, case-control study found a 38% case fatality rate for the MRSA group *versus* 28% for the MSSA group, but the difference lost significance after adjustment for major confounders (Harbarth *et al*., 1998). A large cohort study of 908 consecutive SAB episodes did not find an increased adjusted mortality risk in the MRSA group (Soriano *et al*., 2000). In contrast, a large, single-center cohort study of 385 episodes of SAB reported that methicillin resistance resulted in a 2.59 times higher mortality in the elderly (McClelland *et al*., 1999). Despite the use of appropriate antibiotics in the majority of patients, a large (504 episodes of SAB) retrospective cohort

study demonstrated a significantly higher mortality rate in the MRSA than in the MSSA group (18.6 *versus* 12.9%) (Selvey *et al*., 2000). A steady increase over time of the minimal inhibitory concentration (MIC) for vancomycin is observed in the staphylococcal population (Boucher *et al*., 2007). MRSA strains with an increased MIC for vancomycin (> 1 to 2 µg/ml) impart a higher risk for death (Hidayat *et al*., 2006). MRSA strains with MIC for vancomycin of >2 and <16 µg/ml are referred to as vancomycin intermediate *S. aureus* (VISA) (Tenover *et al*., 2007). VISA strains predispose to treatment failure, even when high dosages of vancomycin are used. Some patients are infected with heteroresistant MRSA (hVISA), defined by the presence of subpopulations with reduced susceptibility to vancomycin. Heteroresistant MRSA are easily missed by commercial automated tests and predispose to treatment failure (Jones, 2006).

10.2 Vancomycin

Recently, vancomycin-resistant *S. aureus* (VRSA) was reported in seven patients from the United States. All patients had chronic colonization with MRSA and vancomycin-resistant enterococci, and most of them had received prolonged therapy with vancomycin for MRSA infection. Of note, three of seven patients had ESRD. All VRSA had acquired the *vanA* gene from vancomycin-resistant enterococci, and the median vancomycin MIC was 512 µg/ml. The mechanism of resistance in VRSA is quite different from VISA. The *vanA* gene results in the replacement of D-Ala-D-Ala-ending peptidoglycan precursors with D-alanyl-D-lactate termini, causing a decreased binding affinity for vancomycin and an almost 1000-fold increase in MIC (Sievert *et al*., 2008). Vancomycin tolerance refers to an inhibition of growth without bacterial killing (and thus cure) and is defined as a MBCMIC ratio of >32, or a MBC-MIC ratio of >16 in case of a MIC $\geq$32 µg/ml (Jones, 2006). Vancomycin tolerance is highly prevalent (74 to 100%) in hVISA, VISA, and VRSA strains and causes clinical treatment failure (Jones, 2006).

10.3 Mupirocin

Mupirocin resistance has been reported (Annigeri *et al*., 2001; Lobbedez *et al*., 2004; Pérez–Fontán *et al*., 2002). Resistance to mupirocin can be classified as "low" if the minimal inhibitory concentration is greater than or equal to 8 µg/mL, or "high" if the minimal inhibitory concentration is greater than or equal to 512 µg/mL. It is expected that high-level resistance will eventually result in clinical failure or a high relapse rate. Resistance to mupirocin does not yet appear to have eliminated the efficacy of that agent, but that consequence is likely with longer periods of individual exposure and with more patients being exposed. Pérez–Fontán et al. have observed a greater incidence of exit-site infections in patients colonized with mupirocin-resistant *S. aureus* than in those colonized with sensitive organisms, suggesting that the development of mupirocin resistance may have adverse clinical consequences and lead to treatment failures (Pérez–Fontán *et al*., 2002).

10.4 Oxazolidinone

Oxazolidinone is a bacteriostatic oxazolidin that has high oral bioavailability and inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit in Gram-positive bacteria and mycobacterial species (Moellering, 2003). On the basis of several randomized, controlled trials, oxazolidinone has been approved for complicated and non-complicated skin and skin-structure

infections and for community-acquired and nosocomial pneumonia in a dosage of 600 mg twice daily, intravenously or orally (Moellering, 2003, 2008). No dosage adjustment is necessary in chronic kidney disease, but a strict monitoring for adverse effects is recommended (Moellering, 2008). Several case reports and smaller series suggested a place for oxazolidinone in the treatment of MRSA osteoarticular infections (Moellering, 2008). Only limited data demonstrated activity of oxazolidinone in MRSA sepsis (mainly in secondary bacteremia), and the antibiotic is not approved for this indication (Lentino *et al*., 2008). The use of oxazolidinone for a period beyond 2 to 3 weeks is associated a dosage- and time-dependent myelosuppression and risk for lactic acidosis that is caused by a depletion of several mitochondrial proteins (Moellering, 2002).

11 Dialysis Associated Infections in Diabetic Patients: A Molecular Approach

One of the most worrisome examples about pathogenic bacteria infections in the hospital setting is rising incidence in patients with CKD and particularly in those patients undergoing HD and PD. Dialysis-related infections (including peritonitis and VA infections) are the second leading cause of death in dialysis patients (Sarnak & Jaber, 2000). Moreover, as for other types of infections, microorganisms causing dialysis-related infections are becoming more resistant to antimicrobials (D'Agata, 2005). Several factors converge to convert infections by far the most common complications affecting ESRD patients. Dialysed patients are extremely vulnerable to infections because of the presence of an access susceptible to be colonized by many infective agents (Butterly & Schwab, 2000). Even more, this population is hospitalised with greater frequency than the general population, which is correlated with higher infection rates (Foley, 2007). To this situation, a greater risk of infection in this population partially caused by impaired host immunity must be added. It has been found that the uremic state interferes with T-cell and B-cell dysfunction, macrophage phagocytosis, and antigen presentation (Ryan *et al*., 2004).

Patients with diabetes, which is the most common cause of treated ESRD (US Renal Data System, 2006), often face unique challenges when it comes to infection. They may have additional immune defects as well as vascular disease which may further increase the risk of certain types of infections. Dialysed patients with diabetes can be more prone to infection because of related conditions related to diabetes. In example, the excess of glucose in blood may prevents white blood cells, which are one of the main defences against infection, from doing their jobs (Minnaganti & Cunha, 2001). It is important to achieve a good glycaemia control.

Staphylococci and other Gram-positive bacteria are the agents most commonly involved in such dialysis infections, accounting for 20% – 40% of the cases of PD–related peritonitis (Zelenitsky *et al*., 2001), and at lesser extent, different species of aerobic Gram-negative bacilli (Sullivan *et al*., 2007).

11.1 Molecular approach for dialysis infections

Although the conventional phenotypic method is still popular to identify common bacteria in clinical microbiology laboratories, it is difficult to use this method when bacteria reveal uncommon

phenotypes, grow slowly, or are not included in commercial kit databases (Petti *et al*., 2005; Shin *et al*., 2005). In addition, we cannot detect uncultivable or fastidious microorganisms or organisms in patients who have recently received antibiotic therapy, even when bacteria are present in the clinical samples (Yoo *et al*., 2006). To overcome these problems, many molecular techniques have been adopted. In this section, we will comment different methods which is used to detect infection's causative pathogen or methods that might be useful to typing the isolates.

HD patients with MRSA infections face high morbidity and mortality. Nasal carriage of *S. aureus* is known to play an important role as an endogenous source for HD-access-related infections that contribute significantly to morbidity, mortality and cost of ESRD management (Lederer *et al*., 2007). Pulsed-field gel electrophoresis (PFGE) with *Smal* digestion of chromosomal DNA has been used for the genotyping of MRSA isolates from haemodialysis patients.

Since the chromosome is the most fundamental component of identity of the cell, methods measuring this molecule represent a preferred approximation for assessing strain interrelatedness. Restriction patterns originated after chromosomal DNA enzymatic digestion generates a restriction fragment length polymorphism (RFLP), after PFGE, which efficiently and accurately allows the differentiation of strains and compare following conventional agarose gel electrophoresis. PFGE methods have been used to evaluate the spread of various antimicrobial resistant bacteria. The finding of isolates that have identical or related restriction endonuclease patterns suggests spread from single strains.

The accuracy and reliability of this technique have led to be considered as the reference method for typing MRSA isolates. Several studies have used this technique to typing isolates from haemodialysis patients (Taylor *et al*., 2002).

Actually, PFGE is being more widely replaced by sequence-based methods that allow for unambiguous identification of isolates, easy data accumulation and comparison. Multi-locus sequence typing (MLST) is the molecular method with highest discriminatory capability and is based in characterizing the sequences of internal fragments of different housekeeping genes. In the case of *S. aureus* MLST, these are *carbamate kinase* (*arcC*), *shikimate 5-dehydrogenase* (*aroE*), *glycerol kinase* (*glpF*), *guanylate kinase* (*gmk*), *phosphate acetyltransferase* (*pta*), *triose-phosphate isomerase* (*tpi*) and *acetyl-CoA C-acetyltransferase* (*yqiL*). The sequences obtained are assigned to allele numbers after comparison with a DNA sequences database. The allele numbers at each of the seven *loci* define the allelic profile or sequence type (ST). Novel alleles and STs not found on the MLST website are confirmed by repeating both the Polymerase Chain Reaction (PCR) and sequencing (Peacock *et al*., 2002).

Peritonitis is one of the most common complications of CAPD, and rapid and accurate identification of the causative pathogen is essential for diagnosis and selection of the appropriate therapy. However, conventional culture takes at least 2 or 3 days to provide the final identification, and we would be in a difficult situation if there were small numbers of bacteria or fastidious bacteria in the CAPD fluid. It would be valuable to use supplementary molecular methods such for detection and identification of pathogens.

A number of novel diagnostic techniques have been explored for the early diagnosis of peritonitis (Akman *et al*., 2005; Park *et al*., 2005) reported that leukocyte esterase reagent strip has excellent accuracy for the diagnosis of peritonitis. Various commercially available strips have been

tested to diagnose non-PD peritonitis but the results vary enormously; more studies are required before this can be applied in a routine setting (Nguyen-Khac *et al*., 2008).

Broad-spectrum PCR with RNA sequencing and quantitative bacterial DNA PCR assays may also complement culture methods in the diagnosis of CAPD peritonitis, especially in patients with previous or current antibiotic use. The latter technique may also help to identify those patients likely to relapse despite apparent clinical improvement with standard antibiotic therapy. Another study suggests that the matrix metalloproteinase-9 test kit may be a reliable method for early diagnosis of PD peritonitis (Ro *et al*., 2004). The role of rapid detection of the causative pathogen of peritonitis using *in situ* hybridization has also been explored (Ota *et al*., 2007).

Amplification and sequencing conserved genes of bacterial genomic DNA are used for identification of staphylococcal species and their genotypes. In *S. aureus* the genes encoding 16S rRNA, factor A essential for methicillin resistance (*femA*), and staphylococcal thermonuclease (*nuc*) (among others) are frequently used for identification at the species level. Moreover, antibiotic resistance is a troubling phenomenon very extended. Another important use of PCR is to determine resistance phenotype based on the holding of genes encoding related factors. Pasqual et al. (2012) reviewed the records of 62 *S. aureus* peritonitis episodes that occurred between 1996 and 2010 in the dialysis unit of a single university hospital and evaluated the host and bacterial (gene resistance) factors influencing peritonitis outcome by PCR (*mec*A gene). Another study could detect and identify bacterial pathogens directly from CAPD culture fluids by application of broad-range PCR using 16S rDNA (Si *et al*., 2012).

Many other genotyping techniques are applied to support epidemiological methods described in order to characterize infection causal agents from dialysis like *spa* typing (Moremi *et al*., 2012; Turlej *et al*., 2011).

In conclusion, catheters are inherently vulnerable to luminal and extra luminal infection and have high rates of associated bacteremia. On the other hand, *S. aureus* peritonitis is a common and serious complication of PD and is associated with a high rate of relapse (20%) and repeat episodes (29%) (Govindarajulu *et al*., 2010). As a result of that, early recognition and treatment of dialysis-related bacteremia minimizes morbidity and mortality from complications.

12 Cardiovascular Risk Associated to Infections

CV morbidity and mortality have always been major concerns for nephrologists managing patients on dialysis, and it has been shown that reduced residual renal function, inflammation, valvular calcification and left ventricular hypertrophy are predictors of CV mortality in patients on peritoneal dialysis. The interaction between infection and CV disease, however, seems to be a new concern. Although the mechanisms linking infection, chronic inflammation and cardiovascular disease have been elusive, this phenomenon of infection being a harbinger of future CV events and death has been repeatedly investigated and confirmed in observational and epidemiological studies (Foley *et al*., 2004; Ishani *et al*., 2005). In a historical cohort study of 393.451 patients on HD or PD, septicemia was identified as a precursor to the development of cardiovascular events and death (Foley *et al*., 2004). Septicemia was associated with the development of myocardial infarction, congestive heart

failure, stroke and peripheral vascular disease, and the adjusted risk ratio of these events remained approximately double that expected for up to 5 years after the initial infection (Foley *et al*., 2004). These observations have been confirmed in another prospective study—the Dialysis Morbidity and Mortality Wave 2 study—in which septicemia or bacteremia were associated with a nearly twofold increase in the risk of myocardial infarction or stroke (Ishani *et al*., 2005).

Although mechanisms linking infection, chronic inflammation, and CV disease in the general population are incompletely understood, this is an active area of basic and clinical research (Ross, 1999). It is known that macrophages and T cells are prominent in fatty streaks and homeostatic abnormalities of lipid metabolism and inflammatory pathways may be synergistically involved in the pathogenesis of fatty streaks. In addition, immune cells are present in early atherosclerotic lesions and effector molecules from these immune cells seem to facilitate progression of these lesions. Inflammation is also thought negatively to affect the stability of established plaques, enhancing the risk of acute coronary syndromes (Hansson, 2005). Acute bacterial infections are prototypical inflammatory events, and are typified by abnormal endothelial function, oxidative stress, and disequilibrium between pro-coagulant and anticoagulant systems, cardiac dysfunction, and diminished cellular oxygen availability (Hotchkiss & Karl, 2003). One further considers that low-grade inflammation and high-grade CV disease are typical features of CKD (Kaysen & Eiserich, 2003). It seems natural to suspect that common macro-inflammatory events in dialysis patients (like pneumonia and septicemia) may contribute to the sizeable burden of CV in this population. Whether infection can be considered a risk factor for atherogenesis and cardiovascular disease, however, remains unclear.

13 Conclusions

Kidney disease represents one of the leading causes of death in the western world and the total cost of treating ESRD patients with dialysis therapies is continuously increasing. Much of the dialysis treatment is provided in the outpatient setting; however the number of hospitalizations for associated conditions, such as diabetes, CVD and infections, is substantial. Dialysis places patients at high risk of infection because of patient comorbidities and numerous human, environmental and procedural factors. Among pathogens gram positive bacteria, mainly *S. aureus*, represents the major cause of infections morbidity and mortality in CKD patients. These agents cause a wide variety of clinical manifestations ranging from colonizing without any sign of disease to localize or invasive bloodstream infections and septicemia. These effects are related to the circumstance that *S. aureus* is provided by several virulence factors permitting rapid tissue invasion and dissemination throughout the body and its genetic plasticity that permits a constant adaptation to changing environmental conditions together with the development of several antibiotic resistance patterns. Invasive devices for vascular and peritoneal procedures for dialysis access represent the leading predisposing factor for infections in dialysis patients. Thus central venous catheters related infections in hemodialysis and peritonitis in peritoneal dialysis are the most frequent type of infections in patients undergoing dialysis treatment. Moreover, infection in patients on either form of dialysis is also associated with an increasing risk of subsequent CV events. The presence of infection in a patient on dialysis has a

substantial effect on CV mortality and morbidity, and should influence decisions regarding the use of therapies and strategies intended to minimize that risk (i.e. arterio-venous fistula as permanent vascular access). Establishing an infection prevention and control program which includes a bundle of strategies and interventions that are consistently performed will reduce the infection risk and associated conditions for both health personnel and patients.

Establishing an infection prevention and control program which includes a bundle of strategies and interventions that are consistently performed will reduce the infection risk for both health personnel and patients. The control and treatment of infectious agents such as *Staphylococcus* spp. , especially methicillin resistant strains, and other Gram-positive bacteria need for developing reliable and rapid methods of detection and characterization of these microorganisms. Nowadays, new insights into the diagnostic and epidemiology of MRSA and other pathogenic staphylococci have been developed employing molecular methods. This has meant an important advance in the diagnostic and treatment plans of such infective bacteria.

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References

Abbott KC, Agodoa LY. 2002. Hospitalizations for bacterial endocarditis after initiation of chronic dialysis in the United States. Nephron 91: 203–209.

Adler AI, Stevens RJ, Manley SE et al. 2003. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 63: 225–232.

Akman S, Uygun V, Guven AG. 2005. Value of the urine strip test in the early diagnosis of bacterial peritonitis. Pediatr Int 47:523-527

Annigeri R, Conly J, Vas S, Dedier H, Prakashan KP, Bargman JM. Emergence of mupirocin-resistant Staphylococcus aureus in chronic peritoneal dialysis patients using mupirocin prophylaxis to prevent exit-site infection. Perit Dial Int 2001; 21:554–9

ANZDATA Registry Report. 2008. Appendix II. pp 1–97. In: McDonald S, Excell L, Livingston B (eds). Australia and New Zealand Dialysis and Transplant Registry: Adelaide. Australia.

Band JD. 1999. Nosocomial infections associated with peritoneal dialysis. In: Hospital Epidemiology and Infection Control, Mayhall CG (ed), 2nd ed. Lippincott Williams & Wilkins, PAIS.

Bernardini, J., B. Piraino, M. Sorkin. 1987. Analysis of continuous ambulatory peritoneal dialysis-related Pseudomonas aeruginosa infections. Am. J. Med. 83: 829-832.

Bloembergen WE, Port FK. 1996. Epidemiological perspective on infections in chronic dialysis patients. Adv Ren Replace Ther 3:201.

Boelaert JR, Van Landuyt HW, De Baere YA, Deruyter Clin J Am Soc Nephrol 4: 1388–1400, 2009 S. aureus Bacteremia in Hemodialysis 1395 MM, Daneels RF, Schurgers ML, Matthys EG, Gordts BZ. Staphylococcus aureus infections in

haemodialysis patients: Pathophysiology and use of nasal mupirocin for prevention. J Chemother 7 [Suppl 3]: 49-53, 1995

Borg D, Shetty A, Williams D, Faber MD. Fivefold reduction in peritonitis using a multifaceted continuous quality initiative program. Adv Perit Dial 2003; 19: 202–5

Boucher HW, Sakoulas G: Perspectives on daptomycin resistance, with emphasis on resistance in Staphylococcus aureus. Clin Infect Dis 45: 601-608, 2007

Butterly D.W., Schwab S.J. 2000. Dialysis access infections. Curr. Opin. Nephrol. Hypertens. 9: 631-635.

Centers for Disease Control and Prevention (CDC). 2007. Invasive methicillin-resistant Staphylococcus aureus infections among dialysis patients-United States, 2005. Morb. Mortal. Wkly. Rep. 56: 197-1999.

Cosgrove S.E., Sakoulas G., Perencevich E.N.,et al. 2003. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin. Infect. Dis. 36, 53-59.

D'Agata E.M. 2005. Antimicrobial-resistant, Grampositive bacteria among patients undergoing chronic hemodialysis. Clin. Infect. Dis. 35, 1212-1218, 2002; Salzer W. Antimicrobial-resistant gram-positive bacteria in PD peritonitis and the newer antibiotics used to treat them. Perit. Dial. Int. 25: 313-319:

Dancer SJ. Importance of the environment in methicillin-resistant Staphylococcus aureus acquisition: The case for hospital cleaning. Lancet Infect Dis 8: 101–113, 2008

Descamps-Latscha B, Herbelin A, Nguyen AT, et al. 1994. The immune system in end-stage renal disease. Semin Nephrol 14: 253.

Diaz-Granados C.A., Zimmer S.M., Klein M., et al. 2005. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a metaanalysis. Clin. Infect. Dis. 41: 327-333.

Diekema D.J., BootsMiller B.J., Vaughn T.E., et al. 2004. Antimicrobial resistance trends and outbreak frequency in United States hospitals. Clin. Infect. Dis. 38: 78-85.

Diskin CJ, Stokes TJ, Dansby LM, Radcliff L, Carter TB. 2007. Is systemic heparin a risk factor for catheter-related sepsis in dialysis patients? An evaluation of various biofilm and traditional risk factors. Nephron Clin Pract 107: c128–c132.

Eknoyan G, Hostetter T, Bakris GL et al. 2003. Proteinuria and other markers of chronic kidney disease: A position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive and kidney diseases (NIDDK) Am J Kidney Dis 42: 617-622.

Ena J, Boelaert JR, Boyken LD, Van Landuyt HW, Godard CA, Herwaldt LA: Epidemiology of Staphylococcus aureus infections in patients on hemodialysis. Infect Control Hosp Epidemiol 15: 78-81, 1994

Foley R.N. 2007. Infections in patients with chronic kidney disease. Infect. Dis. Clin. North Am. 21, 659-672.

Foley, R. N., Guo, H., Snyder, J. J., Gilbertson, D. T. & Collins, A. J. 2004. Septicemia in the United States dialysis population, 1991 to 1999. J. Am. Soc. Nephrol. 15: 1038–1045.

Girndt M, Kohler H, Schiedhelm-Weick E, et al. 1993. T cell activation defect in hemodialysis patients: evidence for a role of the B7/CD28 pathway. Kidney Int 44:359–365.

Girndt M, Sester U, Sester M, et al. 1999. Impaired cellular immune function in patients with end stage renal failure. Nephrol Dial Transplant 14: 2807–2810.

Golper T.A., Schulman G., D'Agata E.M. 2000. Indications for vancomycin in dialysis patients. Semin. Dial. 13: 389-392.

Govindarajulu S, Hawley CM, McDonald SP, Brown FG, Rosman JB, Wiggins KJ, Bannister KM, Johnson DW. 2010. Staphylococcus aureus peritonitis in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in 503 cases. Perit Dial Int. 30: 311-319.

Graham PL III., Lin SX, Larson EL. A U.S. population-based survey of Staphylococcus aureus colonization. Ann Intern Med 144: 318–325, 2006

Hansson GK. 2005. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 352: 1685–1695.

Harbarth S, Rutschmann O, Sudre P, Pittet D. Impact of methicillin resistance on the outcome of patients with bacteremia caused by Staphylococcus aureus. Arch Intern Med 158: 182-189, 1998

Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: Efficacy and toxicity. Arch Intern Med 166: 2138-2144, 2006

Himmelfarb J, and Ikizler T. Alp. Hemodialysis N Engl J Med 2010; 363:1833-1845

Hoen B, Paul-Dauphin A, Hestin D, Kessler M. 1998. EPIBACDIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. J Am Soc Nephrol 9: 869–876.

Hotchkiss RS, Karl IE. 2003. The pathophysiology and treatment of sepsis. N Engl J Med 348:138–150.

Inrig JK, Reed SD, Szczech LA, Engemann JJ, Friedman JY, Corey GR, Schulman KA, Reller LB, Fowler VG Jr. 2006. Relationship between clinical outcomes and vascular access type among hemodialysis patients with Staphylococcus aureus bacteremia. Clin J Am Soc Nephrol 1: 518–524.

Ishani, A., Collins, A. J., Herzog, C. A. & Foley, R. N. 2005. Septicemia, access and cardiovascular disease in dialysis patients: the USRDS Wave 2 study. Kidney Int. 68: 311–318.

Jevons M.P. 1961. "Celbenin-resistant" staphylococci. Brit. Med. J. 1: 124-125.

Jones RN: Microbiological features of vancomycin in the 21st century. Minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. Clin Infect Dis 42[Suppl 1]: S13–S24, 2006

Kaczmarski, E. B., J. A. Tooth, E. Anastassiades, J. Manos, and R. Gokal. 1988. Pseudomonas peritonitis with continuous ambulatory peritoneal dialysis: a six-year study. Am. J. Kidney Dis. 11: 413-417.

Kamalakannan D, Pai RM, Johnson LB, Gardin JM, Saravolatz LD. 2007. Epidemiology and clinical outcomes of infective endocarditis in hemodialysis patients. Ann Thorac Surg 83: 2081–2086.

Kaysen GA, Eiserich JP. 2003. Characteristics and effects of inflammation in end-stage renal disease. Semin Dial 16:438–446.

King H, Aubert R, Herman W. 1998. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 21: 1414–1431.

Kluytmans J, van Belkum A, Verbrugh H. 1997. Nasal carriage of Staphylococcus uureus: Epidemiology, underlying mechanisms, and associated risks. Clin Microbiol Rev 105-20.

Kohler H, Arnold W, Renschin G, et al. 1984. Active hepatitis B vaccination of dialysis patients and medical staff. Kidney Int 25:124–128.

Krothapalli, R., W. B. Duffy, C. Lacke, W. Payne, H. Patel, V. Perez, and H. 0. Senekjian. 1982. Pseudomonas peritonitis and continuous ambulatory peritoneal dialysis. Arch. Intern. Med. 142: 1862-1863.

Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL. 2004. Severe bloodstream infections: A population-based assessment. Crit Care Med 32: 992–997.

Lazar MA, Brown CB, Bull D et al. 1990. Exit site care and exit site infections in continuous ambulatory peritoneal dialysis: Results of a randomized multicenter trial. Perit Dial Int 10: 25-9

Lederer S R, Riedelsdorf G, Schiffl H. 2007. Nasal carriage of meticillin resistant Staphylococcus aureus: the prevalence, patients at risk and the effect of elimination on outcomes among outclinic haemodialysis patients. Eur J Med Res. 12:284-288.

Leehey DJ, Lentino, JR. Peritonite e Infecção do Local de Saída. In: Daurgidas JT, Blake PG, Ing TS. Manual de Diálise. 3 ed. Rio de Janeiro: Medsi, 2003, pp. 385-408.

Lentino JR, Narita M, Yu VL. New antimicrobial agents as therapy for resistant gram-positive cocci. Eur J Clin Microbiol Infect Dis 27: 3-15, 2008

Lewis SL. 1992. Fever: Thermal regulation and alterations in end stage renal disease patients. ANNA J 19:13.

Lobbedez T, Gardam M, Dedier H, Burdzy D, Chu M, Izatt S. Routine use of mupirocin at the peritoneal catheter exit site and mupirocin resistance: still low after 7 years. Nephrol Dial Transplant 2004; 19:3140–3)

Lu PL, Tsai JC, Chiu YW, Chang FY, Chen YW, Hsiao CF, Siu LK. Methicillin-resistant Staphylococcus aureus carriage, infection and transmission in dialysis patients, healthcare workers and their family members. Nephrol Dial Transplant 23: 1659-1665, 2008

Luzar MA. Exit-site infection in CAPD: a review. Contrib Nephrol. 1990;85:57-66. Review.

Lysaght M. 2002. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol 13: S37–S40.

Marr KA, Kong L, Fowler VG, Gopal A, Sexton DJ, Conlon PJ, Corey GR. 1998. Incidence and outcome of Staphylococcus aureus bacteremia in hemodialysis patients. Kidney Int. Nov;54(5):1684-1689.

McClelland RS, Fowler VG Jr, Sanders LL, Gottlieb G, Kong LK, Sexton DJ, Schmader K, Lanclos KD, Corey R. Staphylococcus aureus bacteremia among elderly vs younger adult patients: Comparison of clinical features and mortality. Arch Intern Med 159: 1244-1247, 1999

Melzer M., Eykyn S.J., Gransden W.R., Chinn S. 2003. Is methicillin-resistant Staphylococcus aureus more virulent than methicillin-susceptible S. aureus? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin. Infect. Dis. 37: 1453-1460

Minnaganti VR, Cunha BA. 2001. Infections associated with uremia and dialysis. Infect Dis Clin North Am. 15:385-406.

Moellering RC Jr. Current treatment options for community-acquired methicillin-resistant Staphylococcus aureus infection. Clin Infect Dis 46: 1032-1037, 2008

Moellering RC. Linezolid: The first oxazolidinone antimicrobial. Ann Intern Med 138: 135-142, 2003

Monteon F, Correa-Rotter R, Paniagua R et al. Prevention of peritonitis with disconnect systems in CAPD: a randomized controlled trial. The Mexican Nephrology Collaborative Study Group. Kidney Int 1998; 54:2123-38.

Moremi N, Mshana SE, Kamugisha E, Kataraihya J, Tappe D, Vogel U, Lyamuya EF, Claus H. 2012. Predominance of methicillin resistant Staphylococcus aureus -ST88 and new ST1797 causing wound infection and abscesses. J Infect Dev Ctries. 21: 620-625

Moss AH. 2001. Shared decision-making in dialysis: the new RPA/ASN guideline on appropriate initiation and withdrawal of treatment. Am J Kidney Dis 37: 1081-1091.

Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE. 2007. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. Nephrol Dial Transplant 22: 1955-1962.

Nassar GM, Ayus JC. 2001. Infectious complications of the hemodialysis access. Kidney Int 60: 1–13.

Ng R, Zabetakis PM, Callahan C. 1999. Vancomycin-resistant Enterococcus infection is a rare complication in patients receiving PD on an outpatient basis. Perit Dial Int 19: 273.

Nguyen-Khac E, Cadranel JF, Thevenot T, Nousbaum JB. 2008. The utility of reagent strips in the diagnosis of infected ascites in cirrhotic patients. Aliment Pharmacol Ther 28:282-288

Ninomiya T, Perkovic V, de Galan BE et al. 2009. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 20: 1813–1821.

Nolph KD. 1988. Current status of CAPD and CCID. Dial Transplant 17:457.

Nsouli KA, Lazarus JM, Schoenbaum SC, et al. 1979. Bacteremic infection in hemodialysis. Arch Intern Med 139:1255.

Ota K, Maruyama H, Iino N, Nakamura G, Shimotori M, Tanabe Y, et al. 2007. Rapid detection of causative pathogen of peritonitis using in-situ hybridization in a patient with continuous ambulatory peritoneal dialysis. J Infect Chemother 13: 273-275.

Park SJ, Lee JY, Tak WT, Lee JH. 2005. Using reagent strips for rapid diagnosis of peritonitis in peritoneal dialysis patients. Adv Perit Dial 21:69-71.

Pasqual Barretti, Taíse M. C. Moraes, Carlos H. Camargo, Jacqueline C. T. Caramori, Alessandro L. Mondelli, Augusto C. Montelli, Maria de Lourdes R. S. da Cunha. 2012. Peritoneal Dialysis-Related Peritonitis Due to Staphylococcus aureus: A Single-Center Experience over 15 Years. PLoS One. 7: e31780.

Peacock SJ, de Silva GD, Justice A, Cowland A, Moore CE, Winearls CG, Day NP. 2002. Comparison of multilocus sequence typing and pulsed-field gel electrophoresis as tools for typing Staphylococcus aureus isolates in a microepidemiological setting. J Clin Microbiol. 40: 3764-3770.

Pérez–Fontán M, Rosales M, Rodríguez–Carmona A, Falcón TG, Valdés F. Mupirocin resistance after long-term use for Staphylococcus aureus colonization in patients undergoing chronic peritoneal dialysis. Am J Kidney Dis 2002; 39:337–41)

Petti C. A., Polage C. R., Schreckenberger P. 2005. The Role of 16S rRNA Gene Sequencing in Identification of Microorganisms Misidentified by Conventional Methods J Clin Microbiol. 43: 6123–6125.

Piraino B, Bernardini J, Sorkin M. A five-year study of the microbiologic results of exit site infections and peritonitis in continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1987 Oct;10(4):281-6.

Retnakaran R, Cull CA, Thorne KI et al. 2006. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes 55: 1832–1839.

Reutens AT, Prentice L, Atkins R. 2008. The epidemiology of diabetic kidney disease. In: Ekoé J-M, Rewers M, Williams R, Zimmet P (eds). The Epidemiology of Diabetes mellitus. John Wiley & Sons Ltd. UK.

Ro Y, Hamada C, Io H, Hayashi K, Hirahara I, Tomino Y. 2004. Rapid, simple, and reliable method for the diagnosis of CAPD peritonitis using the new MMP-9 test kit. J Clin Lab Anal 18: 224-230.

Ross R. 1999. Atherosclerosis: an inflammatory disease. N Engl J Med 340: 115–126.

Ruiz, A., B. Ramos, D. Burgos, M. A. Grutos, and E. Lopez de Novales. 1988. Acinetobacter calcoaceticus peritonitis in continuous ambulatory peritoneal dialysis (CAPD) patients. Peritoneal Dialysis Int. 8: 285-286.

Ryan S.V., Calligaro K.D., Dougherty M.J. 2004. Management of hemodialysis access infections. Semin. Vasc. Surg. 17: 40-44.

Sarnak MJ, Jaber BL: Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 58: 1758–1764, 2000

Selvey LA, Whitby M, Johnson B. Nosocomial methicillin resistant Staphylococcus aureus bacteremia: Is it any worse than nosocomial methicillin-sensitive Staphylococcus aureus bacteremia? Infect Control Hosp Epidemiol 21: 645-648, 2000

Shin JH, Kim HR, Lee JN. 2005. Clinical significance and species identification of rapidly growing mycobacteria isolated from routine blood cultures. Korean J Lab Med 26:162-167

Si Hyun Kim, M.S., Haeng Soon Jeong, Yeong Hoon Kim, Sae Am Song. 2012. Evaluation of DNA Extraction Methods and Their Clinical Application for Direct Detection of Causative Bacteria in Continuous Ambulatory Peritoneal Dialysis Culture Fluids from Patients with Peritonitis by Using Broad-Range PCR. Ann Lab Med. 32: 119–125.

Sicree R, Shaw J, Zimmet P. 2006. Diabetes and impaired glucose tolerance. In: Gan D (ed). Diabetes Atlas, 3rd edn. International Diabetes Federation. Brussels, pp 15–109.

Sievert DM, Rudrik JT, Patel JB, McDonald LC, Wilkins MJ, Hageman JC: Vancomycin-resistant Staphylococcus aureus in the United States, 2002-2006. Clin Infect Dis 46: 668-674, 2008

Soriano A, Martinez JA, Mensa J, Marco F, Almela M, Moreno-Martinez A, Sanchez F, Munoz I, Jimenez de Anta MT, Soriano E. Pathogenic significance of methicillin resistance for patients with Staphylococcus aureus bacteremia. Clin Infect Dis 30: 368-373, 2000

Stevenson KB, Hannah EL, Lowder CA, Adcox MJ, Davidson RL, Mallea MC, Narasimhan N, Wagnild JP. 2002. Epidemiology of hemodialysis vascular access infections from longitudinal infection surveillance data: Predicting the impact of NKF-DOQI clinical practice guidelines for vascular access. Am J Kidney Dis 39:549–555.

Sullivan R., Samuel V., Le C. 2007. Hemodialysis vascular catheter-related bacteremia. Am. J.Med. Sci. 334: 458-465.

Sunder-Plassmann G, Patruta SI, Horl WH. 1999. Pathobiology of the role of in infection. Am J Kidney Dis 34: S25.

Swartz R, Messana J, Starmann B. 1991. Preventing Staphylococcus aureus infection during chronic peritoneal dialysis. J Am SOC Nephrol 23: 085-91.

Taylor G, Gravel D, Johnston L, Embil J, Holton D, Paton S. 2002. Prospective surveillance for primary bloodstream infections occurring in Canadian hemodialysis units. Infect Control Hosp Epidemiol 23: 716–720.

Teehan GS, Bahdouch D, Ruthazer R, Balakrishnan VS, Snydman DR, Jaber BL. 2004. Iron storage indices: Novel predictors of bacteremia in hemodialysis patients ca

Vandecasteele SJ, Boelaert JR, De Vriese AS. Staphylococcus aureus infections in hemodialysis: what a nephrologist should know. Clin J Am Soc Nephrol. 2009 Aug;4(8):1388-400. 2009 Jul 9.

Vanholder R, Van Loo A, Dhondt AM. 1996. Influence of uremia and haemodialysis on host defense and infection. Nephrol Dial Transplant 11: 593.

Vascular Access 2006 Work Group. 2006. Clinical practice guidelines for vascular access. Am. J. Kidney Dis. 48: S176–S247.

von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. Study Group. N Engl J Med 344: 11–16, 2001

Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A,Verbrugh HA, Nouwen JL. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis 5: 751–762, 2005

Wertheim HF, Vos MC, Ott A, van Belkum A, Voss A, Kluytmans JA, van Keulen PH, Vandenbroucke-Grauls CM, Meester MH, Verbrugh HA. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. Lancet 364: 703-705, 2004

Whitby M., McLaws M.L., Berry G. 2003. Risk of death from methicillin-resistant Staphylococcus aureus bacteraemia: a meta-analysis. Med. J. Aust. 175: 264-267.

Yamagata K, Iseki K, Nitta K et al. 2008. Chronic kidney disease perspectives in Japan and the importance of urinalysis screening. Clin Exp Nephrol 12: 1–8.

Yip T., Tse K.C., Lam M.F., et al. 2006. Risk factors and outcomes of extended-spectrum beta-lactamase-producing E. coli peritonitis in CAPD patients. Perit. Dial. Int. 26: 191-197.

Yoo TH, Chang KH, Ryu DR, Kim JS, Choi HY, Park HC, et al. 2006. Usefulness of 23S rRNA amplification by PCR in the detection of bacteria in CAPD peritonitis. Am J Nephrol 26:115-120

Yoon JW, Gollapudi S, Pahl MV, et al. 2006. Native and central memory T-cell lymphopenia in end-stage renal disease. Kidney Int 70: 371–376.

Yoon K, Lee JH, Kim JW et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006; 368: 1681–1688.

Zelenitsky S, Barns L, Findlay I, Alfa M, Ariano R, Fine A. 2000. Analysis of microbiological trends in peritoneal dialysis-related peritonitis from 1991 to 1998. Am J Kidney Dis 36: 1009–1013

Zimmet P, Alberti K, Shaw J. 2001. Global and societal implications of the diabetes epidemic. Nature 414: 782–787.