# Oral and Dental Aspects of Chronic Renal Failure

R. Proctor[1,2], N. Kumar[1], A. Stein[3], D. Moles[4], and S. Porter[1]*

[1]Oral Medicine, Division of Maxillofacial Diagnostic, Medical & Surgical Sciences, Eastman Dental Institute for Oral Health Care Sciences, UCL, University of London, 256, Gray's Inn Road, London WC1X 8LD, UK; [2]Community Dental Department, Coventry NHS Primary Care Trust, Abbey View, 271 London Road, Coventry, West Midlands CV3 4AR, UK; [3]Department of Nephrology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, West Midlands CV2 2DX, UK; and [4]Health Services Research, Eastman Dental Institute for Oral Health Care Sciences, UCL, University of London, 256, Gray's Inn Road, London WC1X 8LD, UK; *corresponding author, S.Porter@eastman.ucl.ac.uk

*J Dent Res* 84(3):199-208, 2005

## ABSTRACT

The present article reviews, in detail, the current knowledge of the oral and dental aspects of chronic renal failure (CRF). Worldwide, increasing numbers of persons have CRF; thus, oral health care staffs are increasingly likely to provide care for patients with such disease. Chronic renal failure can give rise to a wide spectrum of oral manifestations, affecting the hard or soft tissues of the mouth. The majority of affected individuals have disease that does not complicate oral health care; nevertheless, the dental management of such individuals does require that the clinician understand the multiple systems that can be affected. The clinician should also consider the adverse side-effects of drug therapy and appropriate prescribing, in view of compromised renal clearance.

**KEY WORDS:** chronic, dental, oral, renal.

Received March 16, 2004; Accepted August 1, 2004

## (I) INTRODUCTION

The incidence of chronic renal failure (CRF) continues to rise worldwide (Ansell and Feest, 2002; McDonald and Russ, 2002; US Renal Data System, 2002), and, as a consequence, increasing numbers of individuals with such disease will probably continue to require oral health care. CRF and its treatment have systemic and oral manifestations. There are few detailed reports of the oral and dental disease manifestations, and of the relevant treatment needs of patients with CRF. Likewise, there are no systematic reviews of the treatment of oral disease in patients with CRF. The present report reviews current information –published in peer-reviewed journals or available from relevant nationally (*e.g.*, within the US or UK) or internationally recognized sources—on the oral and dental aspects of renal disease, highlighting the variable impact of CRF upon the mouth, and provides guidance for the dental treatment of patients with CRF.

## (II) CHRONIC RENAL FAILURE

Chronic renal failure (CRF) is defined as a progressive decline in renal function associated with a reduced glomerular filtration rate (GFR, as measured clinically by the creatinine clearance rate). The most common causes are diabetes mellitus, glomerulonephritis, and chronic hypertension. In older individuals, the most commonly diagnosed causes of CRF are renovascular disease and diabetes mellitus, although other causes include polycystic kidney disease and pyelonephritis (Ansell and Feest, 2002; McDonald and Russ, 2002; US Renal Data System, 2002).

## (III) EPIDEMIOLOGY

Data on the epidemiology of CRF are available in many countries, although different sampling techniques are used in each country, and units in some regions (*e.g.*, the UK) are not obliged to report patient figures. The reported incidence of CRF is 337, 90, 107 and 95 *per* million population (pmp) in the USA, Australia, New Zealand, and the UK, respectively. The incidence increases with age, and males are more commonly affected than females. Incidence also varies with ethnicity. For example, in the USA, Caucasians and Black Americans have higher incidences than Asians and Native Americans. However, in the UK, the incidence of CRF is higher in Asians and Afro-Caribbeans than in Caucasians (Roderick *et al.*, 1994).

The death rate is 178, 189, 217, and 209 *per* 1000 patient years (pyr) in the USA, Australia, New Zealand, and the UK, respectively (Table 1). These figures suggest that the USA has a lower death rate than the UK, but the USA data do not include deaths in the first 90 days following the onset of chronic renal failure. However, the UK death rate at 1 year and 90 days (188/1000 pyr) is comparable with that in the USA. There are only slight differences in the death rates between genders. Ethnicity also affects death rate: In the USA, it is lowest in Asians (130/1000 pyr) and highest in Caucasians (193/1000 pyr).

Survival rates vary with ethnic origin and the underlying cause of renal failure. In the USA, for example, the five-year survival rate

for Caucasians is lower than that for Black Americans (34.7% compared with 46.8%). The prognosis for individuals with diabetes mellitus and/or hypertension is worse than that for individuals with glomerulonephritis (30.9% and 36.5%, compared with 59.9%). A comparison of these figures with the five-year survival rate (62%) for all cancers in the USA highlights the poor prognosis for individuals with chronic renal failure (US Renal Data System, 2002).

The most common cause of death is cardiac failure, followed by infection and malignancy (Ansell and Feest, 2002; McDonald and Russ, 2002; US Renal Data System, 2002). Diabetes mellitus and hypertension greatly increase this risk (Santiago and Chanzan, 1989).

## (IV) CLINICAL FEATURES

The clinical signs and symptoms of renal failure are collectively termed 'uremia'. CRF affects most body systems, and the clinical features are dependent upon the stage of renal failure and the systems involved. For example, early features are typically nocturia, polyuria, and anorexia. Tables 2 and 3 outline the signs, symptoms, and clinical features of CRF (Stein and Wild, 2002).

**Table 1.** International Epidemiology of Chronic Renal Failure: Some Reported Incidence and Death Rates

| Country | Patient Group | Incidence/Million Population | Death/1000 Patient-years |
|---|---|---|---|
| Australia | Dialysis | | 157 |
| | All | 90 | 189 |
| New Zealand | All | 107 | 217 |
| | Dialysis | | 192 |
| | Maori | | 239 |
| | Pacific Islander | | 283 |
| UK | All | | 94.9 |
| | All, 1st 90 days | | 306 |
| | Male, 1st 90 days | | 323 |
| | Female 1st 90 days | | 279 |
| | All, 1 yr + 90 days | | 188.3 |
| | Male, 1 yr + 90 days | | 185 |
| | Female, 1 yr + 90 days | | 192 |
| USA | All | 337 | 177.6 |
| | Male | 368 | 169.6 |
| | Female | 307 | 187.3 |
| | White | 269 | 192.6 |
| | Black | 777 | 157.1 |
| | Native American | 501 | 155.8 |
| | Asian | 281 | 130.4 |

**Table 2.** Signs and Symptoms of Chronic Renal Disease

| Signs | Symptoms |
|---|---|
| Pallor due to anemia | Pruritus |
| Increased photosensitive pigmentation | Lethargy |
| Brown discoloration of the nails | Anorexia, nausea, vomiting, diarrhea |
| Scratch marks due to pruritus | Poor concentration |
| Signs of fluid overload | 'Restless' legs |
| Hypertension | Leg cramps |
| Pericardial frictional rub, pericardial effusion | Ankle edema |
| Flow murmurs | Dyspnea |
| Bruising due to platelet abnormality | Insomnia |
| Confusion, coma, fits (severe uremia) | Loss of libido |
| Renal osteodystrophy (see Table 6) | Feeling cold |

## (V) TREATMENT OF CHRONIC RENAL FAILURE

The treatment of CRF includes dietary changes, correction of systemic complications, and dialysis or renal graft receipt.

Dietary and fluid restrictions may be required to accommodate the reduced excretory capacity of the kidneys. Acidosis and increased levels of potassium can be treated by reducing dietary intake of potassium-rich foods, such as bananas, and sodium restriction can aid the control of hypertension. It is sometimes necessary to reduce protein consumption to minimize nitrogenous waste products. Despite this treatment, most patients progress to end-stage renal failure (ESRF), requiring dialysis or transplantation.

### (a) Dialysis

There are two types of dialysis: hemodialysis and peritoneal dialysis (PD). In each case, the patient's blood is separated from the dialysis fluid (dialysate) by a membrane which allows water and toxins, but not blood cells, to pass out of the blood. In PD, the peritoneal membrane acts as the filter, whereas, in hemodialysis, the membrane is within the dialysis machine. Individuals commonly commence with PD and may progress to hemodialysis if renal function deteriorates further.

Most affected patients receive hemodialysis for up to 4 hrs, 2 or 3 times each week (Ansell and Feest, 2002). Arteriovenous fistulae in the arm are required for regular vascular access *via* wide-bore needles. The fistula is usually fashioned from a native vein; however, it is sometimes necessary to use animal or synthetic grafts if the local anatomy is unsuitable (Werner and Saad, 1999). Hemodialysis increases the risk of viral transmission (such as HIV and hepatitis B and C; Pol, 1995) and is costly.

In comparison of the cost-effectiveness of hemodialysis and PD, one finds that the latter has less initial cost, but the long-term cost of the two techniques is similar. Although the two techniques are equally effective and appropriate for most patients, it is common, at least in the UK, to begin with PD, since the veins will be available should the technique fail and hemodialysis become necessary (Stein and Wild, 2002).

For PD to take place, a catheter is placed into the peritoneum through which the dialysis fluid is exchanged. Continuous ambulatory peritoneal dialysis (CAPD) requires 4 exchanges of approximately 2 liters throughout the day. An alternative method is automated peritoneal dialysis (APD), in which the dialysis fluid exchanges are carried out automatically by machine, during the hours of sleep (for 8-10 hrs).

### (b) Renal Transplantation

Renal allografts may be cadaveric or from living donors, either related or non-related (although those from living relatives give rise to the best prognosis). Cadaveric organs are allocated on the basis of HLA tissue-typing, ABO compatibility, and the age and size of the donor and recipient.

In the UK, during 2001, 1743 (29.6 *per* million population) kidney transplant operations were perfomed (http://www.uktransplant.org.uk/statistics/transplant_activity/, http://www.statistics.gov.uk/census2001/pop2001/united_kingdom.asp). These consisted of 1385 cadaveric and 358 living donor renal transplants. The majority (263) of the living donors were relatives. The one-year success rate is presently 86% for cadaveric- and 95% for living-donor-transplanted kidneys (www.uktransplant.org.uk/). The principal cause of allograft failure is rejection, although adverse drug side-effects may also be a contributing factor.

Immunosuppressant therapy is required to minimize the risk of allograft rejection. Commonly used agents are prednisolone, azathioprine, cyclosporin, and, more recently, tacrolimus. Cyclosporin has been associated with potentially serious side-effects, including nephrotoxicity (Grinyo and Cruzado, 2004), hepatotoxicity, neurotoxicity, hypertrichosis, and diabetes mellitus (Ota and Bradley, 1983; Svirsky and Saravia, 1989; Pirsch *et al.*, 1997; Al-Zayer *et al.*, 2001). Tacrolimus has adverse side-effects similar to those of cyclosporin, such as nephrotoxicity and neurotoxicity (Mihatsch *et al.*, 1998); however, diabetes is a more frequent complication (Zuckermann *et al.*, 2003) and occurs in up to 37% of patients receiving tacrolimus (McDonald and Russ, 2002). Hypertension and cytomegalovirus infection are less common with tacrolimus than with cyclosporin therapy. In addition to immunosuppressants, recipients of renal allografts require an array of medications, some of which can give rise to oral side-effects (see below).

## (VI) ORAL MANIFESTATIONS OF CHRONIC RENAL FAILURE AND RELATED THERAPIES

### (a) Gingival Enlargement

Gingival enlargement secondary to drug therapy is the most-reported oral manifestation of renal disease. It can be induced by cyclosporin and/or calcium channel blockers. It principally affects the labial interdental papillae, although it can become extensive, involving the gingival margins and lingual and palatal surfaces (Somacarrera *et al.*, 1994; Kennedy and Linden 2000).

#### (i) Cyclosporin-induced Gingival Enlargement

The prevalence of gingival enlargement in individuals taking cyclosporin is unclear, and reportedly has a wide range—from 6 to 85% (Seymour *et al.*, 1987; Slavin and Taylor, 1987; Pan *et al.*, 1992; Pernu *et al.*, 1992; King *et al.*, 1993; Thomason *et al.*, 1993; Allman *et al.*, 1994; Somacarrera *et al.*, 1994). It can be evident within 3 mos of the initiation of cyclosporin therapy (Savage *et al.*, 1987; Thomason *et al.*, 1996). Children and adolescents may be more prone to this drug-induced gingival enlargement than adults. If oral hygiene is poor, older individuals are also prone to gingival enlargement (Seymour and Smith, 1991).

Improvement in oral hygiene and professional cleaning results in a reduction in cyclosporin-associated gingival enlargement (Thomason *et al.*, 1993, 1996; Somacarrera *et al.*, 1994; Fu *et al.*, 1997). However, this may be due to reduction in plaque-related inflammation rather than any drug-associated gingival enlargement (Seymour and Smith, 1991). There are conflicting reports on the association between gingival enlargement and cyclosporin dose (Porter and Scully, 1994), but the extent of the gingival enlargement does not seem to be related to the function of the allograft (Thomas *et al.*, 2001).

Regular clinical monitoring of cyclosporin-related gingival

**Table 3.** Clinical Features of Chronic Renal Disease

| System | Features |
|---|---|
| Hematological | Anemia (due to low erythropoietin) |
| | Platelet dysfunction |
| | Impaired cell-mediated immunity |
| Cardiovascular | Left ventricular hypertrophy (secondary to anemia and/or hypertension) |
| | Cardiac failure |
| | Hypertension |
| | Pericarditis |
| | Progressive arteriosclerosis |
| | Cardiac arrhythmias (due to hyperkalemia) |
| Neurological | Confusion, paranoia, apathy |
| | Convulsions |
| | Coma |
| | Peripheral neuropathy |
| | Twitching and fasciculation |
| Gastrointestinal | Xerostomia |
| | Oral malodor |
| | Sialosis |
| | Anorexia |
| | Hiccups |
| | Vomiting |
| | Gastrointestinal bleeding |
| | Constipation (due to perilesional dialysis) |
| | Esophagitis, gastritis, duodenitis, and peptic ulceration (in late CRF) |
| Dermatological | Pruritus |
| | Cutaneous and nail hyperpigmentation |
| | 'Uremic'? |
| Respiratory | Infection |
| | Hyperventilation (Kusmaul's respiration—secondary to acidosis) |
| | Pulmonary edema (secondary to left-sided cardiac failure) |
| Endocrine | Thyroid dysfunction |
| | Reduced growth hormone secretion |
| | Amenorrhea, oligomenorrhea |
| | Increased luteinizing hormone and follicle-stimulatory hormone |
| | Reduced female libido |
| | Male sexual dysfunction (due to reduced testosterone) |

enlargement is essential, since squamous cell carcinoma (Varga and Tyldesley, 1991) and Kaposi's sarcoma have been reported within such gingival lesions (Qunibi *et al.*, 1988; Farge, 1993).

#### (ii) Calcium Channel-blocker-induced Gingival Enlargement

Calcium channel blockers are prescribed to renal allograft recipients to reduce hypertension and cyclosporin-induced nephrotoxicity (Morales *et al.*, 1994). There are many reports of nifedipine, amlodipine (Seymour *et al.*, 1994; Ellis *et al.*, 1999), diltiazem (Colvard *et al.*, 1986; Giustiniani *et al.*, 1987; Bowman *et al.*, 1988; King *et al.*, 1993), verapamil (Cucchi *et al.*, 1985; Pernu *et al.*, 1989), oxidipine, felodipine, and nitrendipine (Hassell and Hefti, 1991; Rees and Levine, 1995) causing this gingival enlargement. The reported prevalence of nifedipine-induced gingival enlargement is variable and occurs in 10-83% of treated patients (Seymour *et al.*, 1987; Barclay *et al.*, 1992; Ellis *et al.*, 1999). There are no data on the frequency of gingival enlargement with the other calcium channel blockers.

The presence of dental plaque may predispose to nifedipine-induced gingival enlargement (Nishikawa *et al.*, 1991), but is not essential to its development (Morisaki *et al.*, 1993). The dose or duration of treatment is not related to the prevalence of gingival enlargement (Barclay *et al.*, 1992; Ellis *et al.*, 1993). Some studies have reported a reduction in gingival enlargement following a change to an alternative calcium channel blocker (Lederman *et al.*, 1984; Cebeci *et al.*, 1996), but these drugs can still cause some gingival enlargement (Westbrook *et al.*, 1997).

#### (iii) Combined Cyclosporin and Calcium Channel-blocker Therapy

There may be an increased incidence (Thomason *et al.*, 1995, 1996; Margiotta *et al.*, 1996; McKaig *et al.*, 2002) and severity (King *et al.*, 1993, 1994; Thomason *et al.*, 1993, 1995, 1996; O'Valle *et al.*, 1995; Margiotta *et al.*, 1996; McKaig *et al.*, 2002) of gingival enlargement when cyclosporin and nifedipine are prescribed together. In contrast, the combination of verapamil with cyclosporin does not seem to increase the frequency or severity of drug-induced gingival enlargement significantly (Cebeci *et al.*, 1996).

#### (iv) Tacrolimus

Tacrolimus has been reported both to cause (Adams and Famili, 1991; Spencer *et al.*, 1997) and to lessen (Asante-Korang *et al.*, 1996; Cox and Freese, 1996) gingival enlargement, although, in a recent study of children with renal allografts, while 41% of those receiving cyclosporin had gingival enlargement, the majority of those receiving tacrolimus did not have this problem (Sheehy *et al.*, 2000). Cyclosporin-associated gingival enlargement may reduce or resolve when cyclosporin is replaced by tacrolimus (Dodd, 1997; Bader *et al.*, 1998; Busque *et al.*, 1998; Hernandez *et al.*, 1998, 2000; James *et al.*, 2000; Kennedy and Linden, 2000).

**Table 4.** Oral Mucosal Lesions Reported in Chronic Renal Disease

| | |
|---|---|
| White patch | Macules/nodules |
| Erythematous patch | Fibro-epithelial polyps |
| Ulceration | Geographic tongue |
| Lichen planus | Black hairy tongue |
| Oral hairy leukoplakia | Papilloma |
| Uremic stomatitis | Pyogenic granuloma |

#### (v) Other Gingival Changes

The gingivae in individuals with CRF can be pale due to anemia (Lohr and Schwab, 1991; London and Drueke, 1997), with possible loss of the demarcation of the mucogingival junction (Buckley *et al.*, 1986), and when there is platelet dysfunction, the gingivae may bleed easily (Opatry, 1997).

### (b) Oral Hygiene and Periodontal Disease

The oral hygiene of individuals receiving hemodialysis can be poor. For example, only 15% of 45 individuals receiving hemodialysis from 4 centers in Virginia, USA, had a good standard of oral hygiene (Naugle *et al.*, 1998). Deposits of calculus may be increased (Epstein *et al.*, 1980; Jaffe *et al.*, 1986; Gavalda *et al.*, 1999).

There is no good evidence of an increased risk of periodontitis (Brown *et al.*, 1989; Thorstensson *et al.*, 1996; Naugle *et al.*, 1998), although premature tooth loss has been reported (Locsey *et al.*, 1986). Localized suppurative osteomyelitis, secondary to periodontitis, was observed in one individual receiving hemodialysis (Tomaselli *et al.*, 1993).

### (c) Xerostomia

Symptoms of xerostomia can arise in many individuals receiving hemodialysis (Eigner *et al.*, 1986; Gavalda *et al.*, 1999; Kho *et al.*, 1999; Kao *et al.*, 2000; Klassen and Krasko, 2002). Possible causes include restricted fluid intake, side-effects of drug therapy, and/or mouth-breathing. Long-term xerostomia may predispose to caries and gingival inflammation and can give rise to difficulties with speech, denture retention, mastication, dysphagia, sore mouth, and loss of taste (Porter *et al.*, 2004).

It also predisposes to caries and infections such as candidosis and acute suppurative sialadenitis (Porter *et al.*, 2004).

### (d) Oral Malodor/Bad Taste

Uremic patients may have an ammonia-like oral odor (Eigner *et al.*, 1986; Kho *et al.*, 1999), which also occurs in about one-third of individuals receiving hemodialysis (Kho *et al.*, 1999). Chronic renal failure can give rise to altered taste sensation, and some patients complain of an unpleasant and/or metallic taste (Levy, 1988), or a sensation of an enlarged tongue (Levy, 1988; Ray, 1989; Kho *et al.*, 1999).

### (e) Mucosal Lesions

A wide range of oral mucosal lesions, particularly white patches and/or ulceration, has been described in individuals receiving dialysis and allografts (Table 4). In particular, lichen-planus-like disease (sometimes termed lichenoid disease) can arise, sometimes, but not always, as a consequence of the associated drug therapy (*e.g.*, diuretics, beta-blockers) (Chau *et al.*, 1984; Hogan *et al.*, 1985; Markitziu *et al.*, 1986; Torrelo *et al.*, 1990). Similarly, oral hairy leukoplakia can occur secondary to drug-related immunosuppression (Greenspan and Greenspan, 1989; King *et al.*, 1993, 1994), although clinically and histopathologically similar lesions lacking Epstein-Barr virus (EBV) have been observed with uremia (McCreary *et al.*, 1997). Of note, this latter lesion may resolve with correction of the uremia.

Uremic stomatitis may manifest as white, red, or grey areas of the oral mucosa. The erythemopultaceous form consists of grey pseudomembrane overlying painful erythema patches, while an ulcerative form is red with a 'pultaceous' covering (Levy, 1988; Ross and Salisbury, 1994). There are no good histological descriptions of uremic stomatitis; thus, it is difficult to define the cause of this unusual oral mucosal change. It has been suggested, but never definitively demonstrated, that uremic stomatitis may be due to chemically based trauma from elevated levels of nitrogenous compounds (Larato, 1975; De Rossi and Glick, 1996; McCreary *et al.*, 1997).

In some instances, the mucosal surface may become erythematous or ulcerate (King *et al.*, 1994; Kho *et al.*, 1999; Klassen and Krasko, 2002). Oral mucosal macules and nodules have also been described in 14% of individuals receiving hemodialysis (Klassen and Krasko, 2002). Other lesions that can occur intra-orally in allograft recipients are listed in Table 4 (King *et al.*, 1994).

## (f) Oral Malignancy

The risk of oral squamous cell carcinoma in patients receiving hemodialysis is generally similar to that of otherwise healthy individuals in the general population (Lee and Gisser, 1978; Bradford *et al.*, 1990), although there have been reports suggesting that therapy following renal transplantation predisposes to epithelial dysplasia and carcinoma of the lip (Regev *et al.*, 1992; Thomas *et al.*, 1993). Perhaps unsurprisingly, Kaposi's sarcoma (KS) can occur in the mouths of immunosuppressed renal transplant recipients (Farge, 1993). There have been reports of squamous cell carcinoma (Varga and Tyldesley, 1991) and KS (Qunibi *et al.*, 1988) arising within areas of cyclosporin-induced gingival enlargement. Any increased risk of oral malignancy in CRF probably reflects the effects of iatrogenic immunosuppression, which increases liability to virally associated tumors, such as Kaposi's sarcoma or non-Hodgkin's lymphoma. The inconsistent association between oral epithelial dysplasia and oral squamous cell carcinoma is in accord with the low risk of such disease in individuals with other, more significant, immunosuppressed states—for example, HIV disease.

## (g) Oral Infections

### (i) Candidosis

Angular cheilitis has been described in up to 4% of hemodialysis and renal allograft recipients (King *et al.*, 1994; Klassen and Krasko, 2002). Other oral candidal lesions—such as pseudomembranous (1.9%), erythematous (3.8%), and chronic atrophic candidosis (3.8%)—have been reported in allograft recipients (King *et al.*, 1994). These figures may underestimate the increased susceptibility of immunosuppressed allograft recipients to fungal infection, since systemic anti-fungal agents are commonly prescribed prophylactically (Quirk *et al.*, 1995).

### (ii) Viral Infection

Prior to the availability of appropriate anti-viral drugs (*e.g.*, acyclovir, gancyclovir, and valacyclovir), about 50% of renal allograft recipients, who were seropositive for herpes simplex, experienced recurrent, severe, and prolonged HSV infections (Korsager *et al.*, 1975; Armstrong *et al.*, 1976; Naraqi *et al.*, 1977). However, in recent years, the use of effective anti-herpetic regimes has significantly reduced the frequency of such infection (Kletzmayr *et al.*, 2000; Ljungman, 2001; McGavin and Goa, 2001; Squifflet and Legendre, 2002). Long-standing post-allograft immunosuppression may predispose subjects to human herpesvirus 8 (HHV-8) and associated Kaposi's sarcoma (Leao *et al.*, 2000).

## (h) Dental Anomalies

Delayed eruption of permanent teeth has been reported in children with CRF (Woodhead *et al.*, 1982; Koppang *et al.*, 1984; Sampson and Meister, 1984; Wolff *et al.*, 1985; Carl, 1987; Levy, 1988; Jaffe *et al.*, 1990). Enamel hypoplasia of the primary and permanent teeth (Wolff *et al.*, 1985; Kho *et al.*, 1999; Koch *et al.*, 1999; Al Nowaiser *et al.*, 2003), with or without brown discoloration (Bottomley *et al.*, 1972; Woodhead *et al.*, 1982; Wolff *et al.*, 1985; Eigner *et al.*, 1986; Carl, 1987; Levy, 1988), can also occur.

Narrowing or calcification of the pulp chamber of teeth of adults with chronic renal disease can occur (Kelly *et al.*, 1980; Spolnik *et al.*, 1981; Wysocki *et al.*, 1983; Nasstrom *et al.*, 1985, 1993; Galili *et al.*, 1991; Nasstrom, 1996; Ganibegovic, 2000). The exact cause of this dental change is not known. Renal allograft recipients have significantly more narrowing of the pulp chamber than those receiving hemodialysis (Nasstrom *et al.*, 1985). There is no consistent association between corticosteroid therapy and narrowing of the pulp chamber (Galili *et al.*, 1991).

Increased (Locsey *et al.*, 1986) and decreased rates of dental caries (Woodhead *et al.*, 1982; Sampson and Meister, 1984; Wolff *et al.*, 1985; Jaffe *et al.*, 1986; Levy, 1988; Klassen and Krasko, 2002; Al Nowaiser *et al.*, 2003) have been observed in groups of patients with CRF. However, there is no evidence of a significantly increased risk of caries in patients with CRF. Although patients may have xerostomia, there would seem to be no increased risk of cervical caries, as might be expected (Porter *et al.*, 2004).

Non-carious tooth tissue loss is more prevalent in individuals with CRF than in the general population (Levy, 1988). This may be due to nausea (Levy, 1988), esophageal regurgitation, or induced vomiting in bulimia nervosa (if a patient finds the restricted diet unpleasant) (Levy, 1988; Klassen and Krasko, 2002).

## (i) Bone Lesions

A wide range of bony anomalies can arise in chronic renal disease. These reflect a variety of defects of calcium metabolism, including: loss of hydroxylation of 1-hydroxycholecalciferol to active vitamin D (1,25-dihydroxycholecalciferol); decreased hydrogen ion excretion (and resultant acidosis); hyperphosphatemia; hypocalcemia and resultant secondary hyperparathyroidism; and finally, interference in phosphate biochemistry by dialysis (Nadimi *et al.*, 1993).

Secondary hyperparathyroidism affects up to 92% of patients receiving hemodialysis (Massry and Ritz, 1978). Hyperparathyroidism may present as a maxillary brown tumor (Okada *et al.*, 2000), enlargement of the skeletal bases (Nadimi *et al.*, 1993; Phelps *et al.*, 1994; Michiwaki *et al.*, 1996; Damm *et al.*, 1997; Vigneswaran, 2001), or tooth mobility (Carmichael *et al.*, 1995).

**Table 5.** Orofacial Features of Renal Osteodystrophy—Bony Features

| |
|---|
| Bone demineralization |
| Decreased trabeculation |
| Decreased thickness of cortical bone |
| Ground-glass appearance of bone |
| Metastatic soft-tissue calcifications |
| Radiolucent fibrocystic lesions |
| Radiolucent giant cell lesions |
| Lytic areas of bone |
| Jaw fracture (due to trauma or during surgery) |
| Abnormal bone healing after extraction |

**Table 6.** Orofacial Features of Renal Osteodystrophy—Tooth and Periodontium

| |
|---|
| Delayed eruption |
| Enamel hypoplasia |
| Loss of the lamina dura |
| Widening of the periodontal ligament |
| Severe periodontal destruction |
| Tooth mobility |
| Drifting |
| Pulp calcifications |
| Pulp narrowing |

Orofacial features of renal osteodystrophy due to hyperparathyroidism are listed in Tables 5 and 6 (Sampson and Meister, 1984; Locsey *et al.*, 1986; Carl, 1987; Levy, 1988; Molpus *et al.*, 1991; Nadimi *et al.*, 1993; Michiwaki *et al.*, 1996; Damm *et al.*, 1997; Ganibegovic, 2000; Okada *et al.*, 2000; Klassen and Krasko, 2002).

## (VII) DENTAL MANAGEMENT OF PATIENTS WITH CHRONIC RENAL FAILURE

Untreated dental infection in immunosuppressed individuals can potentially contribute to morbidity and transplant rejection (Greenberg and Cohen, 1977). Thus, there is a need for detailed assessment and provision of good dental care following the diagnosis of CRF. Regular clinical review is important for the early identification of oral complications of renal disease (Bottomley *et al.*, 1972; Naylor *et al.*, 1988). Regular, non-surgical, periodontal treatment is indicated (Bottomley *et al.*, 1972; Potter and Wilson, 1979; Naugle *et al.*, 1998). However, several studies have found that individuals receiving dialysis have unmet restorative dental need (Potter and Wilson, 1979; Naugle *et al.*, 1998). In addition, despite sometimes having high levels of dental need, the attendance by affected patients for dental care is no better than that of those without renal disease (King and Thornhill, 1996; Naugle *et al.*, 1998; Klassen and Krasko, 2002).

It has been recommended that patients requiring a renal transplant have a detailed oral assessment and treatment prior to surgery (Kirkpatrick and Morton, 1971; Sowell, 1982; Eigner *et al.*, 1986; Naylor and Fredericks, 1996; Ferguson and Whyman, 1998), perhaps highlighting a need for appropriately trained oral health professionals to collaborate with renal physicians. The dental examination should be timed appropriately to allow any necessary dental treatment to be carried out in a planned manner (Klassen and Krasko, 2002). Most transplant centers worldwide have a dental check in their pre-transplant protocol (Yamalik *et al.*, 1993).

**Table 7.** Drugs Commonly Used in Dentistry That May Have Implications for Patients with Renal Disease

| Drug | Caution |
|---|---|
| ***Antibiotics*** | |
| Amoxicillin, ampicillin | Reduce dose, rash more common |
| Erythromycin | Maximum 1.5 g daily (ototoxicity) |
| | Increases plasma-tacrolimus concentration |
| | Increases plasma-cyclosporin concentration |
| Tetracyclines | Avoid—use doxycycline or minocycline if necessary (avoid excessive doses) |
| | Doxycycline increases plasma-cyclosporin concentration |
| Cefalexin, cefradine | Reduce dose |
| Probenecid | Avoid (ineffective, increased toxicity) |
| ***Antifungals*** | |
| Amphotericin | Use only if no alternative |
| | Cyclosporin, tacrolimus: increases risk of nephrotoxicity |
| Fluconazole | Usual initial dose then halve subsequent doses |
| | Increases plasma-cyclosporin concentration |
| | Increases plasma-tacrolimus concentration |
| Miconazole | Increases plasma-cyclosporin concentration |
| ***Antivirals*** | |
| Acyclovir | Reduce dose |
| ***Analgesics*** | |
| Aspirin | Avoid (sodium, water retention; deterioration in renal function; risk of gastric hemorrhage) |
| Ibuprofen, diflunisal | Avoid if possible/use lowest effective dose, monitor renal function (sodium, water retention; deterioration in renal function) |
| | Cyclosporin, tacrolimus: increases risk of nephrotoxicity |
| Dihydrocodeine, pethidine | Reduce dose/avoid (increased and prolonged effect, increased cerebral sensitivity) |
| ***Other drugs*** | |
| Carbamazepine | Caution |
| | Reduces plasma-cyclosporin concentration |
| Nitrazepam, temazepam | Start with small doses (increased cerebral sensitivity) |
| Povidone-iodine | Avoid regular application to inflamed or broken mucosa |
| Ephedrine | Avoid (CNS toxicity) |

However, Klassen and Krasko (2002) found that pre-transplant oral care was not meticulous. There is no evidence that poor oral hygiene or consequent dental disease significantly affects the morbidity or mortality associated with CRD. Nevertheless, there have been very occasional reports of the severe local and systemic spread of odontogenic infection in renal transplant recipients (Reyna *et al.*, 1982; Wilson *et al.*, 1982).

There may be a bleeding tendency in hemodialysis recipients, due to anti-coagulants or platelet dysfunction, but its effects can be minimized if dental treatment is carried out on the day following dialysis (Stewart, 1967; Dobkin *et al.*, 1978; Precious *et al.*, 1981; Sowell, 1982; Mannucci *et al.*, 1983; Buckley *et al.*, 1986; Eschbach and Adamson, 1989; Jameson and Wiegmann, 1990; De Rossi and Glick, 1996; Naylor and Fredericks, 1996). This is a practical solution, since the patients will still be in the hospital.

To minimize the risk of adrenal crisis in individuals who have taken large doses of corticosteroid (10 mg prednisolone daily or equivalent during the preceding 3 mos) and undergoing major surgical procedures (such as extraction of more than one tooth), appropriate corticosteroid cover should be administered (Seymour *et al.*, 1994). In the past, large doses were used (up to 200 mg hydrocortisone), but more recent guidelines have recommended lower physiological doses (25 mg intravenous hydrocortisone pre-operatively) (Nicholson *et al.*, 1998).

Impaired renal function can result in high blood levels of drugs or their metabolites (Perneger *et al.*, 1994); thus, it may be necessary to reduce the dosage of many drugs or use alternative agents (Bennett *et al.*, 1983). Potential medication complications are listed in Table 7 (British National Formulary, 2002).

Infective endocarditis, affecting previously healthy cardiac tissue, has been reported in individuals on hemodialysis (Leonard *et al.*, 1973). In countries such as the USA and New Zealand, bacteremia-producing antibiotic prophylaxis prior to dental procedures is recommended for individuals receiving renal dialysis and allografts, since there is a risk of infective endocarditis or infection of the vascular access site (Levy, 1988; Hay *et al.*, 1992; Hall *et al.*, 1994; Naylor and Fredericks, 1996; Werner and Saad, 1999). The British Society for Antimicrobial Chemotherapy (BSAC) guidelines (Simmons, 1993) do not recommend antibiotic prophylaxis for individuals with renal disease who require dental procedures that are likely to give rise to a bacteremia. Klassen and Krasko (2002) have stressed that good oral health lowers the risk of oral infection, and, therefore, the risk of septicemia, endocarditis, or endarteritis at the site of vascular dialysis access. There is, thus, no simple answer to the need for antibiotic prophylaxis for the bacteremia-producing dental procedures in patients with chronic renal disease. Nevertheless, there are instances when antibiotic prophylaxis may be important—for example, mitral valve prolapse and mitral valve regurgitation are common in patients with polycystic kidney disease type 1 (Lumiaho *et al.*, 2001).

The ideal management of drug-induced gingival enlargement is to substitute another drug (Khocht and Schneider, 1997), but this may not always be possible. Meticulous oral hygiene (Daley *et al.*, 1986; Hassell and Hefti, 1991; Nishikawa *et al.*, 1991; Seymour and Smith, 1991; Hancock and Swan, 1992; Somacarrera *et al.*, 1996, 1997; Hall, 1997; Westbrook *et al.*, 1997; Bader *et al.*, 1998; Oettinger-Barak *et al.*, 2000) can lessen any plaque-related gingival disease, but there may still be some drug-associated gingival enlargement. Single case reports have advocated the use of antimicrobial agents (Nash and Zaltzman, 1998; Wirnsberger *et al.*, 1998) such as metronidazole (Wong *et al.*, 1994) to lessen the gingival enlargement, but metronidazole may also increase the cyclosporin concentration and the potential for nephrotoxicity (Seymour *et al.*, 1997). Scalpel or laser excision of the gingival enlargement is necessary if the excess gingival tissue is unsightly and/or interferes with mastication, speech, or oral care (Khocht and Schneider, 1997). Recurrence is common, especially when the oral hygiene is inadequate (Seymour *et al.*, 1994; Hall, 1997), highlighting the need for long-term effective plaque control and consideration of additional anti-plaque measures such as topical chlorhexidine gluconate or triclosan preparations.

## CONCLUSION

The prevalence of chronic renal failure (CRF) is increasing worldwide. Oral and systemic complications can occur as a result of CRF or its treatment. In recent years, the pattern of oral manifestations has changed, principally as a consequence of the adverse oral side-effects of drug therapy and immunosuppressant drugs. The incidence of gingival enlargement may fall as tacrolimus (and related agents) is used in place of cyclosporin. The dental management of patients with CRF is complicated by some systemic consequences of CRF, in particular, anemia, liability to bleeding, and cardiovascular or endocrine disease, but with the use of well-supervised treatment protocols, the dental management of individuals with chronic renal failure can be effective and safe.

## REFERENCES


Adams CKS, Famili P (1991). A study of the effects of the drug FK506 on gingival tissues. *Transpl Proc* 23:3193-3194.

Al Nowaiser A, Roberts GJ, Trompeter RS, Wilson M, Lucas VS (2003). Oral health in children with chronic renal failure. *Pediatr Nephrol* 18:39-45.

Al-Zayer M, da Fonseca M, Ship JA (2001). Pyogenic granuloma in a renal transplant patient: case report. *Spec Care Dentist* 21:187-190.

Allman SD, McWhorter AG, Seale NS (1994). Evaluation of cyclosporin-induced gingival overgrowth in pediatric transplant patients. *Pediatr Dent* 16:35-40.

Ansell D, Feest T, editors (2002). UK Renal Registry Report 2002. Bristol, UK: UK Renal Registry.

Armstrong JA, Evans AS, Rao N, Ho M (1976). Viral infections in renal transplant recipients. *Infect Immun* 14:970-975.

Asante-Korang A, Boyle GJ, Webber SA, Miller SA, Fricker FJ (1996). Experience of FK506 immune suppression in paediatric heart transplantation: a study of long-term adverse effects. *J Heart Lung Transplant* 15:415-422.

Bader G, Lejeune S, Messner M (1998). Reduction of cyclosporin-induced gingival overgrowth following a change to tacrolimus. A case history involving a liver transplant patient. *J Periodontol* 69:729-732.

Barclay S, Thomason JM, Idle JR, Seymour RA (1992). The incidence and severity of nifedipine-induced gingival overgrowth. *J Clin Periodontol* 19:311-314.

Bennett WM, Aronoff GR, Morrison G, Golper TA, Pulliam J, Wolfson M, *et al.* (1983). Drug prescribing in renal failure: dosing guidelines for adults. *Am J Kidney Dis* 3:155-193.

Bottomley WK, Cioffi RF, Martin AJ (1972). Dental management of the patient treated by renal transplantation: preoperative and postoperative considerations. *J Am Dent Assoc* 85:1330-1335.

Bowman JM, Levey BA, Grubb RV (1988). Gingival overgrowth induced by diltiazem. *Oral Surg Oral Med Oral Pathol* 65:183-185.

Bradford CR, Hoffman HT, Wolf GT, Carey TE, Baker SR, McClatchey KD (1990). Squamous carcinoma of the head and neck in organ transplant recipients: possible role of oncogenic viruses. *Laryngoscope* 100:190-194.

British National Formulary 44 (2002). London: British Medical Association.

Brown LJ, Oliver RC, Löe H (1989). Periodontal diseases in the US in 1981: prevalence, severity, extent and role in tooth mortality. *J Periodontol* 60:353-370.

Buckley DJ, Barrett AP, Koutts J, Stewart JH (1986). Control of bleeding in severely uremic patients undergoing oral surgery. *Oral Surg Oral Med Oral Pathol* 61:546-549.

Busque S, Derners P, St Louis G, Boily JG, Tousignant J, Lemieux F, *et al.* (1998). Conversion from Neoral (ciclosporin) to tacrolimus of kidney transplant recipients for gingival hyperplasia or hypertrichosis. *Transpl Proc* 30:1247-1248.

Carl W (1987). Chronic renal disease and hyperparathyroidism: dental manifestations and management. *Compend Contin Educ Dent* 8:697-704.

Carmichael DT, Williams CA, Aller MS (1995). Renal dysplasia with secondary hyperparathyroidism and loose teeth in a young dog. *J Vet Dent* 12:143-146.

Cebeci I, Kantarci A, Firatli E, Carin M, Tuncer O (1996). The effect of verapamil on the prevalence and severity of ciclosporin-induced gingival overgrowth in renal allograft recipients. *J Periodontol* 67:1201-1205.

Chau NY, Reade PC, Rich AM, Hay KD (1984). Allopurinol-amplified lichenoid reactions of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 38:397-400.

Colvard MD, Bishop J, Weissman D, Bargiulo AV (1986). Cardiazem-induced gingival hyperplasia. *Periodontal Case Rep* 8:67-68.

Cox KL, Freese DK (1996). Tacrolimus (FK506): the pros and cons of its use as an immunosuppressant in paediatric liver transplantation. *Clin Invest Med* 19:389-392.

Cucchi G, Giustiniani S, Robustelli F (1985). Gingival hyperplasia caused by verapamil. *Ital J Cardiol* 15:556-557.

Daley TD, Wysocki GP, May C (1986). Clinical and pharmacological correlations in ciclosporin-induced gingival hyperplasia. *Oral Surg* 62:417-421.

Damm DD, Neville BW, McKenna S, Jones AC, Freedman PD, Anderson WR, *et al.* (1997). Macrognathia of renal osteodystrophy in dialysis patients. *Oral Surg Oral Med Oral Pathol* 83:489-495.

De Rossi S, Glick M (1996). Dental considerations for the patient with renal disease receiving haemodialysis. *J Am Dent Assoc* 127:211-219.

Dobkin JF, Miller MH, Steigbigel NH (1978). Septicemia in patients on chronic hemodialysis. *Ann Intern Med* 88:28-33.

Dodd DA (1997). Rapid resolution of gingival hyperplasia after switching from cyclosporine A to tacrolimus (abstract). *J Heart Lung Transplant* 16:579.

Eigner TL, Justak TJ, Bennett WM (1986). Achieving oral health in patients with renal failure and renal transplants. *J Am Dent Assoc* 113:112-114.

Ellis JS, Seymour RA, Monkman SC, Idle JR (1993). Disposition of nifedipine in plasma and gingival crevicular fluid in relation to drug-induced gingival overgrowth. *J Periodontal Res* 28:373-378.

Ellis JS, Seymour RA, Steele J, Robertson P, Butler TJ, Thomason JM (1999). Prevalence of gingival overgrowth induced by calcium channel blockers: a community based study. *J Periodontol* 70:63-67.

Epstein SR, Mandell L, Scopp IW (1980). Salivary composition and calculus formation in patients undergoing hemodialysis. *J Periodontol* 51:336-338.

Eschbach JW, Adamson JW (1989). Guidelines for recombinant human erythropoietin therapy. *Am J Kidney Dis* 14(Suppl 1):2-8.

Farge D (1993). Kaposi's sarcoma in organ transplant recipients. *Eur J Med* 2:339-343.

Ferguson CA, Whyman RA (1998). Dental management of people with renal disease and renal transplants. *New Zealand Dent J* 94:125-130.

Fu E, Nieh S, Wikesjo UME (1997). The effect of plaque retention on ciclosporin-induced gingival overgrowth in rats. *J Periodontol* 68:92-98.

Galili D, Berger E, Kaufman E (1991). Pulp narrowing in renal end stage and transplanted patients. *J Endod* 17:442-443.

Ganibegovic M (2000). Dental radiographic changes in chronic renal disease. *Med Arch* 54:115-118.

Gavalda C, Bagan JV, Scully C, Silvestre F, Milian M, Jimenez V (1999). Renal haemodialysis patients: oral, salivary, dental and periodontal findings in 105 adult cases. *Oral Dis* 5:299-302.

Giustiniani S, Robustelli della Cuna FR, Marieni M (1987). Hyperplastic gingivitis during diltiazem therapy. *Int J Cardiol* 15:247-249.

Greenberg MS, Cohen G (1977). Oral infection in immunosuppressed renal transplant patients. *Oral Surg Oral Med Oral Pathol* 43:879-885.

Greenspan JS, Greenspan D (1989). Oral hairy leukoplakia: diagnosis and management. *Oral Surg Oral Med Oral Pathol* 67:396-403.

Grinyo JM, Cruzado JM (2004). Cyclosporine nephrotoxicity. *Transplant Proc* 36(2 Suppl):240S-242S.

Hall EE (1997). Prevention and treatment considerations in patients with drug-induced gingival enlargement. *Curr Opin Periodontol* 4:59-63.

Hall EH, Sherman RG, Emmons WW 3rd, Naylor GD (1994). Antibacterial prophylaxis. *Dent Clin North Am* 38:707-718.

Hancock RH, Swan RH (1992). Nifedipine-induced gingival overgrowth. *J Clin Periodontol* 19:12-14.

Hassell TM, Hefti AF (1991). Drug-induced gingival overgrowth: old problem, new problem. *Crit Rev Oral Biol Med* 2:103-137.

Hay DR, Chambers ST, Ellis-Pegler RB, Jones MR, Leslie PN, Neutze JM (1992). Prevention of infective endocarditis associated with dental treatment and other medical interventions. *New Zealand Dent J* 88:99-101.

Hernandez G, Arriba L, Jimenez C, Somacarrera ML, Lopez AF, Lucas M, *et al.* (1998). Effect on gingival overgrowth of replacing ciclosporin-A by FK-506 (abstract). *J Dent Res* 77(Spec Iss):1253.

Hernandez G, Arriba L, Lucas M, de Andres A (2000). Reduction of severe gingival overgrowth in a kidney transplant patient by replacing ciclosporin A with tacrolimus. *J Periodontol* 71:1630-1636.

Hogan DJ, Murphy F, Burgess WR, Epstein JD, Lane PR (1985). Lichenoid stomatitis associated with lithium carbonate. *J Am Acad Dermatol* 13:243-246.

Jaffe EC, Roberts J, Chantler C, Carter JE (1986). Dental findings in chronic renal failure. *Br Dent J* 160:18-20.

Jaffe EC, Roberts J, Chantler C, Carter JE (1990). Dental maturity in children with chronic renal failure assessed from dental panoramic tomographs. *J Int Assoc Dent Child* 20:54-58.

James JA, Boomer S, Maxwell AP, Hull PS, Short CD, Campbell BA, *et al.* (2000). Reduction in gingival overgrowth associated with conversion from ciclosporin A to tacrolimus. *J Clin Periodontol* 27:144-148.

Jameson MD, Wiegmann TB (1990). Principles, uses and complications of haemodialysis. *Med Clin North Am* 74:945-960.

Kao CH, Hsieh JF, Tsai SC, Ho YJ, Chang HR (2000). Decreased salivary function in patients with end-stage renal disease requiring haemodialysis. *Am J Kidney Dis* 36:1110-1114.

Kelly WH, Mirahmadi MK, Simon JH, Gorman JT (1980). Radiographic changes of the jawbones in end stage renal disease. *Oral Surg Oral Med Oral Pathol* 50:372-380.

Kennedy DS, Linden GJ (2000). Resolution of gingival overgrowth following change from ciclosporin to tacrolimus therapy in a renal transplant patient. *J Ir Dent Assoc* 46:3-4.

Kho H, Lee S, Chung SC, Kim YK (1999). Oral manifestations and salivary flow rate, pH, and buffer capacity in patients with end-stage renal disease undergoing haemodialysis. *Oral Surg Oral Med Oral Pathol* 88:316-319.

Khocht A, Schneider LC (1997). Periodontal management of gingival overgrowth in the heart transplant patient: a case report. *J Periodontol* 68:1140-1146.

King GN, Thornhill MH (1996). Dental attendance patterns in renal transplant recipients. *Oral Dis* 2:145-147.

King GN, Fullinfaw R, Higgings TJ, Walker RG, Francis DM, Wiesenfeld D (1993). Gingival hyperplasia in renal allograft recipients receiving ciclosporin A and calcium antagonists. *J Clin Periodontol* 20:286-293.

King GN, Healy CM, Glover MT, Kwan JT, Williams DM, Leigh IM, *et al.* (1994). Prevalence and risk factors associated with leukoplakia, hairy leukoplakia, erythematous candidosis, and gingival hyperplasia in renal transplant recipients. *Oral Surg Oral Med Oral Pathol* 78:718-726.

Kirkpatrick TJ, Morton JB (1971). Factors influencing the dental management of renal transplant and dialysis patients. *Br J Oral Surg* 9:57-64.

Klassen JT, Krasko BM (2002). The dental health status of dialysis patients. *J Can Dent Assoc* 68:34-38.

Kletzmayr J, Kreuzwieser E, Watkins-Riedel T, Berlakovich G, Kovarik J, Klauser R (2000). Long-term oral ganciclovir prophylaxis for prevention of cytomegalovirus infection and disease in cytomegalovirus high-risk renal transplant recipients. *Transplantation*

70:1174-1180.
Koch MJ, Buhrer R, Pioch T, Scharer K (1999). Enamel hypoplasia of primary teeth in chronic renal failure. *Pediatr Nephrol* 13:68-72.
Koppang HS, Stene T, Solheim T, Larheim TA, Winsnes A, Monn E, *et al.* (1984). Dental features in congenital persistent renal tubular acidosis of proximal type. *Scand J Dent Res* 92:489-495.
Korsager B, Spencer ES, Mordhorst CH, Andersen HK (1975). Herpes virus hominis infections in renal transplant recipients. *Scand J Infect Dis* 7:11-19.
Larato DC (1975). Uremic stomatitis: report of a case. *J Periodontol* 46:731-733.
Lederman D, Lumernan H, Reuben S, Freedman PD (1984). Gingival hyperplasia associated with nifedipine therapy. *Oral Surg Oral Med Oral Pathol* 57:620-622.
Lee YW, Gisser SD (1978). Squamous cell carcinoma of the tongue in a nine-year renal transplant survivor. *Cancer* 41:1-6.
Leonard A, Raij L, Shapiro FL (1973). Bacterial endocarditis in regularly dialyzed patients. *Kidney Int* 4:407-422.
Levy HM (1988). Dental considerations for the patient receiving dialysis for renal failure. *Spec Care Dentist* 8:34-36.
Ljungman P (2001). Prophylaxis against herpesvirus infections in transplant recipients. *Drugs* 61:187-196.
Loesey L, Alberth M, Mauks G (1986). Dental management of chronic haemodialysis patients. *Int Urol Nephrol* 18:211-213.
Lohr JW, Schwab SJ (1991). Minimizing hemorrhagic complications in dialysis patients. *J Am Soc Nephrol* 2:961-975.
London GM, Drueke TB (1997). Atherosclerosis and arteriosclerosis in chronic renal failure. *Kidney Int* 57:1678-1695.
Lumiaho A, Ikaheimo R, Miettinen R, Niemitukia L, Laitinen T, Rantala A, *et al.* (2001). Mitral valve prolapse and mitral regurgitation are common in patients with polycystic kidney disease type 1. *Am J Kidney Dis* 38:1208-1216.
Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, *et al.* (1983). Deamino-8-D-arginine vasopressin shortens bleeding time in uremia. *N Engl J Med* 308:3-12.
Margiotta V, Pizzo I, Pizzo G, Barbaro A (1996). Ciclosporin- and nifedipine-induced gingival overgrowth in renal transplant patients: correlations with periodontal and pharmacological parameters, and HLA-antigens. *J Oral Pathol Med* 25:128-134.
Markitziu A, Katz J, Pisanty S (1986). Lichenoid lesions of oral mucosa associated with ketoconazole. *Mykosen* 29:317-322.
Massry SG, Ritz E (1978). The pathogenesis of secondary hyperparathyroidism of renal failure: is there a controversy? *Arch Intern Med* 138(Spec No):853-856.
McCreary CE, Flint SR, McCartan BE, Shields JA, Mabruk M, Toner ME (1997). Uremic stomatitis mimicking oral hairy leucoplakia. *Oral Surg Oral Med Oral Pathol* 83:350-353.
McDonald SP, Russ GR (editors) (2002). ANZDATA Registry Report, Australia and New Zealand Dialysis and Transplant Registry. Adelaide, South Australia.
McGavin JK, Goa KL (2001). Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 61:1153-1183.
McKaig SJ, Kelly D, Shaw L (2002). Investigation of the effect of FK506 (tacrolimus) and cyclosporin on gingival overgrowth following paediatric liver transplantation. *Int J Paed Dent* 12:398-403.
Michiwaki Y, Michi K, Yamaguchi A (1996). Marked enlargement of jaws in secondary hyperparathyroidism—a case report. *Int J Oral Maxillofac Surg* 25:54-56.
Mihatsch MJ, Kyo M, Morozumi K, Yamaguchi Y, Nickeleit V, Ryffel B (1998). The side-effects of ciclosporin A and tacrolimus. *Clin Nephrol* 49:356-363.
Molpus WM, Pritchard RS, Walker CW, Fitzrandolph FL (1991). The radiographic spectrum of renal osteodystrophy. *Am Fam Phys* 43:151-158.
Morales JM, Rodriguez-Paternina A, Araque A, Andres A, Hernandez E, Ruilope LM, *et al.* (1994). Long-term protective effect of a calcium antagonist on renal function in hypertensive renal transplant patients on ciclosporin therapy: a 5-year prospective randomised study. *Transplant Proc* 26:2598-2599.
Morisaki I, Kato K, Loyola-Rodriguez JP, Nagata T, Ishida H (1993). Nifedipine-induced gingival overgrowth in the presence of gingival inflammation in rats. *J Periodontal Res* 28:396-403.
Nadimi H, Bergamini J, Lilien B (1993). Uremic mixed bone disease. A case report. *Int J Maxillofac Surg* 22:268-270.
Naraqi S, Jackson CG, Jonasson O, Yamashiroya HM (1977). Prospective study of prevalence, incidence and source of herpes virus infections in patients with renal allografts. *J Infect Dis* 136:531-540.
Nash MM, Zaltzman JS (1998). Efficacy of azithromycin in the treatment of ciclosporin-induced gingival hyperplasia in renal transplant recipients. *Transplantation* 65:1611-1615.
Nasstrom K (1996). Dentin formation after corticosteroid treatment. A clinical study and an experimental study on rats. *Swed Dent J* 115:1-45.
Nasstrom K, Forsberg B, Petersson A, Westesson PL (1985). Narrowing of the dental pulp chamber in patients with renal diseases. *Oral Surg Oral Med Oral Pathol* 59:242-246.
Nasstrom K, Moller B, Petersson A (1993). Effect on human teeth of renal transplantation: a post-mortem study. *Scand J Dent Res* 101:202-209.
Naugle K, Darby ML, Bauman DB, Lineberger LT, Powers R (1998). The oral health status of individuals on renal dialysis. *Ann Periodontol* 3:197-205.
Naylor GD, Fredericks MR (1996). Pharmacologic considerations in the dental management of the patient with disorders of the renal system. *Dent Clin North Am* 40:665-683.
Naylor GD, Hall EH, Terezhalmy GT (1988). The patient with chronic renal failure who is undergoing dialysis or renal transplantation: another consideration for antimicrobial prophylaxis. *Oral Surg Oral Med Oral Pathol* 65:116-121.
Nicholson G, Burrin JM, Hall GM (1998). Peri-operative steroid supplementation. *Anaesthesia* 53:1091-1104.
Nishikawa S, Tada H, Namasaki A, Kasahara S, Kido J, Nagata T, *et al.* (1991). Nifedipine-induced gingival hyperplasia: a clinical and in vitro study. *J Periodontol* 62:30-35.
O'Valle F, Mesa F, Aneiros J, Gomez-Morales M, Lucena MA, Ramirez C, *et al.* (1995). Gingival overgrowth induced by nifedipine and ciclosporin A. Clinical and morphometric study with image analysis. *J Clin Periodontol* 22:591-597.
Oettinger-Barak O, Machtei EE, Peled M, Barak S, L-Naaj IA, Laufer D (2000). Ciclosporin A-induced gingival hyperplasia pemphigus vulgaris: literature review and report of a case. *J Periodontol* 71:650-656.
Okada H, Davies JE, Yamamoto H (2000). Brown tumour of the maxilla in a patient with secondary hyperparathyroidism: a case study involving immunohistochemistry and electron microscopy. *J Oral Maxillofac Surg* 58:233-238.
Opatry K (1997). Hemostasis disorders in chronic renal failure. *Kidney Intl* 52(Suppl 62):87-89.
Ota B, Bradley M (1983). Side effects of ciclosporin in 100 renal allograft recipients. *Transplant Proc* 15:3150-3156.
Pan WL, Chan CP, Huang CC, Lai MK (1992). Ciclosporin-induced gingival overgrowth. *Transplant Proc* 24:1393-1394.
Perneger TV, Whelton PK, Klag MJ (1994). Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 331:1675-1679.
Pernu HE, Oikarinen K, Hietanen J, Knuuttila M (1989). Verapamil-induced gingival overgrowth: a clinical histologic and biochemic approach. *J Oral Med Pathol* 18:422-425.
Pernu HE, Pernu LMH, Huttunen KRH, Nieminen PA, Knuuttila ML (1992). Gingival overgrowth among renal transplant recipients related to immunosuppressive medication and possible local background factors. *J Periodontol* 63:548-553.
Phelps KR, Bansal M, Twersky L (1994). Jaw enlargement complicating secondary hyperparathyroidism in three haemodialysis patients. *Clin Nephrol* 41:173-179.
Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS (1997). A comparison of tacrolimus and ciclosporin for immunosuppression after cadaveric renal transplantation. *Transplantation* 63:977-983.
Pol S (1995). Hepatitis C virus infection in haemodialysed patients and kidney allograft recipients. *Adv Nephrol* 24:315-330.
Porter SR, Scully C (1994) Periodontal aspects of systemic disease. A system of classification. In: European Workshop of Periodontology. Lang NP, Karring T, editors. London: Quintessence, pp. 374-419.
Porter SR, Hegarty A, Scully C (2004). An update of the etiology and

management of xerostomia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 97:28-46.

Potter JL, Wilson NHF (1979). A dental survey of renal dialysis patients. *J Public Health* 93:153-155.

Precious DS, Laba JP, Hinrichsen GJ (1981). Dental considerations for patients on chronic dialysis and renal transplant recipients. *Can Dent Assoc J* 9:595-599.

Quirk PC, Osborne PJ, Walsh LJ (1995). Efficacy of antifungal prophylaxis in bone marrow transplantation. *Aust Dent J* 40:267-270.

Qunibi WY, Akhtar M, Ginn E, Smith P (1988). Kaposi's sarcoma in ciclosporin-induced gingival hyperplasia. *Am J Kidney Dis* 11:349-352.

Ray KL (1989). Renal failure. Complications and oral findings. *J Dent Hyg* 63:52-55.

Rees TD, Levine RA (1995). Systematic drugs as a risk factor for periodontal disease initiation and progression. *Compendium* 16:20,22,26.

Regev E, Zeltser R, Lustman J (1992). Lip carcinoma in renal allograft recipient with long-term immunosuppressive therapy. *Oral Surg Oral Med Oral Pathol* 73:412-414.

Reyna M, Richardson JM, Mattox DE, Banowsky LH, Nicastro-Lutton JJ (1982). Head and neck infection after renal transplantation. *J Am Med Assoc* 247:3337-3339.

Roderick PJ, Jones I, Raleigh VS, McGeown M, Mallick N (1994). Population need for renal replacement therapy in Thames regions: ethnic dimension. *Br Med J* 309:1111-1114.

Ross WF 3rd, Salisbury PL 3rd (1994). Uremic stomatitis associated with undiagnosed renal failure. *Gen Dent* 42:410-412.

Sampson E, Meister F Jr (1984). Dental complications in the end stage of renal disease. *Gen Dent* 32:297-299.

Santiago A, Chanzan JA (1989). The cause of death and co-morbid factors in 405 chronic haemodialysis patients. *Dial Transplant* 18:484-488.

Savage NW, Seymour GJ, Robinson MF (1987). Cyclosporin-A-induced gingival enlargement. A case report. *J Periodontol* 58:475-480.

Seymour RA, Smith DG (1991). The effect of a plaque control programme on the incidence and severity of ciclosporin-induced gingival changes. *J Clin Periodontol* 18:107-110.

Seymour RA, Smith DG, Rogers SR (1987). The comparative effects of azathioprine and ciclosporin on some gingival health parameters of renal transplant patients. A longitudinal study. *J Clin Periodontol* 14:610-613.

Seymour RA, Thomason JM, Ellis JS (1994). Oral and dental problems in the organ transplant patient. *Dent Update* 21:209-212.

Seymour RA, Thomason JM, Nolan A (1997). Oral lesions in organ transplant patients. *J Oral Pathol Med* 26:297-304.

Sheehy EC, Roberts GJ, Beighton D, O'Brien G (2000). Oral health in children undergoing liver transplantation. *Int J Paediatr Dent* 10:109-119.

Simmons NA (1993). Recommendations for endocarditis prophylaxis. The endocarditis working party for antimicrobial chemotherapy. *J Antimicrob Chemother* 31:437-438.

Slavin J, Taylor J (1987). Cyclosporin, nifedipine and gingival hyperplasia (letter). *Lancet* 26:739.

Somacarrera ML, Hernandez G, Acero J, Moskow BS (1994). Factors related to the incidence and severity of ciclosporin-induced gingival overgrowth in transplant patients. A longitudinal study. *J Periodontol* 65:671-675.

Somacarrera ML, Lucas M, Cuervas-Mons V, Hernandez G (1996). Oral care planning and handling of immunosuppressed heart, liver and kidney transplant patients. *Spec Care Dentist* 16:242-246.

Somacarrera ML, Lucas M, Scully CS, Barrios C (1997). Effectiveness of periodontal treatments on ciclosporin-induced gingival overgrowth in transplant patients. *Br Dent J* 183:89-94.

Sowell SB (1982). Dental care for patients with renal failure and renal transplants. *J Am Dent Assoc* 104:171-177.

Spencer CM, Goa KL, Gillis JC (1997). Tacrolimus. An update of its pharmacology and clinical efficacy in the management of organ transplantation. *Drugs* 54:925-975.

Spolnik KJ, Patterson SS, Maxwell DR, Kleit SA, Cockerill EM (1981). Dental radiographic manifestations of end-stage renal disease. *Dent Radiogr Photogr* 54:21-31.

Squifflet JP, Legendre C (2002). The economic value of valacyclovir prophylaxis in transplantation. *J Infect Dis* 186(Suppl 1):S116-S122.

Stein A, Wild J (2002). Kidney failure explained. 2nd ed. London: Class Publishing, p. 5.

Stewart JH (1967). Platelet numbers and life span in acute and chronic renal failure. *Thromb Diath Haemorrh* 17:532-542.

Svirsky JA, Saravia ME (1989). Dental management of patients after liver transplantation. *Oral Surg Oral Med Oral Pathol* 67:541-546.

Thomas DW, Seddon SV, Shepherd JP (1993). Systemic immunosuppression and oral malignancy: a report of a case and review of the literature. *Br J Oral Maxillofac Surg* 31:391-393.

Thomas DW, Baboolal K, Subraminian N, Newcombe RG (2001). Ciclosporin A induced gingival overgrowth is unrelated to allograft function in renal transplant recipients. *J Clin Periodontol* 28:706-709.

Thomason JM, Seymour RA, Rice N (1993). The prevalence and severity of ciclosporin- and nifedipine-induced gingival hyperplasia. *J Clin Periodontol* 20:37-40.

Thomason JM, Seymour RA, Ellis JS, Kelly PJ, Parry G, Dark J, *et al.* (1995). Iatrogenic gingival overgrowth in cardiac transplantation. *J Periodontol* 66:742-746.

Thomason JM, Seymour RA, Ellis JS, Kelly PJ, Parry G, Dark J, *et al.* (1996). Determinants of gingival overgrowth severity in organ transplant patients: an examination of the role of HLA phenotype. *J Clin Periodontol* 23:628-634.

Thorstensson H, Kuylenstierna J, Hugoson A (1996). Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J Clin Periodontol* 23:194-202.

Tomaselli DL Jr, Feldman RS, Krochtengel AL, Fernandez P (1993). Osteomyelitis associated with chronic periodontitis in a patient with end-stage renal disease: a case report. *Periodontal Clin Investig* 15:8-12.

Torrelo A, Soria C, Rocamora A, Moreno R, Ledo A (1990). Lichen planus-like eruption with esophageal involvement as a result of cyanamide. *J Am Acad Dermatol* 23:1168-1190.

Varga E, Tyldesley WR (1991). Carcinoma arising in ciclosporin-induced gingival hyperplasia. *Br Dent J* 171:26-27.

Vigneswaran N (2001). Oral and maxillofacial pathology case of the month. Renal-osteodystrophy induced macrognathia. *TX Dent J* 118:570-571, 582-583.

Werner CW, Saad TF (1999). Prophylactic antibiotic therapy prior to dental treatment for patients with end-stage renal disease. *Spec Care Dentist* 19:106-111.

Westbrook P, Bednarczye EM, Carlson M, Sheehan H, Bissada NF (1997). Regression of nifedipine-induced gingival hyperplasia following switch to a same class calcium channel blocker, isradipine. *J Periodontol* 68:645-650.

Wilson RL, Martinez-Tiraddo J, Whelchel J, Lordon RE (1982). Occult dental infection causing fever in renal transplant patients. *Am J Kidney Dis* 2:354-356.

Wirnsberger GH, Pfragner R, Mauric A, Zach R, Bogiatzis A, Holzer H (1998). Effect of antibiotic treatment with azithromycin on ciclosporin A-induced gingival hyperplasia among renal transplant recipients. *Transplant Proc* 30:2117-2119.

Wolff A, Stark H, Sarnat H, Binderman I, Eisenstein B, Drukker A (1985). The dental status of children with chronic renal failure. *Int J Pediatr Nephrol* 6:127-132.

Wong W, Hodge MG, Lewis A, Sharpstone P, Kingswood JC (1994). Resolution of cyclosporin-induced gingival hypertrophy with metronidazole (letter). *Lancet* 343:986.

Woodhead JC, Nowak AJ, Crall JJ, Robillard JE (1982). Dental abnormalities in children with chronic renal failure. *Pediatric Dentist* 4:281-285.

Wysocki GP, Daley TD, Ulan RA (1983). Predentin changes in patients with chronic renal failure. *Oral Surg Oral Med Oral Pathol* 56:167-173.

Yamalik N, Avcikurt UF, Caglayan F, Eratalay K (1993). The importance of oral foci of infection in renal transplantation. *Aust Dent J* 38:108-113.

Zuckermann A, Reichenspurner H, Birsan T, Treede H, Deviatko E, Reichart B, *et al.* (2003). Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial. *J Thorac Cardiovasc Surg* 125:891-900.