Dental management in renal failure: Patients on dialysis

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Abstract

Chronic renal failure is an important health care problem throughout the world, with an incidence of 337, 90, 107 and 95 new cases per million inhabitants/year in the United States, Australia, New Zealand and the United Kingdom, respectively. These figures moreover invariably tend to increase. During the progression of renal damage, clinical manifestations are noted in practically all body organs and systems, and 90% of all affected patients experience oral symptoms. The existing management options range from simple measures based on changes in diet and life style, to different forms of dialysis (hemodialysis and peritoneal dialysis), and also kidney transplantation. Given the multiple oral manifestations of chronic renal failure, and the different repercussions of its treatment upon the oral cavity, these patients require special considerations and precautions in the face of dental treatment. Consultation with the nephrologist is essential before any dental treatment is carried out, in order to determine the condition of the patient, define the best moment for dental treatment, introduce the necessary pharmacological adjustments, or to establish other important aspects for preventing complications in the dental clinic.

The present study reviews the characteristics of the disease, the existing therapeutic options, and the considerations of relevance for the dental professional.

Key words: *Chronic renal failure, glomerular filtration rate, dialysis, renal transplant, immunosuppressive therapy, renal osteodystrophy, oral lesions, gingival hyperplasia, dental management.*

Introduction

Each human kidney is composed of about one million anatomical and functional units called nephrons. In turn, each nephron is composed of a glomerule and tubule. The glomerule consists of an interconnected network of capillaries contained within a cup-like sac known as Bowman's capsule, which continues with the proximal convoluted tubule. The latter in turn gives rise to different sequential segments: the loop of Henle, the distal convoluted tubule, and the collector ducts. The final segment collects the urine from a number of distal convoluted tubules and drains it directly into the renal papilla (1).

The kidneys have a number of important functions: (a) Excretion of metabolic waste products. (b) Electrolyte regulation through the control of sodium, potassium and water excretion, and acid-base homeostasis. (c) Endocrine regulatory functions: eicosanoids (prostaglandins, thromboxanes, leukotrienes, prostacyclins, etc.), erythropoietin (EPO), the renin-angiotensin system, and vitamin D metabolism (2). In particular, the renin-angiotensin system comprises one of the mechanisms involved in the control

of blood pressure (BP): when the latter decreases, the kidney releases renin, which in turn triggers an enzymatic cascade that produces abundant blood angiotensin II – a hormone that increases global peripheral vascular resistance and thus increases BP (3).

Classification of renal failure

When a nephron is destroyed it is unable to regenerate, and the kidneys compensate the loss through hypertrophy of the remaining nephrons, so that normal kidney function can be maintained until approximately half of all the existing nephrons have been destroyed. Once this point has been reached, symptoms of renal functional impairment begin to appear:

- Acute renal failure (ARF) is characterized by a sudden and important reduction in glomerular filtration rate (GFR) lasting for hours or days. The underlying causes are classified as pre-renal, intrinsically renal or post-renal (Table 1). In general, renal function is restored once the underlying cause has been resolved (4,5), and it is not common for the dental professional to treat a patient with ARF.

Table 1. Causes of renal failure.

Acute renal failure
Pre-renal
Gastrointestinal losses
Excessive perspiration
Bleeding
Burns with fluid sequestration
Renal losses
Cardiovascular failure
Liver failure
Intrinsic renal causes
Acute tubular necrosis (vasomotor nephropathy)
Severe cortical necrosis
Severe acute glomerulonephritis
Vasculitis
Malignant hypertension
Accelerated scleroderma
Allergic interstitial nephritis
Post-renal
Bilateral ureteral obstruction or ureteral obstruction in patients with a single kidney
Bladder obstruction
Bladder rupture
Urethral obstruction
Chronic renal failure
Chronic immune glomerulopathy
Hypertensive nephrosclerosis
Chronic tubulointerstitial diseases
Metabolic diseases (e.g., diabetes mellitus)
Congenital and hereditary renal processes (e.g., renal polycystic disease)

- Chronic renal failure (CRF) is characterized by a gradual reduction in the number of functional nephrons. There are many possible causes (Table 1) (5), and the natural course of CRF leads to terminal or end-stage renal failure (ESRF)(1,4).
- In ESRF, renal function has deteriorated to the point where the body suffers chronic systemic abnormalities. In this situation renal replacement therapy is required in the form of dialysis and/or kidney transplantation (1,2,4).

Chronic renal failure

CRF is defined on the basis of a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m2, or by the evidence of renal damage (micro- or macroalbuminuria, persistent hematuria, radiological anomalies) during a period of more than three months (5,6).

As a result of the progressive renal damage, the excretion of body metabolic waste products is impaired, resulting in a state of intoxication called uremia, which is characterized by increased levels of acute phase proteins, certain cytokines, and even macrophages. The endocrine functions of the kidney (secretion of vitamin D and erythropoietin) are also affected. CRF represents an extra-renal multiorgan disease state affecting the skeleton, lungs, gastrointestinal tract, heart and blood vessels, central and peripheral nervous systems, and endocrine and reproductive functions (7,8).

Epidemiological data are available in different countries, and although the reported incidences differ from one region to another (337, 90, 107 and 95 new cases per million inhabitants/year in the United States, Australia, New Zealand and the United Kingdom, respectively), CRF is a major health care problem throughout the world. The incidence increases with age; men are more often affected than women; and there are also ethnic differences (e.g., in the United States, Caucasians and Afro-Americans show a higher incidence of CRF than Asians or Native Americans)(9). In Spain, the reported prevalence of grade IV disease (severely diminished GFR: 30-59 ml/min/1.73 m^2) is 0.7-1.5% of the population, while grade III CRF (moderately diminished GFR: 15-29 ml/min/1.73 m^2) affects 3.3-8.5% of the population (10).

The most frequent causes of CRF are diabetes mellitus, present in 40-60% of all patients with CRF that progress to ESRF (5,8); arterial hypertension, which affects 15-30%; and glomerulonephritis, which is seen in less than 10% of all cases. Only 2-3% of all CRF patients present renal polycystosis (5).

Following initial parenchymal damage, renal impairment gradually intensifies – ESRF being the end condition of the disease process. The causes of such progression are not fully clear, but may include: hyperfunction of the remaining functional nephrons, systemic and intra-renal hypertension, the progression of immune damage, proteinuria, and protein and fat dietary loading (7).

Diagnosis. The glomerular filtration rate is the best parameter for assessing renal function. The standard for measuring GFR is inulin clearance, though in practice this is not the most widely used method. Creatinine clearance overestimates GFR, and precise collection of the 24-hour urine samples needed to calculate such clearance is not easy (6,11). As a result, in recent years effort has centered on the development of formulas capable of determining GFR as exactly as possible, based on a simple plasma sample used to determine serum creatinine concentration (11). These formulas take into account patient age (GFR undergoes a physiological decline with age), sex (120 ml/min/1.73 m2 is considered normal in males, versus 100 ml/min/1.73 m2 in females) and race (5). Table 2 provides an estimate of equivalent GFR according to plasma creatinine and the clinical situation of the patient.

When evaluating the risk of progression of CRF and of the possible development of ESRF, it is necessary to detect and quantify proteinuria. In addition, in the early stages of CRF, normal or only slightly reduced GFR values may be observed despite an already manifest increase in protein excretion in urine. The latter is therefore more useful as an early marker of CRF (12). Albumin, the protein predominantly excreted by the kidneys in different types of disease, is easily detectable by means of a reactive strip test, or by means of other more precise techniques (11). Under some conditions, immunoglobulins can also be excreted in urine.

Clinical manifestations

a) General. The clinical signs and symptoms are related to the type of underlying renal or systemic problem, and to the rate of impairment of renal functional.

Uremic patients show generalized paleness as a result of anemia (7,9), brown hyperpigmentation of the nails and skin due to the retention of dietary pigments, and skin excoriations or scratches produced by intense generalized itching secondary to the accumulation of calcium and phosphate microcrystals (9).

Arterial hypertension is the most common complication, and is attributed to the retention of sodium and water, and to activation of the renin-angiotensin-aldosterone system (7,9,13).

These patients also suffer dyspnea (9) and gastrointestinal alterations such as anorexia, nausea and vomiting associated to the uremia (7,9), as well as an increased incidence of gastrointestinal bleeding episodes (13).

A frequent observation is anemia secondary to deficient erythropoiesis (1,7,13), and hemostasia is altered as a result of platelet dysfunction (7,13,14) and of the anticoagulants used in dialysis. The mechanical trauma to which the platelets are exposed during dialysis can reduce their counts. In addition, diminished platelet adhesion is observed, together with an increase in prostacyclin activity, lesser availability of platelet factor 3, and increased capillary fragility. All these factors can lead to an increased risk of bleeding problems (2).

The decrease in cellular immune function and the chemotactic defects induced by uremia predispose patients to infection, which represents the second most important cause of death in such individuals (8).

The alterations in mineral metabolism in turn lead to renal osteodystrophy, which manifests in the form of skeletal defects, fractures, pain, and joint and periarticular calcifications (7).

Involvement of the central nervous system is expressed in the form of restlessness, apathy and insomnia (9).

The endocrine-metabolic alterations can manifest as hypoparathyroidism (9), retarded growth (7,9), diminished libido, erectile dysfunction in males, and infertility in women (9).

b) Oral. A full 90% of all patients with CRF suffer oral signs and symptoms (2) affecting both the bone and soft tissue structures (7).

- Bad odor (secondary to uremia) and metallic taste resulting from the increased concentration of urea in saliva and its posterior transformation into ammonium (2,8,9,14).

Table 2. Equivalences between renal function tests and clinical expression.

Glomerular function % filtrate	Creatinine clearance	Blood creatinine	Clinical condition
100%	90-120 ml/min	0.5-1.3 mg/dl	Normal
>50%	>45-60 ml/min	<1.3 mg/dl	Renal compensation
25-50%	20-60 ml/min	1.3-2.5 mg/dl	Onset of clinically manifest chronic renal failure
10-25%	10-25 ml/min	2.5-10 mg/dl	Established clinical condition
<10%	<10 ml/min	>10 mg/dl	Dialysis

- Xerostomia (dry mouth), as a result of the restriction in fluid intake, the side effects of drugs (fundamentally antihypertensive agents), possible salivary gland alteration, and oral breathing secondary to lung perfusion problems (2,8,9).
- Paleness of the mucosal membranes due to anemia (1,2,7,8).
- Uremic stomatitis, and uncommon clinical observation associated to uremia (1,2). As many as four types of uremic stomatitis have been described: erythemo-pultaceous, ulcerative (1,2,8,15), hemorrhagic and hyperkeratotic. The lesions are very painful and most often appear on the ventral surface of the tongue and on the anterior mucosal surfaces (2). These lesions are resistant to treatment for as long as the blood urea levels remain high (15), and heal spontaneously within 2-3 weeks once the background renal disorder has been resolved (2,15).
- Gingival bleeding (7,13), petechiae and ecchymosis (7), resulting from platelet dysfunction (13,14) and the effects of anticoagulants (14).
- Gingival inflammation. There is some controversy in the literature in relation to gingival inflammation in patients with CRF, since some studies report low incidences of gingivitis – explained in terms of immune suppression and uremia, which would inhibit gingival inflammatory response to plaque accumulation – while other studies report the opposite (16).
- Gingival hyperplasia secondary to drug treatment, which is one of the most widely documented oral manifestations in patients with renal failure (9). Such hyperplasia can be induced by cyclosporine, which is used in transplant patients, and/or calcium channel blockers (nifedipine, amlodipine, diltiazem, verapamil, etc.), in pre-dialyzed and dialyzed patients (7,9,16-18). The condition in turn is aggravated by the deficient oral hygiene (8,17,18). A number of studies suggest that replacing cyclosporine with tacrolimus may reduce the severity of gingival hyperplasia (7,9,16-18), and in any case thorough oral hygiene is required (7,17,18). The problem also can increase in incidence and severity when combining cyclosporine and nifedipine – this suggesting an additive effect (9,16,18). Hyperplasia mainly affects the labial surface of the interdental papilla, though greater extensions can be affected - including the gingival margins and lingual and palatal surfaces (9).
- Periodontal problems with important attachment loss, recesses and deep pockets (4,16).
- Enamel hypoplasia secondary to alterations in calcium and phosphorus metabolism (7), which can affect both the primary and permanent dentition (9). The severity of such hypoplasia is related to patient age at the time of presentation of these metabolic disorders, the duration of renal failure, and dialysis (16).
- Severe erosions on the lingual surfaces of the teeth, due to frequent regurgitation and vomiting induced by uremia and medication, and nausea associated to dialysis (2,14).
- Pulp obliteration, possibly related to the alterations in calcium and phosphorus metabolism (7).
- Delays or alterations in eruption (2,7).
- Changes in maxillary bone, secondary to renal osteodystrophy (2,14). These changes comprise bone demineralization with trabeculation and cortical loss (1,2,7,14), giant cell radiotransparencies or metastatic calcifications of the soft tissues (2). The patients are at increased risk of fracture during dental treatments such as extractions (1,2). Tooth mobility (2,9,14), malocclusion, crowding, pulp chamber calcifications (2) and temporomandibular joint problems are also observed (19).
- A diminished prevalence of caries has been observed and attributed to a protective effect on the part of urea, which inhibits bacterial growth and neutralizes bacterial plaque acids (1,4,14,19).
- Important tartar formation, induced by the increased levels of urea in saliva (19) and altered calcium and phosphorus metabolism (1).
- Infections. Candidiasis is common among both transplant patients and subjects on dialysis (1,9). Cytomegalovirus (CMV) infection is frequent in the first months after transplantation (7), and prolonged immune suppression can increase patient vulnerability to human herpesvirus 8 (9).
- Mucosal lesions, particularly white lesions and/or ulcerations. Common observations are lichenoid lesions often (though not always) associated to medication (9), or oral hairy leukoplakia (OHL) secondary to drug-induced immune suppression (9,17). OHL is associated to the Epstein-Barr virus (EBV), and different studies suggest that primary infection occurs in the oropharynx, where the virus remains latent in the basal layers of the epithelium until reactivation takes place as a result of immune depression – with the generation of tongue lesions (20).
- Malignization. An increased susceptibility to epithelial dysplasia and carcinoma of the lip attributable to the treatment following renal transplantation has been postulated (9,17). The increased risk of malignization in CRF probably reflects the effects of iatrogenic immune suppression, which increases mucosal susceptibility to virus-related tumors such as Kaposi's sarcoma (9) or non-Hodgkin lymphoma (9,17).

Treatment

a) Conservative management. Such treatment aims to prevent or correct the metabolic alterations and preserve the remaining renal functional capacity. The measures include a high carbohydrate and low protein diet (though consensus is lacking on this point) (6,9,21), body weight control (6), treatment with antihypertensive drugs, lipid-lowering agents and vitamin D supplements (2,6,22), and correction of the anemia with erythropoietin (7).

b) Renal replacement therapy is considered when conservative management fails to be effective against the progression of renal deterioration, and comprises dialysis and renal transplantation (4,7).

Dialysis is an artificial mechanism that clears blood of nitrogen waste and other toxic products of metabolism (1,2,19). Two modalities are currently used: peritoneal dialysis (PD) and hemodialysis (HD). In PD, access to the body is gained through a catheter placed in the abdominal wall and inserted in the peritoneum. The dialysate (sterile electrolyte solution) is introduced through the catheter, and the peritoneal membrane filters the blood waste products via an osmotic mechanism (2,7,19). In HD, blood filtration is carried out by a machine (dialyzer) (Figure 1) equipped with a semipermeable membrane (Figure 2) allowing passage of the excess fluids and waste products (2,19). Most patients are subjected to dialysis three days a week. To this effect, an artificial permanent vascular access is placed in the form of a catheter or surgically performed arteriovenous fistula (2,9,23). During HD, the patients receive anticoagulation, generally in the form of heparin, to facilitate blood cycling through the dialyzer, and for ensuring permeability of the vascular access.

Renal transplantation is the treatment of choice in patients with irreversible renal failure (2,17). Immediately before transplantation, and after the surgical operation, immunosuppressive therapy must be provided to avoid acute rejection (7). This generally comprises combined treatment in the form of corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus), and lymphocyte proliferation inhibitors (azathioprine, mycophenolate mofetil) (7,9). All transplant patients, with the exception of those receiving an organ from an identical twin, require life-long immunosuppressive therapy (4).

c) Prevention of infections. Infections are one of the most important causes of morbidity and mortality in CRF. Vaccination is therefore potentially very useful in patients of this kind, though such treatment is underused, since no clear guidelines have been established, and vaccination response with the normal doses and regimens may be limited (24).

Prognosis

The life expectancy of patients on dialysis remains somber (approximately one-third that of the general population) (23). The prognosis of individuals with diabetes mellitus and/or hypertension is poorer than that of patients with glomerulonephritis (7).

The most common causes of death among patients with ESRF are cardiovascular problems (about 50% of global mortality) (7,22,23), followed by infections (7,23) and malignization (7).

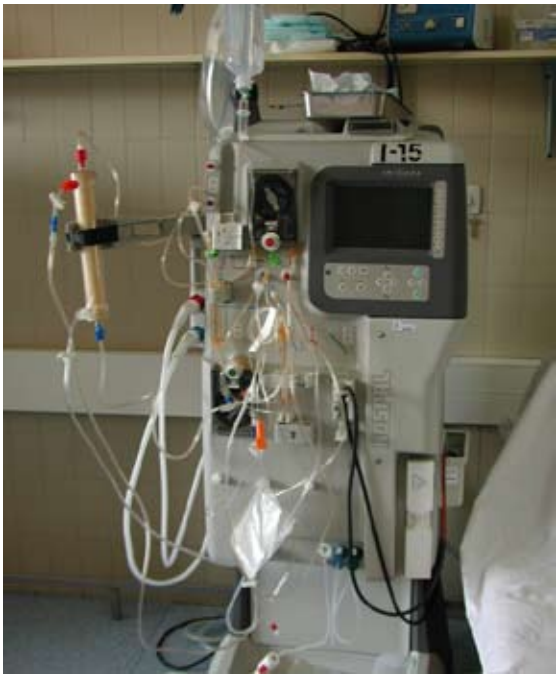

Fig. 1. Hemodialysis machine in a hospital center.

Fig. 2. Detail of the hemodialysis membrane.

Dental management of renal failure patients

Patients with renal failure require special considerations in relation to dental treatment, not only because of the conditions inherent to the disease and its multiple oral manifestations, but also because of the side effects and characteristics of the treatments they receive.

1.- Consultation with the nephrologist provides information on the state of the disease, the type of treatment, the best timing of dental management, or the medical complications that may arise (7). Any modification of the usual medication used by the patients or of other aspects of their treatment must first be consulted with the nephrologist (1).

2.- Close cooperation between medical and dental professionals is desirable in order to improve the oral and general health of the patient, based on the creation of a dental care program in the context of a multidiscipline approach to the disease (25).
3.- Prior to any invasive dental treatment, a complete blood count is to be obtained, together with coagulation tests, in view of the possible hematological alterations (1).
4.- It is essential to eliminate any infection in the oral cavity as soon as possible (2), with the consideration of antibiotic prophylaxis when bleeding and/or a risk of septicemia is expected (extractions, periodontal treatments, endodontics and periapical surgery, the placement of orthodontic braces, tartrectomy when bleeding is expected, implant surgery, and the reimplantation of avulsioned teeth) (26,27).
5.- Blood pressure is to be monitored before and during treatment, with the administration of sedation to lessen anxiety (2).
6.- The metabolism and elimination of certain drugs are altered in situations of renal failure. In such cases dose adjustment or modification of the dosing frequency is needed (Table 3). The prescription of aminoglycoside antibiotics and tetracyclines is to be avoided, because of their nephrotoxicity (1,2,9). Penicillins, clindamycin and cephalosporins can be administered at the usual doses, and are the antibiotics of choice – though the dosing interval should be prolonged (2,9). As regards analgesics, paracetamol is the non-narcotic analgesic of choice in application to episodic pain. Aspirin possesses antiplatelet activity, and as such should be avoided in uremic patients (13). As regards the rest of nonsteroidal antiinflammatory drugs (indomethacin, ibuprofen, naproxen and sodium diclofenac), dose reduction or even avoidance is indicated in the more advanced stages of renal failure (1,2,9), since they inhibit prostaglandins and generate a hypertensive effect (1,9). Benzodiazepines can be prescribed without the need of dose adjustments, though excessive sedation may occur (1,2,13). The narcotic analgesics (codeine, morphine, fentanyl) are metabolized by the liver, and so usually do not require dose adjustment (1,2).

Dialyzed patients

Patients on peritoneal dialysis require no special measures as regards dental treatment, beyond those already commented above. We therefore will center our attention on hemodialysis.

Table 3. Dose adjustment of drugs used in dental practice, in patients with renal failure.

Drug substance	Elimination [1]	Adjustment method [2]	Adjustment in renal failure according to glomerular filtration rate (GFR)(ml/min)		
			> 50	10-50	< 10
ANTIMICROBIALS					
Amoxicillin	R (H)	I	8	8-12	12-18
Erythromycin	H	D	100	100	50-75
Clindamycin	H	D	100	100	100
Metronidazole	H (R)	D	100	100	50
Doxycycline	H (R)	D	100	100	100
Ampicillin	R (H)	I	6	6-9	9-12
Tetracycline	R (H)	I	6-8	12-24	Avoid
Aciclovir	R	I	8	12-24	48
Ketoconazole	H	D	100	100	100
ANALGESICS / ANTIINFLAMMATORY					
Aspirin	H (R)	I	4	4-6	Avoid
Paracetamol	H (R)	I	4	6-8	8-12
Ibuprofen	H (R)	I	100	100	Avoid
Diclofenac	H	D	100	100	Avoid
Naproxen	H	D	100	100	Avoid
SEDATIVES					
Codeine	H (R)	D	100	100	100
Diazepam	H	D	100	100	100
Alprazolam	H (R)	D	100	100	100
ANESTHETICS					
Lidocaine	H	D	100	100	100
Mepivacaine	H	D	100	100	100
OTHERS					
Prednisone	H	D	100	100	100

1. R = mainly renal elimination; H = liver metabolism. The letter in parentheses corresponds to the less important (but significant) elimination route.
2. D = dose reduction expressed as % of the usual dose; I = prolongation of the dosing interval (in hours).

- Due to the already mentioned reasons, dialyzed patients are at an increased risk of bleeding. It is advisable to provide dental treatment on non-dialysis days, to ensure the absence of circulating heparin, which has a half-life of about four hours (9,14). In any case, prior to invasive procedures, it is important to request a complete blood count and coagulation tests (2), and to ensure that local hemostatic measures are available: mechanical compression, sutures (2,14), topical thrombin, microfibrilar collagen and oxidized regenerated cellulose. Desmopressin has been proposed for the control of severe bleeding in patients with renal failure, and conjugated estrogens can be used to achieve longer term hemostasia (13). Tranexamic acid in the form of a rinse (2) or administered via the oral route at a dose of 10-15 mg/kg body weight a day distributed in 2-3 doses, may also prove useful (28).
- Although there is some controversy in the literature regarding the need for antibiotic coverage to prevent bacterial endocarditis in dialyzed patients (2,26,27), endocarditis is effectively a potential complication in such patients. The recommended antibiotic regimen is 2 g of amoxicillin via the oral route one hour before the dental procedure. In the case of patients with allergy to penicillin, clindamycin is the drug of choice (600 mg via the oral route, one hour before the intervention).
- Dialyzed patients are subjected to numerous transfusions and blood exchanges, and this implies an increased risk of infection in the form of HIV, HBV, HCV and tuberculosis. Periodic monitoring is required, with the adoption of measures to avoid both personal contagion on the part of the dental professional and cross-contamination in the dental clinic (2,13).
- Hemodialysis can affect the serum concentrations of different drugs used by CRF patients, when such substances are administered before the dialysis session. Supplementary dosing after dialysis therefore may be needed (13).

Transplant patients

- It is important to conduct dental evaluation prior to renal transplantation, in order to eliminate the existing infectious foci. Teeth offering an uncertain prognosis are to be removed (1,7,9,14).
- The potential for oral infections after transplantation is very high, since these patients receive immunosuppressive therapy. Prophylactic antibiotic treatment is therefore indicated before invasive dental procedures are carried out (1).
- Prolonged corticosteroid therapy may make it necessary to administer a supplementary dose in situations of stress, such as when visiting the dentist, in order to avoid an adrenal crisis (1,7,9). The most recent guides recommend a dose of 25 mg of hydrocortisone via the intravenous route, before the intervention (9).
- In the first 6 months after transplantation, patients should avoid any elective dental treatment (1).

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