Gruppo di ricerca geriatrica

Gruppo di Ricerca Geriatrica

Journal Club

2 dicembre 2005

INSUFFICIENZA RENALE CRONICA

Alessandra Marrè

FISIOLOGIA DEL RENE

- Il flusso ematico renale si riduce da 1200 ml/min a 30-40 anni a 600 ml/min a 80 anni
- Anche la massa renale si riduce: da 250 g a 30 anni passa a 180 g a 70 anni
- In ragione di ciò la velocità di filtrazione glomerulare (GFR) cala di 8 ml/min/1.73 m^2/decennio in due terzi degli anziani non nefropatici
- Tale variabilità indica che fattori diversi dall'invecchiamento potrebbero essere responsabili del calo della funzionalità renale (es.: rialzi pressori)
- Con l'età si riducono anche la capacità di concentrare e diluire le urine e la soglia di glicosuria

Harrison's Principles of Internal Medicine
The Merck Manual of Geriatrics

IRC: definizione

- E’ una sindrome che risulta dalla progressiva e irreversibile distruzione dei nefroni, indipendentemente dalla causa. Si può diagnosticare quando si riscontra una riduzione stabile del tasso di filtrazione glomerulare per 3-6 mesi
- Supportano la diagnosi: riduzione della dimensione dei reni, osteodistrofia renale, sintomi e segni di uremia
- Non sono invece indici attendibili di cronicità l’anemia, l’iperfosfatemia e l’ipocalcemia

Harrison’s Principles of Internal Medicine
The Merck Manual of Geriatrics

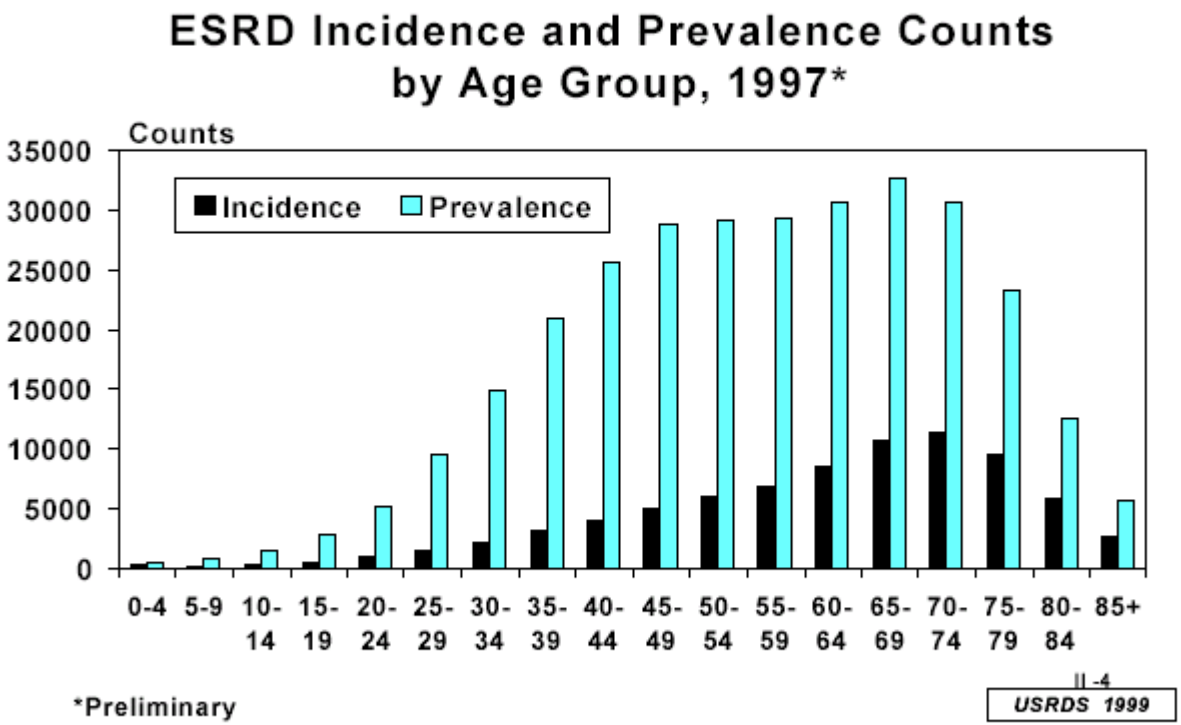

ESRD Incidence and Prevalence Counts
by Age Group, 1997*
Counts
35000
30000
25000
20000
15000
10000
5000
0
Incidence
Prevalence
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+
*Preliminary
II-4
USRDS 1999

Figure II-4

IRC: epidemiologia e cause

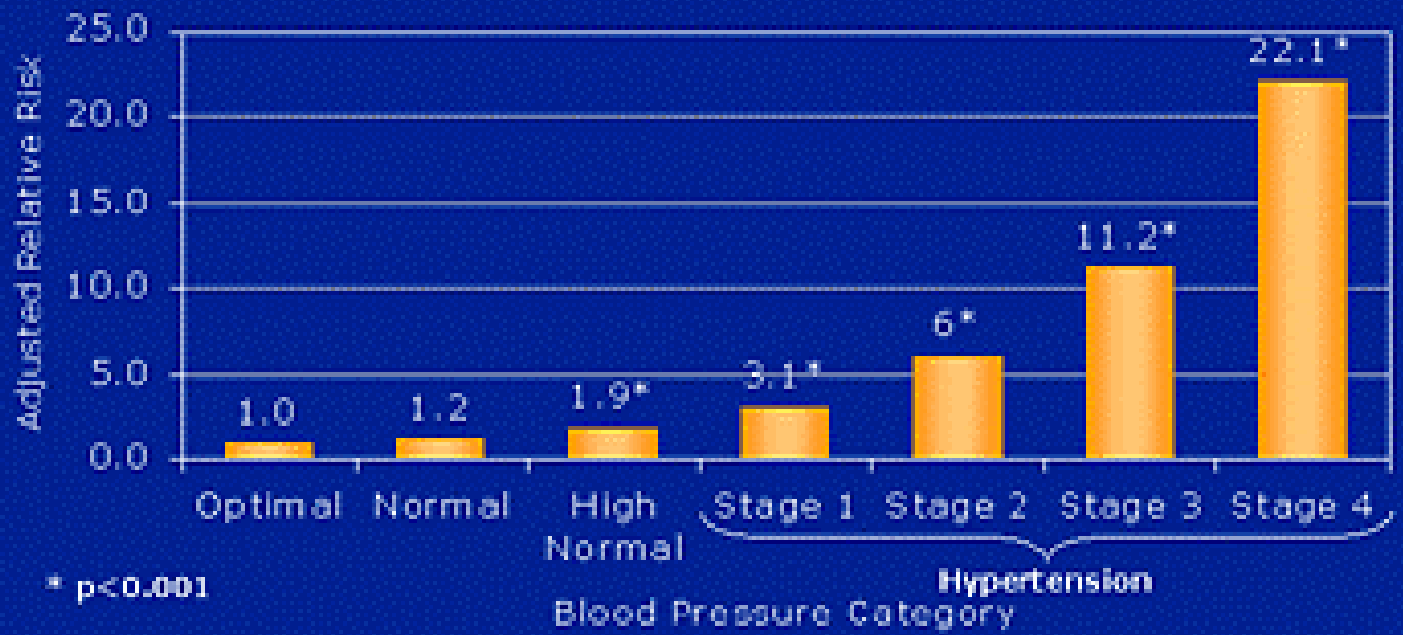
Prevalenza e incidenza delle principali cause di IR terminale nel '97 (dati U.S. Medicare)

	Prevalenza n=304 083		**Incidenza** n=79 102	
	numero	***%***	***numero***	***%***
Diabete	100 892	33.2	33 096	41.8
Ipertensione	72 961	24	20 066	25.4
Glomerulonefriti	52 229	17.2	7 390	9.3
Malattia cistica	13 992	4.6	1 772	2.2

US Renal Data System 1999 Annual Report

ESRD Due to Any Cause In 332,544 Men Screened for MRFIT

Adjusted Relative Risk[1]



* p<0.001

1 Men with optimal blood pressure was the reference category.

Klag MJ, et al. N Engl J Med. 1996;334(1):13-18.

www.hypertensiononline.org

IRC: epidemiologia

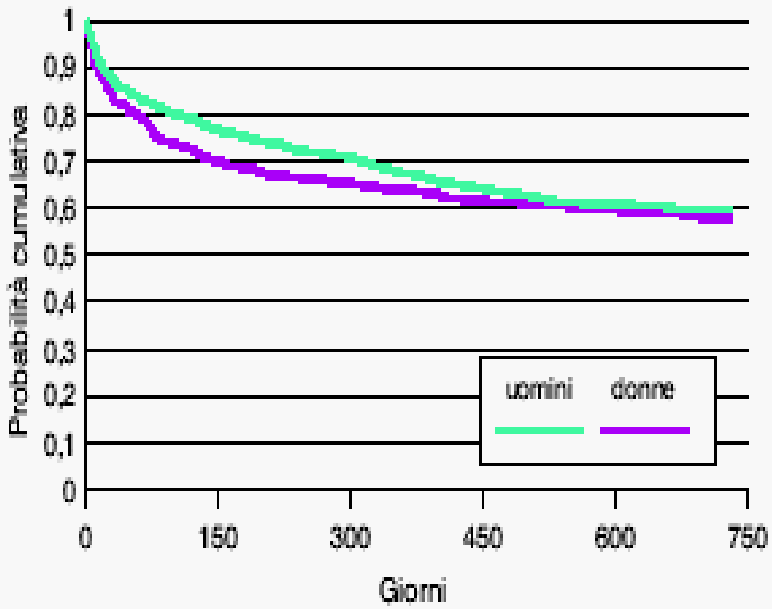
- Il numero di nuovi casi si è di recente stabilizzato, dopo 2 decadi di costante aumento di incidenza annuale
- Il National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), nell'Ottobre 2005, ha riportato un numero di nuovi casi nel 2003 pari a 338/milione, (nel 2002 340/milione)
- Negli anni '90 il tasso di crescita annuo era 5-10%
- Questo è dovuto alla maggiore attenzione nella cura di ipertensione, diabete e proteinuria, e, in particolare, al maggiore utilizzo di Ace-inibitori e ARBs
- Queste rimangono le cause principali di nuovi casi di IRC (diabete 44%, HTA 28%)
- Ace-I e ARBs sono sottoutilizzati: solo il 32% dei pazienti con IRC li assume

JAMA, Nov 2005

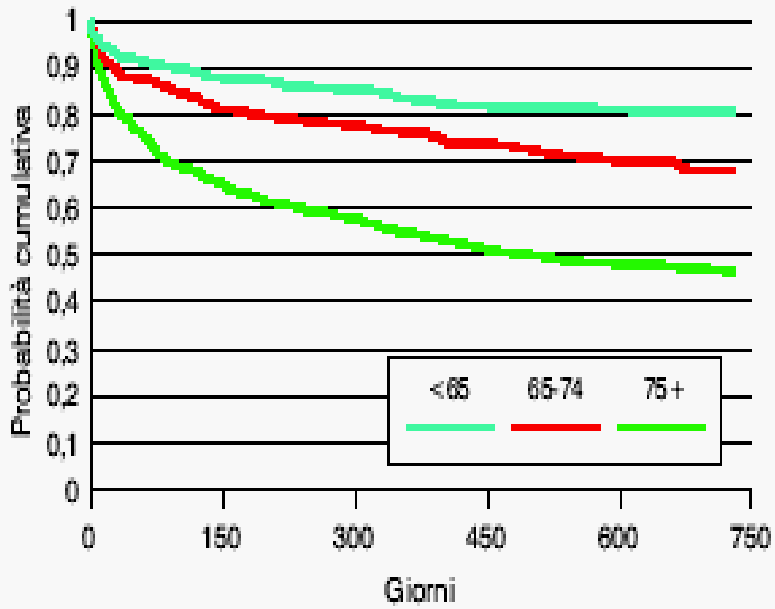
IRC: storia naturale

- Esiste un'ampia variabilità di progressione della malattia cronica renale
- I fattori che influenzano la velocità di riduzione del GFR sono: la malattia di base ed il suo eventuale controllo, fattori genetici, razza africana, sesso maschile, età avanzata, trattamento (dieta?, Ace-inibitori, altri farmaci), grado di proteinuria, fumo di sigaretta, dislipidemia
- Il GRF può calare da 5 a 12 ml/min/1.73 m^2/anno, con variazioni anche nello stesso paziente
- La deviazione standard della perdita annua di GFR, espressa come percentuale del declino medio, può variare da 25% a 150%

Sopravvivenza a due anni dalla diagnosi per genere



Sopravvivenza a due anni dalla diagnosi per età



IRA su IRC

- Deplezione di volume (soprattutto negli anziani)
- Farmaci (antibiotici, FANS, Ace-inibitori e ARBs, diuretici, Ciclosporina)
- Sepsi
- Scompenso cardiaco
- Mezzo di contrasto EV
- Uropatia ostruttiva

UREMIA

- E’ la “via finale comune” clinica dell’IRC
- E’ provocata dalla ritenzione dei prodotti tossici del metabolismo proteico
- Astenia, disturbi del sonno, cefalea, irritabilità muscolare, neuropatia periferica, ipertensione arteriosa, anoressia, nausea, vomito, alito uremico, ulcera peptica, anemia normocitica, espansione di volume, SCC, iperkaliemia, ipocalcemia, iperPTH secondario, osteodistrofia renale, ipotermia, iperuricemia, malnutrizione calorico-proteica, emorragie, amenorrea, infertilità, prurito

Harrison’s Principles of Internal Medicine
The Merck Manual of Geriatric

OSTEODISTROFIA RENALE

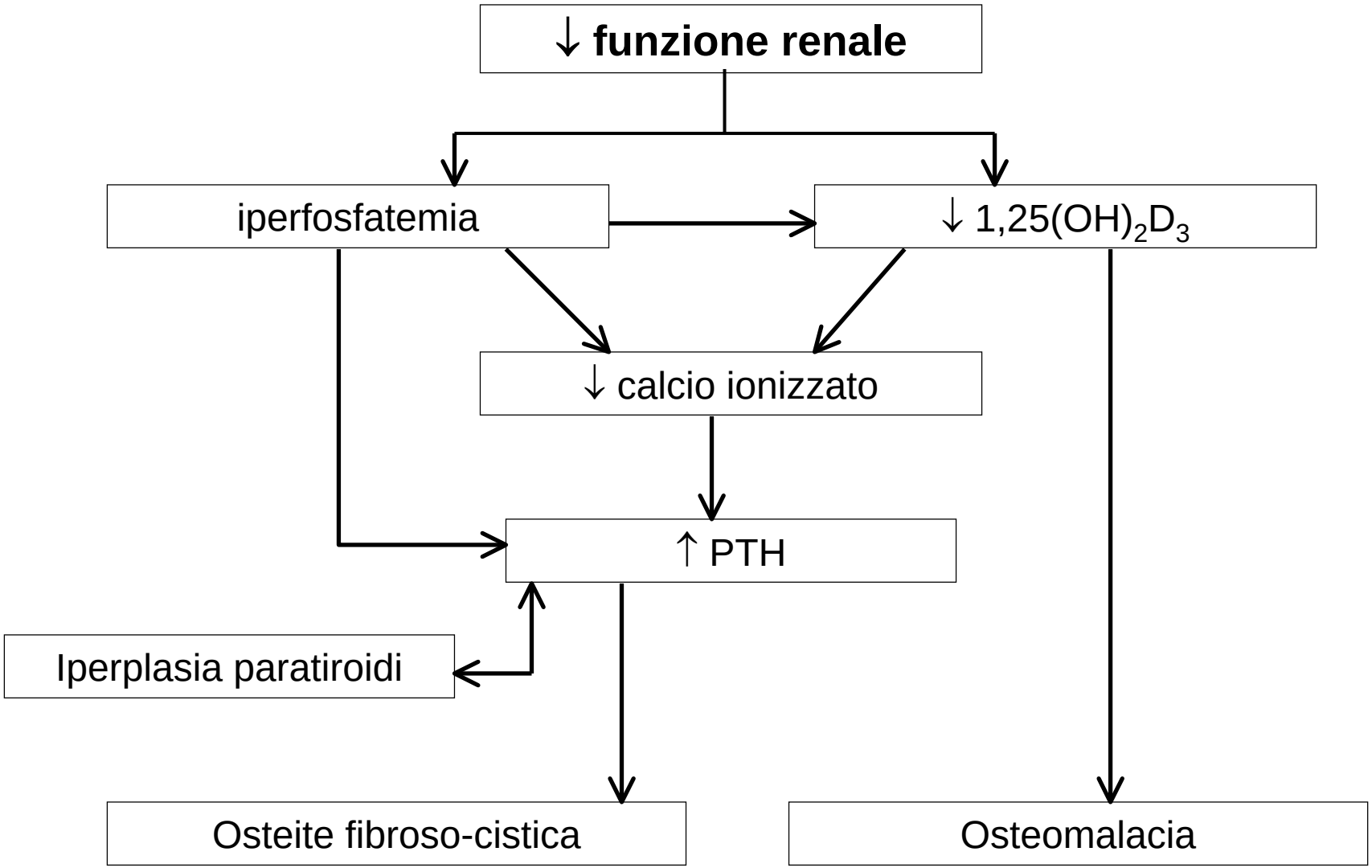


Table 3: Classification of Chronic Kidney Disease (CKD)

Stage	Description	Minimum test frequency
1	Normal GFR GFR >90 mL/min/1.73 m^2 **with other evidence of chronic kidney damage***	12 monthly
2	Mild impairment GFR 60-89 mL/min/1.73 m^2 **with other evidence of chronic kidney damage***	12 monthly
3	Moderate impairment GFR 30-59 mL/min/1.73 m^2	6 monthly (12 if stable**)
4	Severe impairment GFR 15-29 mL/min/1.73 m^2	3 monthly (6 if stable)**
5	Established renal failure (ERF) GFR < 15 mL/min/1.73 m^2 or on dialysis	3 monthly
	* The "**other evidence of chronic kidney damage**" may be one of the following: • Persistent microalbuminuria • Persistent proteinuria • Persistent haematuria (after exclusion of other causes, e.g. urological disease) • Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests, e.g. polycystic kidney disease, reflux nephropathy • Biopsy-proven chronic glomerulonephritis Patients found to have a GFR of 60-89 mL/min/1.73 m^2 <u>without</u> one of these markers • should not be considered to have CKD and • should not be subjected to further investigation (unless there are additional reasons to do so)	
	** stable = < 2ml/min/1.73 m^2 change over 6 months or more	

UK CKD Guidelines, 2005

A. Identification and classification of CKD

1. Glomerular fitration rate (GFR)

- **Kidney function should be assessed by estimated GFR** and CKD is to be classified on this basis (see Table 3)
- **The GFR should be estimated from serum creatinine** using the 4-variable MDRD equation. (See Box 1 for calculation if not provided by local laboratories) **(Level 2)**

2. Serum Creatinine measurement *to allow estimation of the GFR:*

Serum creatinine concentration should be measured at initial assessment and then **at least annually** in all adult patients with:

- Previously diagnosed CKD including:
  - Identified renal pathology (e.g. polycystic kidney, Biopsy proven GN, reflux nephropathy)
  - Persistent proteinuria (see page **X** section **X**)
  - Urologically unexplained haematuria
- Conditions associated with a high risk of silent development of obstructive kidney disease:
  - Bladder voiding dysfunction (outflow obstruction, neurogenic bladder)
  - Urinary diversion surgery
  - Urinary stone disease (>one episode/year)
- Conditions associated with a high risk of silent development of parenchymal kidney disease:
  - Hypertension, diabetes mellitus, heart failure,
  - Atherosclerotic coronary, cerebral, or peripheral vascular disease
- Conditions requiring long-term treatment with potentially nephrotoxic drugs
  - e.g ACEIs, ARBs, NSAIDs, Lithium, Mesalazine, Cyclosporin, Tacrolimus
- Multi-system diseases that may involve the kidney
  - e.g. systemic lupus erythematosus (SLE), vasculitis, myeloma, rheumatoid arthritis.

UK CKD Guidelines, 2005

Box 1: Estimation of the Glomerular Filtration Rate

The GFR may be estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation:

$$GFR\ (ml/min/1.73\ m^2) = 186 \times \{[\text{Serum Creatinine } \mu mol/l/88.4]^{-1.154}\}$$
$$\times \text{age (years)}$$
$$\times 0.742 \text{ if female and}$$
$$\times 1.21 \text{ if African American.}$$

Until laboratories are able to report results in this way, prediction tables can be used to estimate GFR from serum creatinine, age, gender and ethnicity (see Appendix).
Alternatively, an on-line GFR calculator based on this equation is available at
<http://cgi.www.renal.org/cgi-bin/www.renal.org/eGFR/GFR.pl

UK CKD Guidelines, 2005

Estimating renal function in the elderly: concordance of the Cockroft-Gault and Modification of Diet in Renal Disease formulas

C. PEDONE, A. CORSONELLO*, R. ANTONELLI INCALZI** PER I RICERCATORI DEL GIFA

1) formula di CG[3] (CG-VFG) corretta per la superficie corporea (*body surface area* – BSA):
CG-VFG = [(140-età)*(peso in kg)]/(72*creatina sierica)*0,85 nelle donne /1,73 m^2 BSA

2) formula MDRD (MDRD-VFG):
MDRD-VFG = [170*(creatinina sierica)$^{-0,999}$*(età)$^{-0,176}$*(azoto ureico)$^{-0,170}$ *(albumina sierica)^{0,318}*0,762 nelle donne]/1,73 m^2 BSA.

Conclusions. **The CG and MDRD formulas have a good average agreement, but at the individual level they can give estimates that differ substantially, and cannot be used interchangeably to measure renal function in elderly people.**

G GERONTOL 2005;53:127-133

3.	***Testing for urinary protein***
	
	Dipstick urinalysis for protein should be undertaken:
	
	• As part of the initial assessment of patients with
	  ○ Newly discovered hypertension, haematuria or reduced GFR
	  ○ Unexplained oedema or suspected heart failure
	  ○ Suspected multi-system disease, e.g. SLE, vasculitis, myeloma
	  ○ Diabetes mellitus
	• As part of the annual monitoring of patients with
	  ○ Biopsy-proven glomerulonephritis
	  ○ Reflux nephropathy
	  ○ Urologically unexplained haematuria or persistent proteinuria
	  ○ Diabetes mellitus
	  (patients with diabetes mellitus should also have annual testing for albumin:creatinine ratio to exclude 'microalbuminuria' if the dipstick urinalysis for protein is negative)
	• As part of routine monitoring for patients receiving nephrotoxic agents eg gold, penicillamine, according to the recommendations in the British National Formulary.	

4.	***Confirmation of proteinuria***
	There is no need to perform 24 hr urine collections for quantification of proteinuria **(Level 3 DA)**
	
	If protein dipstick test is positive (≥1+) the following should be undertaken
	• MSU for culture to exclude urinary tract infection (UTI).
	• Laboratory confirmation of proteinuria, **(Level 3DA)**
	preferably on early morning urine (EMU) sample, to exclude postural proteinuria
	
	• Positive tests for proteinuria are
	  ○ Urine protein:creatinine ratio ≥45 mg/mmol or
	  ○ Albumin:creatinine ratio of ≥30 mg/mmol
	
	• Persistent proteinuria should be defined as
	  ○ two or more positive tests for proteinuria, preferably spaced by 1 to 2 weeks
	
	In annual diabetes monitoring if dipstick test negative request albumin/creatinine ratio. Microalbuminuria is defined as ACR > 2.5 mg/mmol (men) or >3.5 mg/mmol (women) on 2 or 3 occasions (see section 10).
		3 DA

5.	***Haematuria***
	Routine screening for haematuria is not recommended.
	
	• **Dipstick urinalysis for blood is the test of choice (Level 3DA)** for
	  • confirmation of macroscopic haematuria
	  • detection of microscopic haematuria.
	
	Infection, trauma, and menstruation should t be excluded first.
	There is no need for microscopy of an MSU sample to detect or confirm haematuria.
	
	• Dipstick urinalysis for blood is indicated as part of initial assessment of patients with
	  • Newly found increased serum creatinine concentration/ reduced GFR
	  • Newly discovered proteinuria
	  • Suspected multi-system disease with possible renal involvement
		3 DA

UK CKD Guidelines, 2005

	B. Interpretation of tests / Initial management	Level of evidence
6	**Recognition of acute renal failure (ARF)** ARF is characterised by rapid deterioration of renal function over a period of hours or days ARF should be suspected in the context of an acute illness in the presence of: • A 50% rise in serum creatinine concentration • A fall in estimated GFR of >25% (if baseline unknown assume 75 ml/min/1.73m^2) but GFR must be interpreted with caution as formulae rely on a stable creatinine concentration **(Level 3 DA)** • Oliguria (urinary output <0.5 ml/kg/hr) Because it requires emergency treatment, all patients with newly detected abnormal renal function should be assumed to have ARF until proven otherwise, although the majority will turn out to have CKD	

7	**In newly diagnosed GFR <60 ml/min/1.73 m^2: Management should include:**
	• Review of all previous measurements of serum creatinine
	  ○ to estimate GFR and assess rate of deterioration.
	• Review of medication, particularly
	  ○ recent additions (e.g. diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), or any drug capable of causing interstitial nephritis eg penicillins, cephalosporins, mesalazine, diuretics)
	• Urinalysis: (see page **X**)
	  ○ haematuria and proteinuria suggest glomerulonephritis, which may progress rapidly
	• Clinical assessment,
	  ○ eg. looking for sepsis, heart failure, hypovolaemia, palpable bladder.
	• Repeat serum creatinine measurement within 5 days
	  ○ to exclude rapid progression.
	• **Check criteria for referral (see Table 4 and Box 2)**
	  ○ if not indicated ensure entry into a chronic disease management programme.	

UK CKD Guidelines, 2005

8	***Management of haematuria* should include:** • Check serum creatinine concentration in all patients ○ refer to nephrologist if GFR < 60 mL/min/1.73 m^2. • Check for proteinuria in all patients. If GFR normal: Macroscopic haematuria, with or without proteinuria: • **fast track urology referral; refer to nephrology if initial investigations negative.** Microscopic haematuria (dipstick **or** laboratory microscopy) without dipstick proteinuria: • Age >50 yrs: refer to urology • Age <50 yrs, or >50 yrs after exclusion of urological cancer: treat as CKD (includes measurement of serum creatinine concentration, annual repeat if initially normal) Microscopic haematuria with urine protein:creatinine ratio > 45 mg/mmol • **refer to nephrology.** There is no need for laboratory confirmation of dipstick positive haematuria. **Level 3 DA**	**3DA**

9	***Proteinuria:*** **If found, management should include**
	• Quantification of proteinuria (see section A4), test for haematuria, estimate GFR.
	  ○ Urine PCR > 100 mg/mmol – refer to Nephrologist irrespective of GFR.
	  ○ Urine PCR >45 mg/mmol with microscopic haematuria – refer irrespective of GFR.
	• Check criteria for referral (see Table 4 and Box 2)
	  ○ **if not indicated ensure entry into chronic disease management programme.**	

N.B. ematuria e proteinuria sono spesso associate: la presenza isolata di una delle due alterazioni è indice di una condizione patologica a prognosi migliore rispetto a quelle in cui sono entrambe presenti

UK CKD Guidelines, 2005

Diabetes Mellitus (DM) and 'microalbuminuria' or proteinuria

- Urinary albumin/creatinine ratio should be measured using a laboratory method if dipstick protein negative (see section 4) preferably on an EMU, but not during acute illness, intercurrent infection or menstruation.
- Persistent urinary albumin/creatinine ratios of ≥2.5 mg/mmol (male) or ≥3.5 mg/mmol(female) on 2-3 occasions are consistent with micro-albuminuria

Manage patients with DM (Type I or II) and microalbuminuria or proteinuria as follows:

- Achieve good glycaemic control (HbA1c 6.5-7.5%). **Level 1**
- Prescription of an ACEI (or ARB in the presence of a firm contraindication to ACEI), titrated to full dose, irrespective of initial blood pressure **Level 1**
- Control of hypertension if necessary: Addition of other antihypertensive drugs in combination to reach the blood pressure goal. **(Level 1)**
- Measurement at least once a year of
  - urine albumin:creatinine ratio (or PCR)
  - serum creatinine concentration (for estimated GFR).
- **Referral to diabetes team for review.**
- **Referral to a nephrologist**
  - **as for patients without diabetes.**
- Co-ordination of care between the primary care team and specialist teams (including nephrology, ophthalmology, cardiology, and vascular surgery) at all stages of CKD including stage 5.

UK CKD Guidelines, 2005

11	***Investigation for atherosclerotic renal artery stenosis***	
	Patients should be referred for further investigation for atherosclerotic renal artery stenosis (ARAS), with a view to intervention, in the following situations:	
	• Refractory hypertension (ie BP > 150/90 mm Hg despite 3 anti-hypertensive agents). **Level 3 DA**	**3 DA**
	• Recurrent episodes of pulmonary oedema despite normal left ventricular function on echocardiography (so-called "flash pulmonary oedema", usually associated with hypertension). **Level 3 DA**	**3 DA**
	• Rising serum creatinine concentration (rise of >=20% or fall of GFR of >15%) ○ over 12 months with a high clinical suspicion of widespread atherosclerosis. ○ or during the first 2 months after initiation of ACEI or ARB treatment **(Level 3DA)**	**3 DA**
	• Unexplained hypokalaemia with hypertension.	

UK CKD Guidelines, 2005

	C. Management of CKD	Level of evidence
	All Stages	
12	Local arrangements should be made for the implementation of care plans for all adult patients with CKD irrespective of age, shared between primary, secondary and tertiary care as appropriate and to include:	
	• Regular measurements of kidney function and other laboratory tests depending on the severity of kidney impairment (see Table 3).	
	• General health advice as appropriate on:	2
	○ smoking cessation. **(Level 2)**	1
	○ weight loss **(Level 1)**	
	○ aerobic exercise	
	○ limiting alcohol intake	
	○ limiting sodium intake	
	• Cardiovascular Prophylaxis For patients with 10 year risk of cardiovascular disease of > 20% (Joint British Society Guidelines) consider:	
	○ Aspirin treatment if BP < 150/90 mm Hg **(Level 2)**	2
	○ Lipid-lowering drug therapy (or entry into a trial). **(Level 2)**	2
	• Blood pressure monitoring	
	○ Blood pressure should be measured according to BHS standards at least annually	
	• Control of hypertension	
	○ Hypertension should be meticulously controlled.	2
	○ Threshold for initiation of anti-hypertensive medication: **(Level 2)**	
	▪ If urine protein/creatinine ratio (PCR) <100 mg/mmol	
	• Threshold 140/90 mmHg – Target 130/80	
	▪ If urine PCR >100 mg/mmol	
	• Threshold 130/80 mmHg – Target 125/75	
	○ ACEIs or ARBs to be included: **(Level 1)**	1
	▪ if urine PCR >100 mg/mmol	
	▪ in diabetic patients with micro-albuminuria (see sections 4 and 10)	
	Serum creatinine and potassium should be checked	
	• before starting medication	
	• two weeks after starting, and after subsequent increases in dose.	
	If Creatinine increase of >20% or fall in GFR of >15%	
	• Repeat creatinine, check potassium, and refer for specialist opinion on whether to stop treatment or to investigate for renal artery stenosis.	
	• If Hyperkalaemia present (serum K >6 mmol/l)	
	• stop relevant drugs, eg. NSAIDs and potassium-retaining diuretics	
	• check diet and proprietary treatments, eg. LoSalt.	
	If hyperkalaemia persists the ACE or ARB should be stopped.	

UK CKD Guidelines, 2005

	CKD stage 3 - additional management	

13	***Additional management for CKD stage 3*** **should include:**
	• Annual measurement of Hb, potassium, calcium and phosphate
	• If Hb <11 and other causes excluded:
	  • treat with erythropoiesis stimulating agents to maintain Hb 11-12 g/dl depending on the patient's functional needs. (**Level 1)**
	• Request renal ultrasonography in
	  • patients with lower urinary tract symptoms,
	  • refractory hypertension
	  • unexpected progressive fall in GFR.
	• Immunise against influenza and pneumococcus.
	• Review all prescribed medication regularly to ensure appropriate doses
	  • avoid nephrotoxic drugs including NSAIDs wherever possible .
	• Check parathyroid hormone (PTH) concentration when Stage 3 first diagnosed.
	  • If raised check serum 25-hydroxyvitamin D;
	  • if this is low treat with ergocalciferol or cholecalciferol with calcium supplement (not calcium phosphate).
	  • Repeat PTH after 3 months and **refer if still raised**.
		1

UK CKD Guidelines, 2005

CKD Stages 4-5 additional management

14

Care of all patients with stage 4 or 5 CKD should be discussed formally **with a nephrologist once the appropriate investigations are obtained, even if it is not anticipated that RRT will be appropriate.**

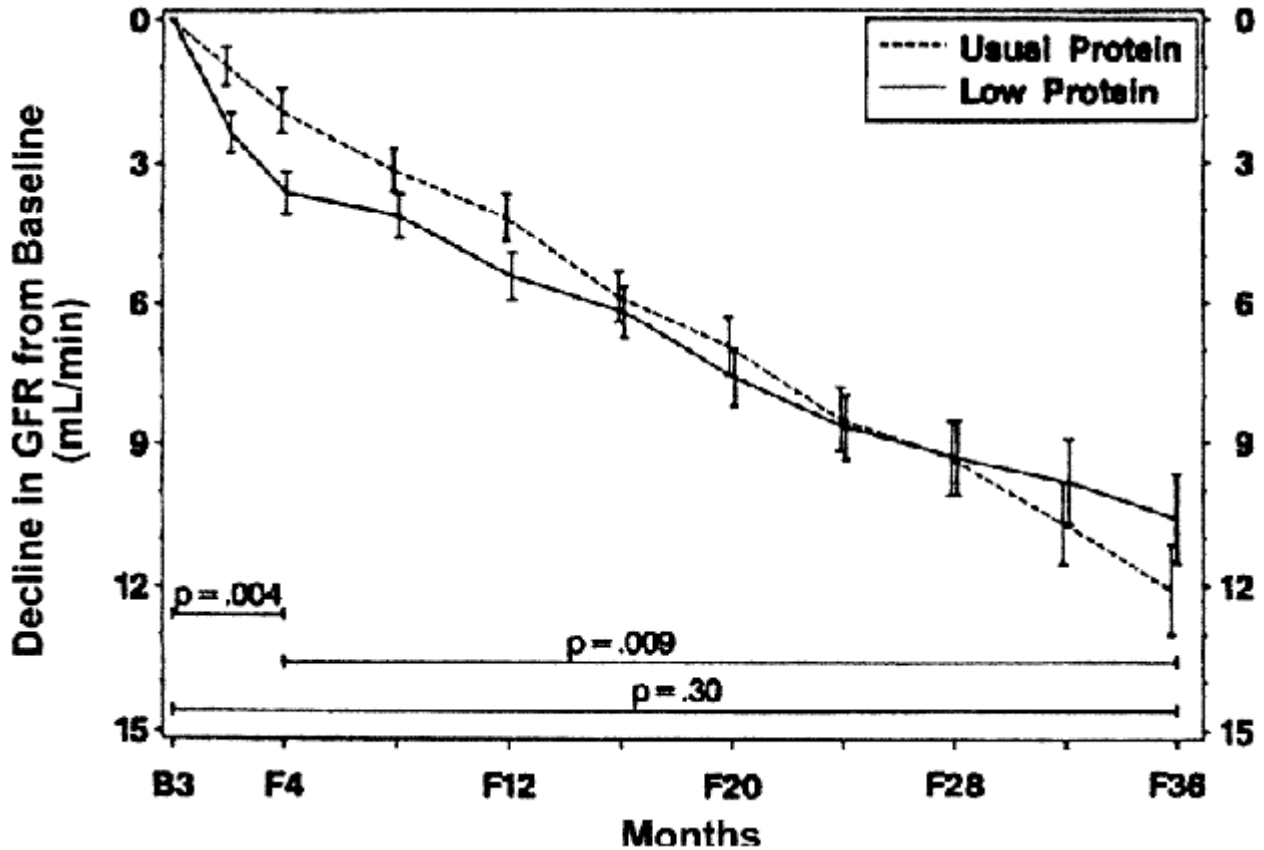
Exceptions may include:

- patients in whom stage 4 or 5 CKD supervenes as part of another terminal illness
- patients with stable function in whom all the appropriate investigations and management interventions have been performed and who have an agreed and understood care pathway
- patients in whom further investigation and management is clearly inappropriate

Management should be shared with GP and/or other healthcare professionals and should include:

- 3-monthly tests: serum creatinine (for GFR), Hb, calcium, phosphate, bicarbonate, PTH
- dietary assessment
- immunisation against hepatitis B
- investigation and treatment of phosphate retention and hyper-parathyroidism
- correction of acidosis (**Level 2**)
- information about options for treatment
- timely provision of dialysis access depending on treatment choice (**Level 2**)

UK CKD Guidelines, 2005



J Am Soc Nephrol, 1996

IRC E IPERTENSIONE

- Il farmaco di scelta è l'Ace-inibitore, anche nelle forme non-diabetiche
- Per valori di creatinina >3 mg/ml devono essere usati con cautela
- Riducono il rischio di CKD in ipertesi (diabetici e non) di circa 30%, indipendentemente dai valori di PA; tale effetto è più evidente in pazienti con proteinuria > 500 mg/24 ore (*Ann Int Med, 2001*)
- Ramipril ha dimostrato di ridurre significativamente la progressione del danno renale anche in pazienti con proteinuria > 300 mg/24 ore (AASK Study, *JAMA, 2001*)

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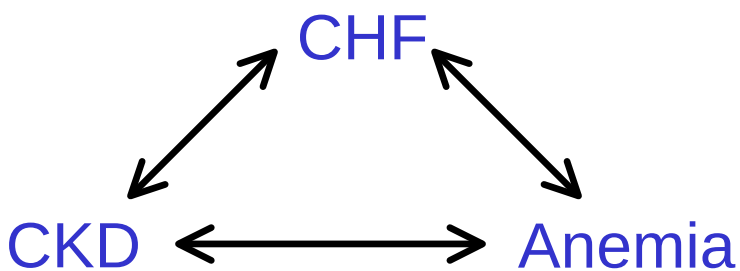
IRC E MALATTIE CV

- I pazienti con IRC hanno maggior rischio di malattia coronarica, CVD, AOCP e SCC
- Le malattie CV sono responsabili del 50-60% dei decessi dei pazienti con ESRD; il rischio è 15 volte quello della popolazione di controllo
- Questa associazione è molto spesso legata alla più elevata prevalenza di età avanzata, diabete, ipertensione, dislipidemia, iperomocisteinemia (*ASFAST Trial*)



UK CKD Guidelines, 2005

ANEMIA e IRC

- In pazienti anziani la riduzione della funzione renale (Clcrea < 50 ml/min) è il principale fattore correlato alla presenza di anemia, mediata dal deficit di EPO (studio NHANES III, *Blood, 2004*; studio InCHIANTI, *Arch Int Med, 2005*)
- Il trattamento con rHu EPO (80-120 U/Kg/w sc) in pazienti pre-dialisi riduce la necessità di emotrasfusioni, migliora le performances funzionali e non peggiora la funzione renale (*Cochrane Database Syst Review, 2005*)
- La terapia marziale EV, associata ad EPO, riduce la necessità di emotrasfusioni in un terzo dei pazienti pre-dialisi (*Nephrol Dial Transplant, 2001*)

EMODIALISI

- Nel ‘96 284 000 americani erano affetti da insufficienza renale terminale (ESRD): di questi il 62% era in emodialisi
- La maggior parte delle linee guida raccomanda di iniziare la “preparazione” alla terapia sostitutiva quando GFR>30 ml/min/1.73 m2 (interventi educazionali, informazione, accesso vascolare)
- L’indicazione ad iniziare l’emodialisi (e in generale la terapia sostitutiva) è la presenza di segni o sintomi di uremia; in genere questo accade con GFR $\leq$15 ml/min/1.73 m2

UK CKD Guidelines, 2005

CONCLUSIONI (I)

- L’insufficienza renale cronica è una condizione comune nell’adulto e nell’anziano
- I progressi nella terapia delle principali malattie responsabili, diabete e ipertensione, rendono ragione dell’aumento di incidenza di IRC, anche se tale aumento non si riflette sulla fase terminale della malattia
- Tutti i pazienti con queste malattie devono essere considerati a rischio di IRC (screening, calcolo GFR)

CONCLUSIONI (II)

- Esistono farmaci con evidenza di efficacia nel ridurre incidenza e progressione di IRC (Ace-inibitori)
- In tutti i pazienti vanno evitati i fattori in grado di peggiorare il danno (farmaci, disidratazione, ecc.)
- Vanno ricercate e trattate le possibili complicanze (anemia, osteodistrofia)

A BEN GUARDARE ANCHE LA VECCHIAIA HA IL SUO BELLO.
DEVO CAMBIARE OCCHIALI.