CHRONIC KIDNEY DISEASE

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CASE

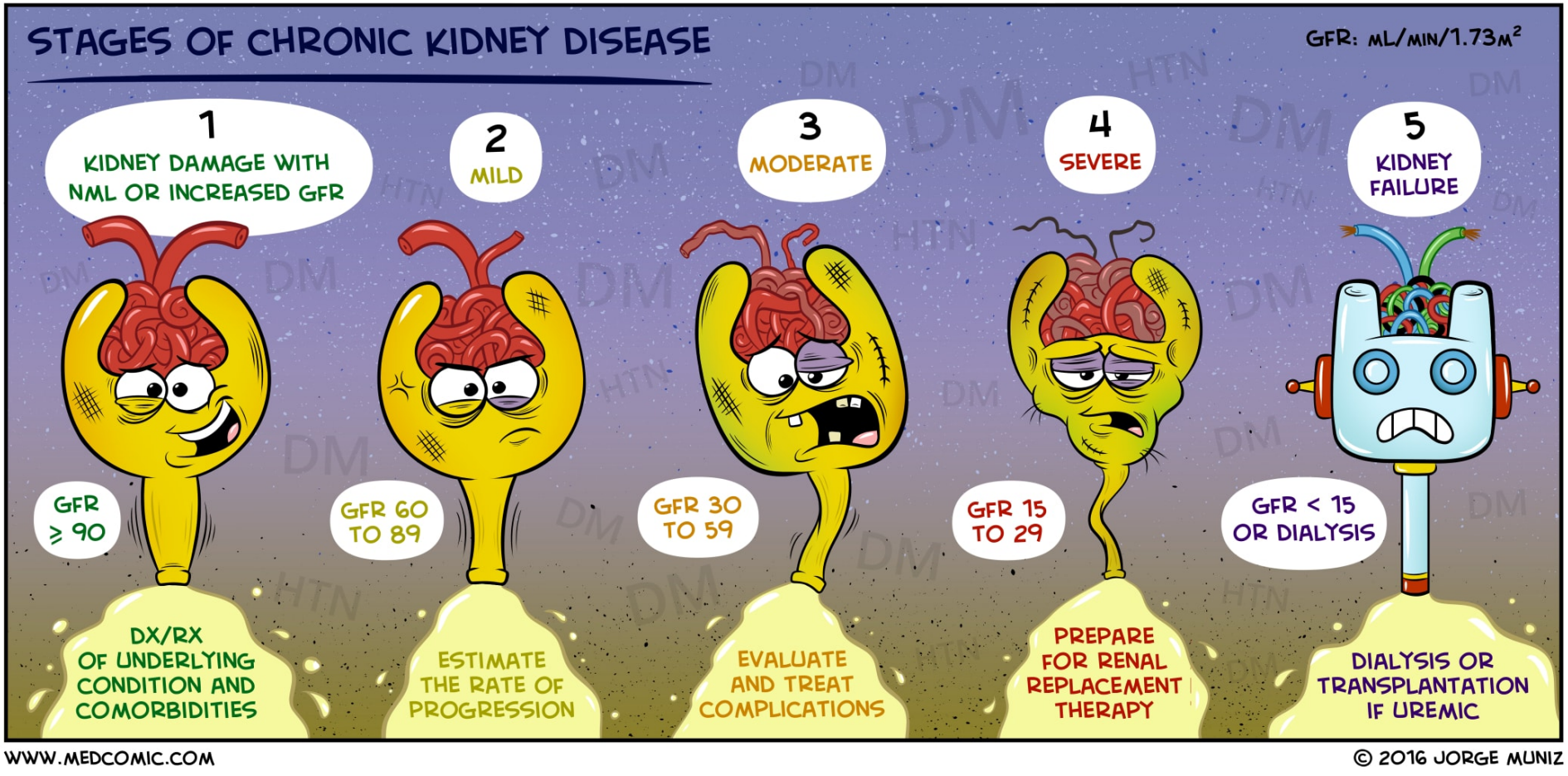
- 65 YEAR OLD FEMALE REFERRED WITH DIABETIC NEPHROPATHY, PROTEINURIA 3 G/DAY, EGFR 23
- DENIES NAUSEA, VOMITING, WEIGHT LOSS, ANOREXIA. DOES NOTE MEAT AVERSION
- MEDS AMLODIPINE & HCTZ
- BP 150/90, PERIPHERAL EDEMA
- LABS: HB 8.9, K 5.6, CA 7.0, $P0_4$ 6.0, PTH 300, LDL 140

DEFINITION OF CKD

KIDNEY DISEASE OUTCOME QUALITY INITIATIVE (K/DOQI)

- KIDNEY DAMAGE FOR ≥ 3 MONTHS, AS DEFINED BY STRUCTURAL / FUNCTIONAL ABNORMALITIES, WITH OR WITHOUT ↓ GFR, MANIFEST BY EITHER:
  - PATHOLOGICAL ABNORMALITIES; OR
  - MARKERS OF DAMAGE, INCLUDING ABNORMALITIES OF
    - BLOOD TESTS
    - URINE TESTS
    - IMAGING
- GFR ≤ 60 ML/MIN/1.73 M^2 FOR ≥ 3 MONTHS, WITH OR WITHOUT KIDNEY DAMAGE

STAGES OF CKD

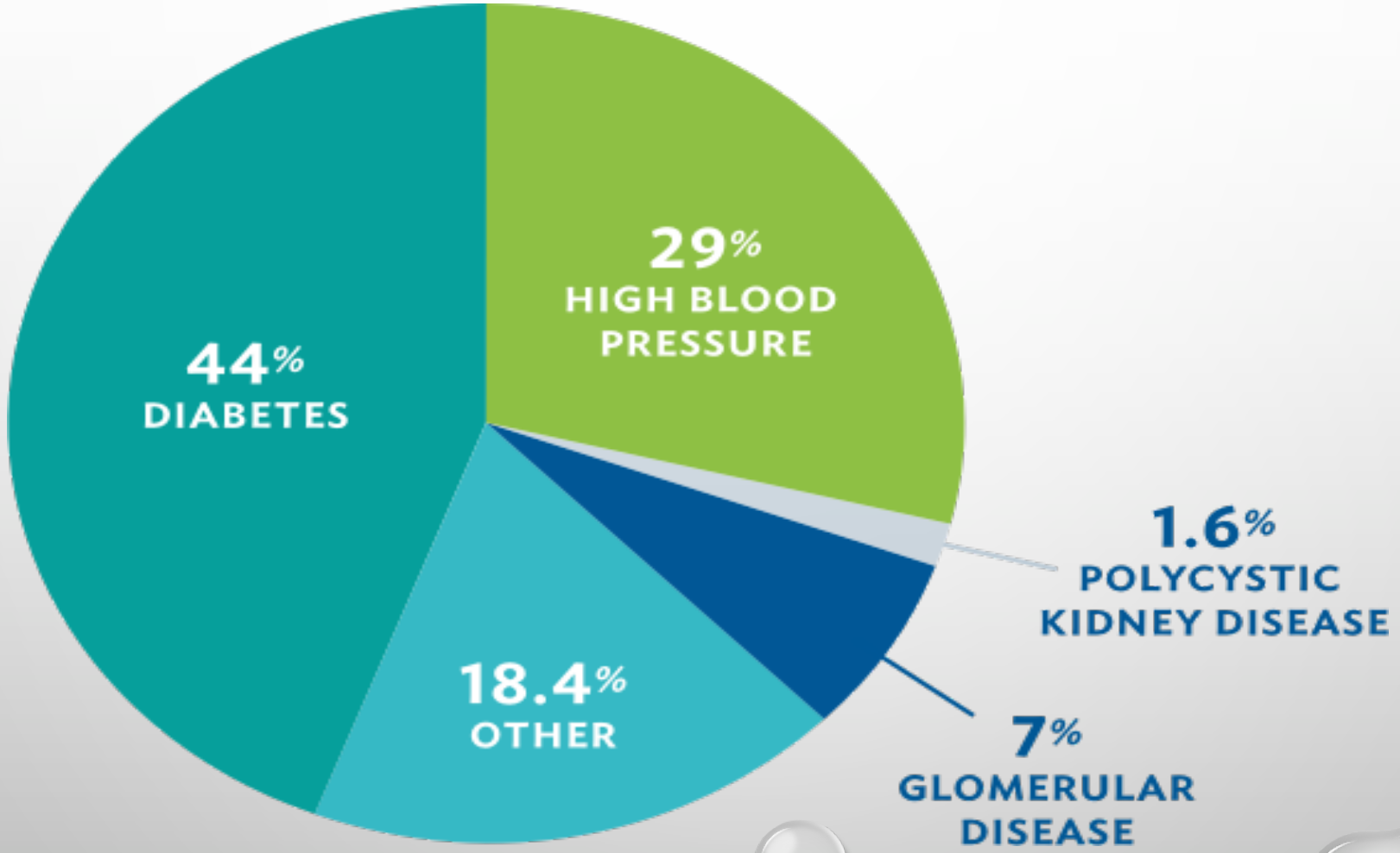


STAGES OF CKD

- STAGE 1 DISEASE
  - NORMAL GFR (≥ 90 ML/MIN)
  - PERSISTENT ALBUMINURIA OR HEMATURIA
- STAGE 2 DISEASE
  - GFR 60-89 ML/MIN
  - PERSISTENT ALBUMINURIA OR HEMATURIA
- STAGE 3 DISEASE
  - GFR 30-59 ML/MIN
- STAGE 4 DISEASE
  - GFR 15-29 ML/MIN
- STAGE 5 DISEASE
  - GFR < 15 ML/MIN OR ESRD

				Albuminuria stages, description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<3 mg/mmol	**3-29 mg/mmol**	**≥30 mg/mmol**
GFR stages, descriptions and range (ml/min per 1.73m^2)	Stage 1 (G1)	Normal or high	**≥90**			
	Stage 2 (G2)	Mildly decreased	**60-90**			
	Stage 3 (G3a)	Mildly to moderately decreased	**45-59**			
	Stage 3 (G3b)	Moderately to severely decreased	**30-44**			
	Stage 4 (G4)	Severely decreased	**15-29**			
	Stage 5 (G5)	Kidney failure	**<15**			

CAUSES OF CKD



PROGRESSION OF CKD

- GFR TENDS TO DECLINE PROGRESSIVELY OVER TIME .
- RATE OF GFR DECLINE SHOULD BE ASSESSED TO
  - PREDICT THE INTERVAL UNTIL THE ONSET OF ESRD .
  - ASSESS EFFECT OF INTERVENTIONS TO SLOW THE GFR DECLINE.
- AMONG PATIENTS WITH CKD, THE RATE OF DECLINE SHOULD BE ESTIMATED BY:
  - COMPUTING FROM PAST AND ONGOING MEASUREMENTS OF SERUM CREATININE;
  - ASCERTAINING RISK FACTORS FOR FASTER GFR DECLINE .
- INTERVENTIONS TO SLOW PROGRESSION SHOULD BE CONSIDERED IN ALL PATIENTS WITH CKD .

PROGRESSION OF CKD (CONT)

- MEASUREMENTS OF CREATININE FOR ESTIMATION OF GFR SHOULD BE OBTAINED AT LEAST YEARLY
- MORE OFTEN IN PATIENTS WITH:
  - GFR <60 ML/MIN/1.73 M^2;
  - FAST GFR DECLINE IN THE PAST (>4 ML/ MIN/1.73 M^2 PER YEAR);
  - RISK FACTORS FOR FASTER PROGRESSION;
  - ONGOING TREATMENT TO SLOW PROGRESSION;
  - EXPOSURE TO RISK FACTORS FOR ACUTE GFR DECLINE.

Initial injury
(GN, ATN, AIN, PCKD)

↓

Loss of renal parenchyma

↓

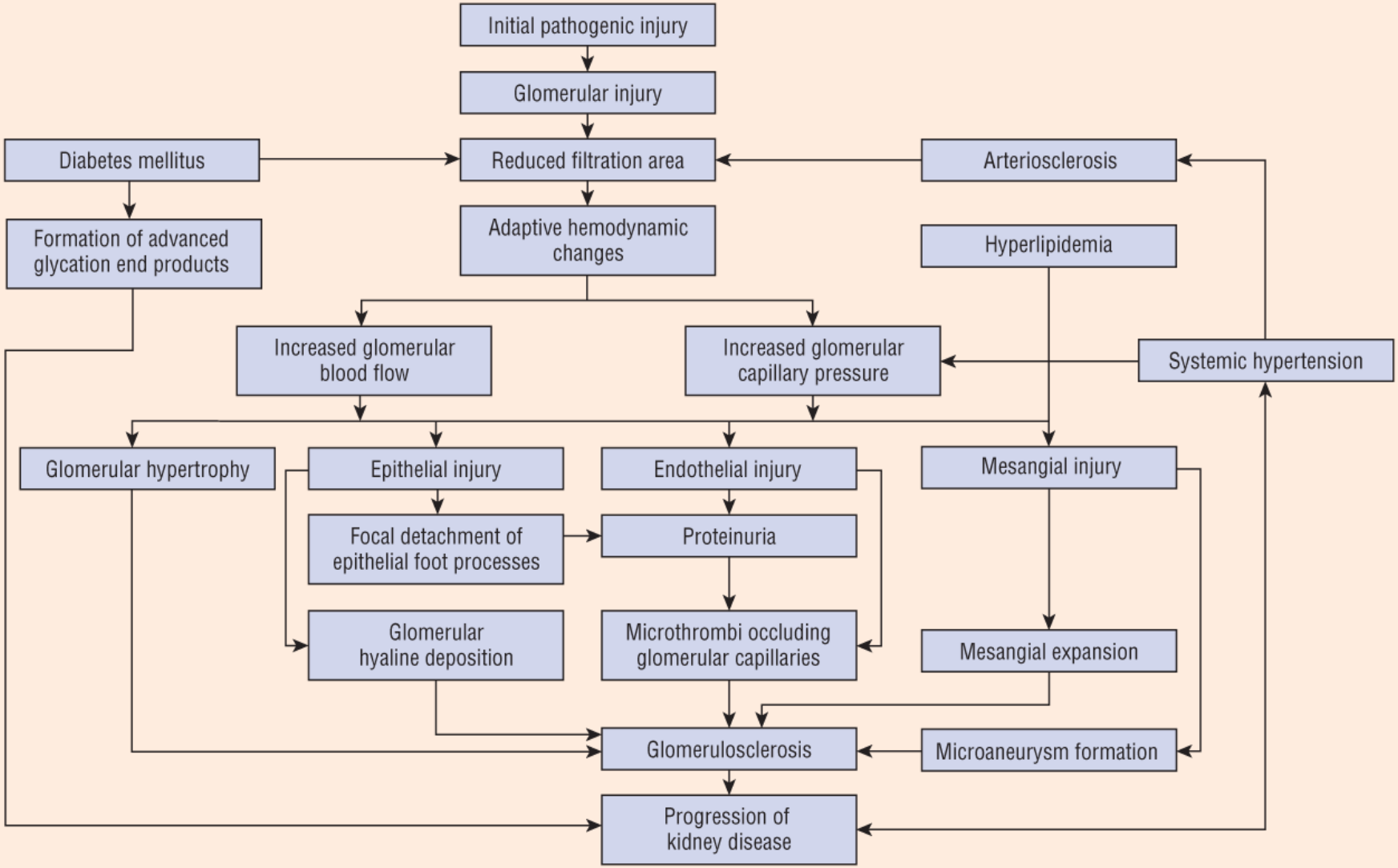
Adaptive hyperfiltration
(↑ P_{GC} → ↑ SNGFR → wall stress → ↑ TGFß)

↓

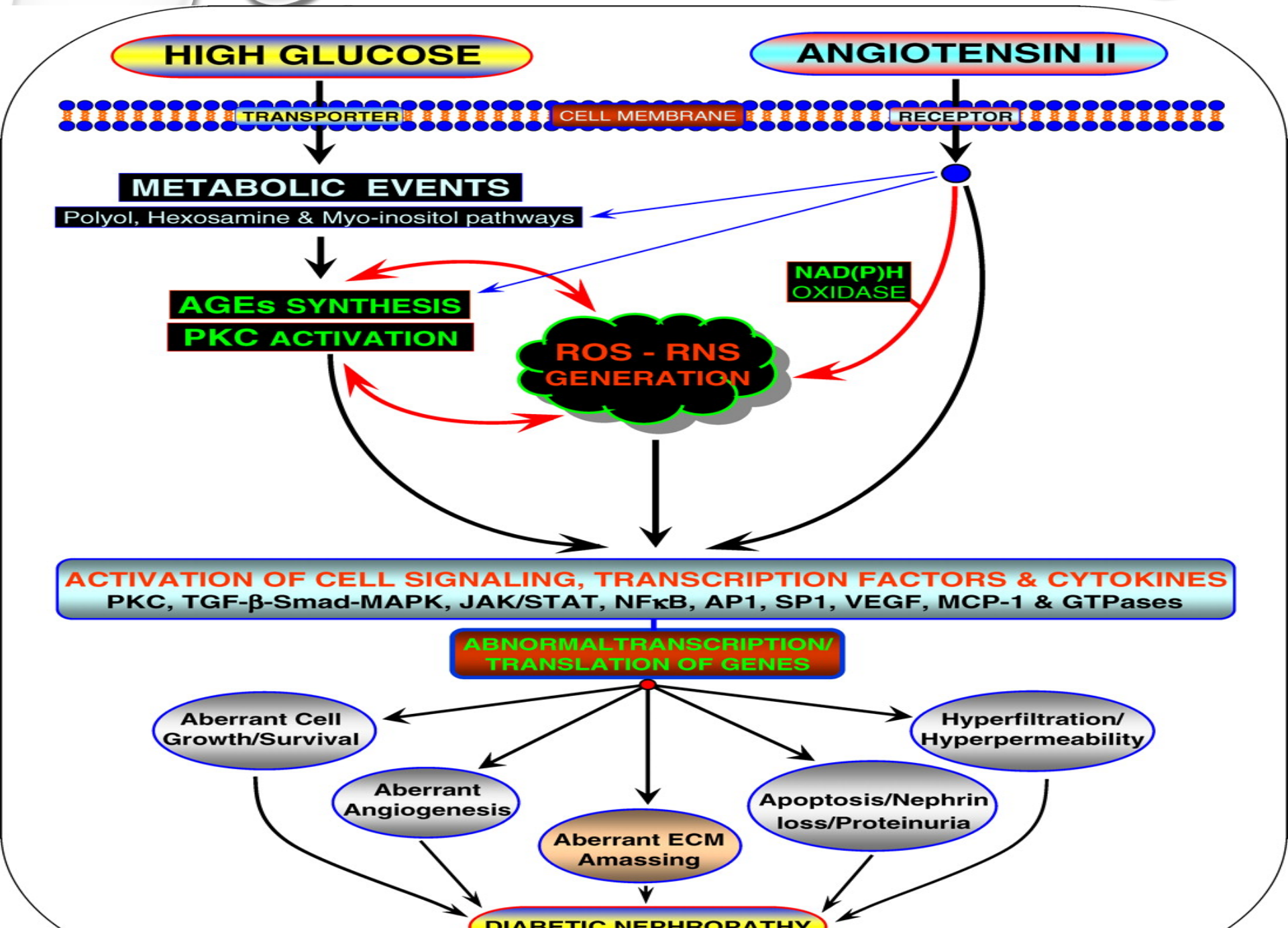
Long-term damage
to remaining nephrons

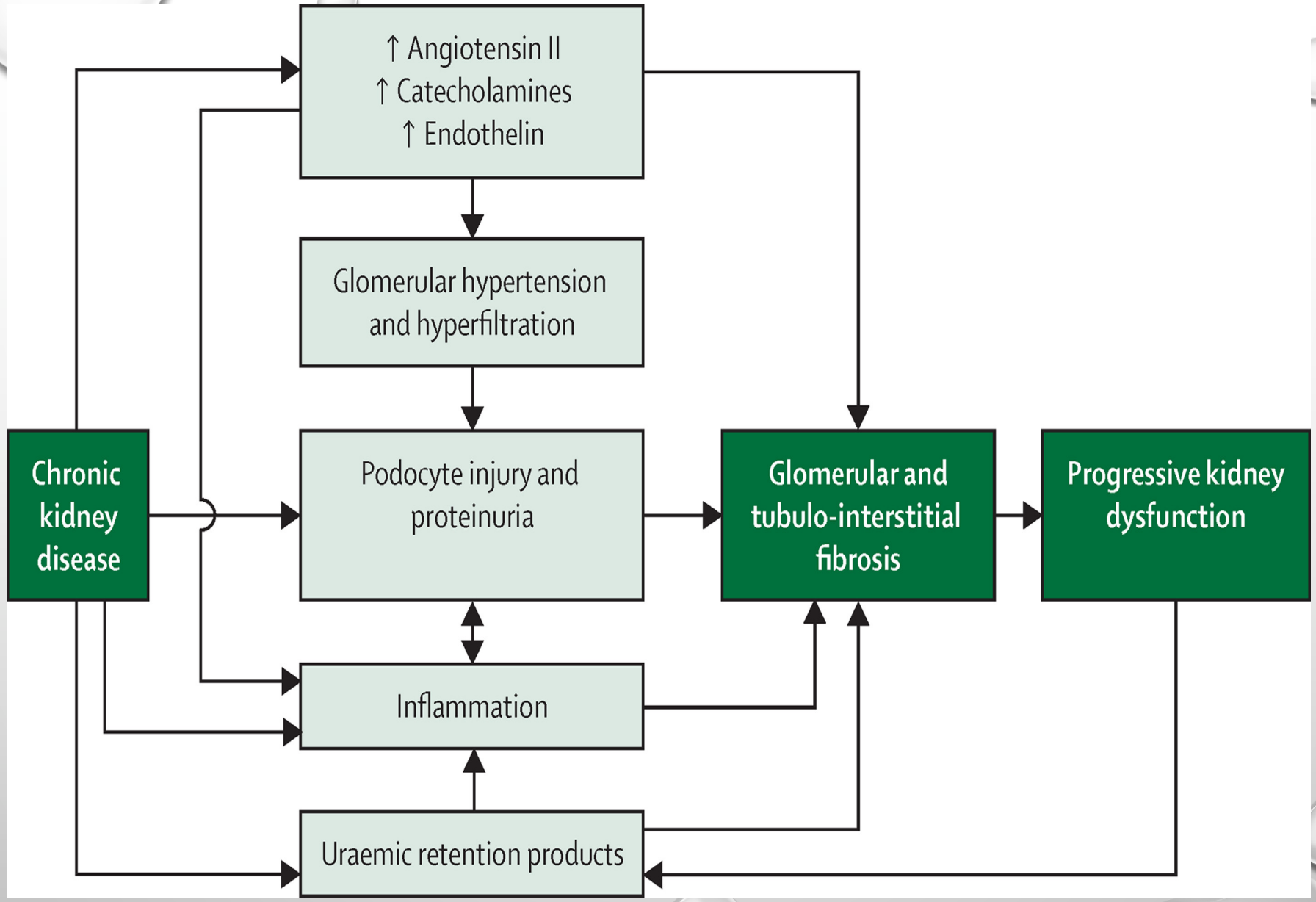
↓

Proteinuria,
progressive renal
insufficiency



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM:
Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:
www.accesspharmacy.com


HIGH GLUCOSE
ANGIOTENSIN II
TRANSPORTER
CELL MEMBRANE
RECEPTOR
METABOLIC EVENTS
Polyol, Hexosamine & Myo-inositol pathways
AGEs SYNTHESIS
PKC ACTIVATION
NAD(P)H OXIDASE
ROS - RNS GENERATION
ACTIVATION OF CELL SIGNALING, TRANSCRIPTION FACTORS & CYTOKINES
PKC, TGF-β-Smad-MAPK, JAK/STAT, NFκB, AP1, SP1, VEGF, MCP-1 & GTPases
ABNORMALTRANSCRIPTION/ TRANSLATION OF GENES
Aberrant Cell Growth/Survival
Aberrant Angiogenesis
Aberrant ECM Amassing
Apoptosis/Nephrin loss/Proteinuria
Hyperfiltration/ Hyperpermeability
DIABETIC NEPHROPATHY

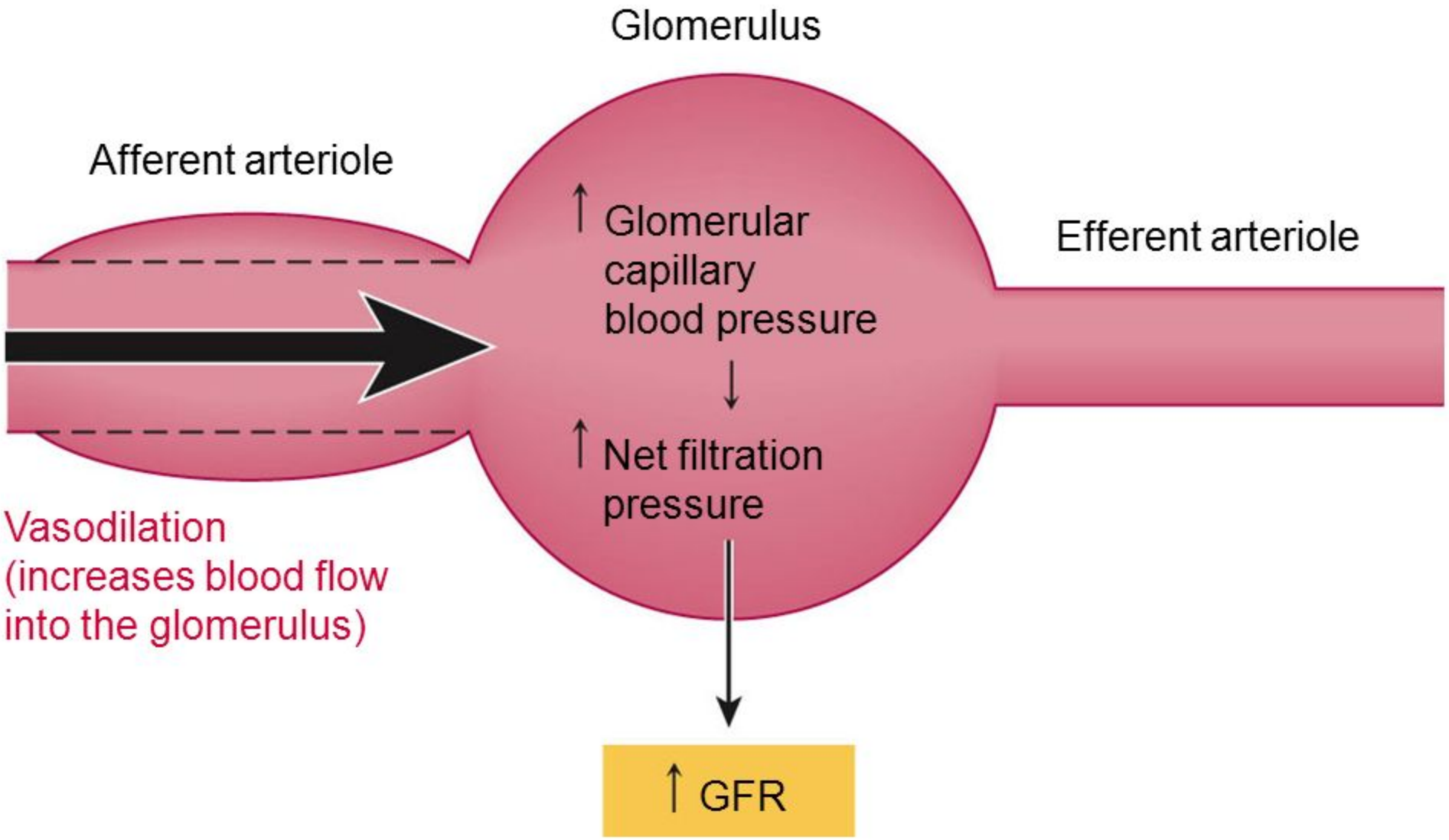

↑ Angiotensin II
↑ Catecholamines
↑ Endothelin
Glomerular hypertension and hyperfiltration
Chronic kidney disease
Podocyte injury and proteinuria
Glomerular and tubulo-interstitial fibrosis
Progressive kidney dysfunction
Inflammation
Uraemic retention products

CHANGES IN RENAL HEMODYNAMICS

- INTRAGLOMERULAR HYPERTENSION ($\uparrow P_{GC}$)
  - COMPENSATORY RESPONSE TO NEPHRON LOSS IN AN ATTEMPT TO MAINTAIN GFR
  - PRIMARY AFFERENT VASODILATATION
  - PRIMARY EFFERENT VASOCONSTRICTION

FALL IN GFR IS MINIMIZED BY ↑ P_{GC}

RESPONSE IS MEDIATED BY ↓ FLOW TO THE MACULA DENSA AND ACTIVATION OF TGF



(c) Arteriolar vasodilation increases the GFR

Figure 12-15c p580

MEASUREMENT OF GFR

- CREATININE
- EGFR (MDRD, COCKCROFT-GAULT)
- CREATININE CLEARANCE .
- CREATININE CLEARANCE + CIMETIDINE
- RADIONUCLIDE MARKERS .
- INULIN CLEARANCE .
- CYSTATIN C .

CHARACTERISTICS OF AN IDEAL MARKER

- CONSTANT PRODUCTION
- SAFE AND CONVENIENT
- READILY DIFFUSABLE IN ECF
- NO PROTEIN BINDING, FREELY FILTERABLE
- NO TUBULAR REABSORPTION OR SECRETION
- NO EXTRARENAL ELIMINATION OR DEGRADATION
- ACCURATE AND REPRODUCIBLE ASSAY
- MINIMAL INTERFERENCE WITH OTHER COMPOUNDS
- INEXPENSIVE

COCKCROFT-GAULT (140-AGE)*WT*1.2/CREATININE (X.85 IN WOMEN)

- DERIVED FROM MEASURED CREATININE CLEARANCE IN A SMALL POPULATION WITH CKD
- GIVES UNCORRECTED CREATININE CLEARANCE
- INCORPORATES AGE, WEIGHT, GENDER
- NO CORRECTION FOR BLACK RACE
- UNDER-ESTIMATES CREATININE CLEARANCE IN NORMAL PEOPLE

MDRD – SIMPLIFIED

- DERIVED FROM STUDY OF PEOPLE WITH KIDNEY DISEASE AT RISK OF PROGRESSION
- FACTORS FOR AGE, GENDER, RACE
- RESULT IS GFR IN ML/MIN/1.73 M^2
- EGFR =186 X (SCR X $.0113^{-1.154}$) X $AGE^{-0.203}$ WITH CORRECTIONS FOR BLACK/FEMALE
- UNDER-ESTIMATES GFR IN NORMALS
- NOT VALIDATED IN ASIANS, OLD AGE

LIMITATIONS OF EGFR

- MDRD STUDY EQUATION IS REASONABLY ACCURATE IN NON-HOSPITALIZED PATIENTS KNOWN TO HAVE CKD.
- THE COCKCROFT-GAULT EQUATION IS LESS ACCURATE IN INDIVIDUALS ABOVE OR BELOW IDEAL BODY WEIGHT
- THE MDRD AND COCKCROFT-GAULT EQUATIONS ARE LESS ACCURATE IN POPULATIONS WITH NORMAL OR NEAR NORMAL GFR
- ESTIMATION EQUATIONS MAY BE LESS ACCURATE IN POPULATIONS OF DIFFERENT ETHNICITIES AND FROM OUTSIDE OF THE US.

CYSTATIN C

- NON-GLYCOSYLATED 13-KDA PROTEIN .
- MEMBER OF FAMILY OF CYSTEINE PROTEASE INHIBITORS .
- SYNTHESIZED BY ALL NUCLEATED CELLS .
- ENDOGENOUS PRODUCTION RATE IS CONSTANT .
- FREELY FILTERED BY THE GLOMERULUS .
- CATABOLIZED IN THE PROXIMAL TUBULE CELL .
- NOT INFLUENCED BY DIET, CONSTITUTIONAL FACTOR
- INVESTIGATIONAL .

INVESTIGATION OF CKD

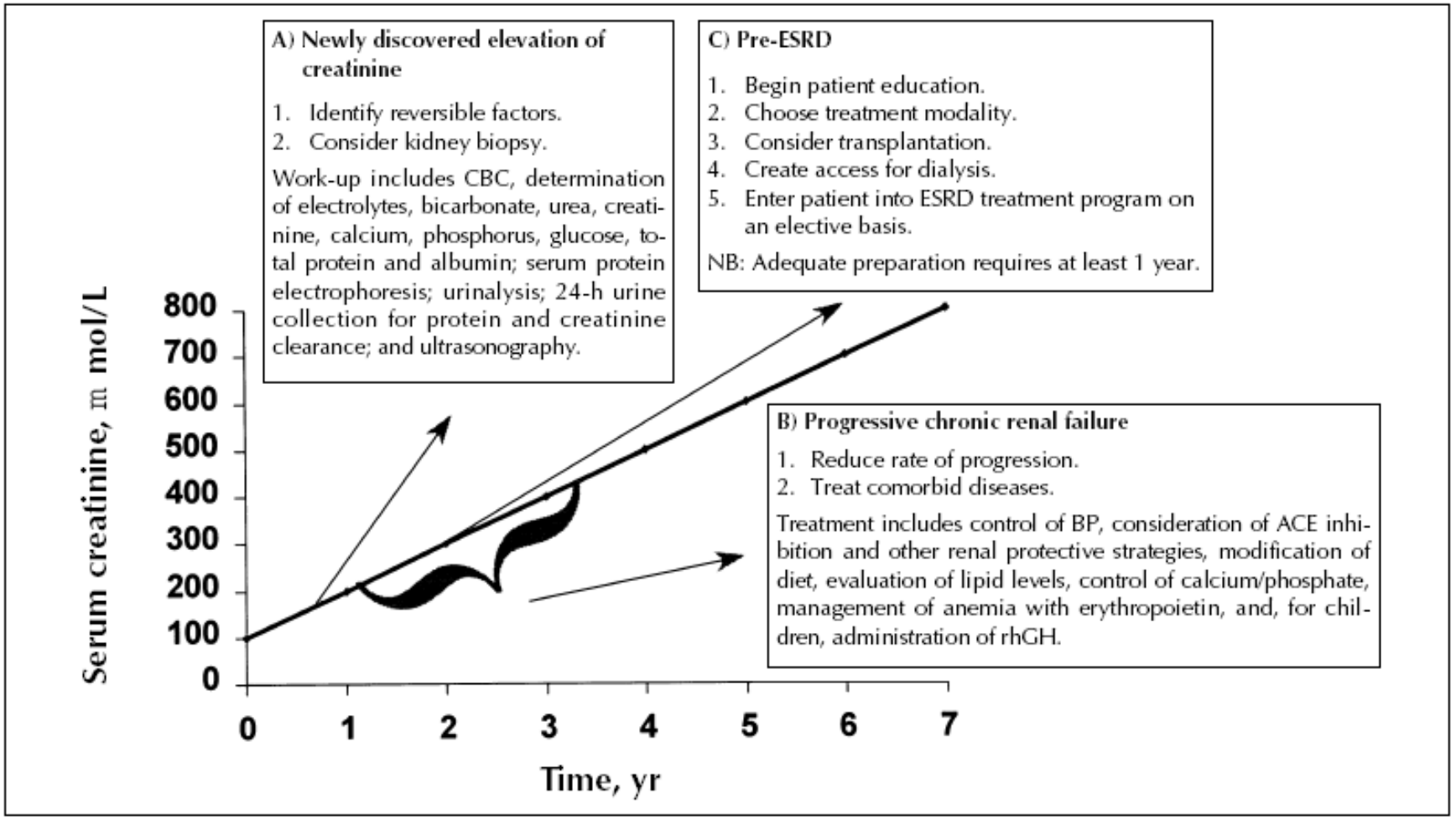
- ACUTE OR CHRONIC:
  - URINALYSIS – LOOK FOR HEMATURIA, PROTEINURIA, RBC CASTS (ACTIVE URINE)
  - KIDNEY SIZE (USEFUL IF SMALL)
  - PREVIOUS SERUM CREATININE VALUES
  - HEMOGLOBIN, MINERAL METABOLISM
  - FOLLOW-UP SERUM CREATININE

INVESTIGATION OF CKD

WHO TO BIOPSY?

- EARLY > LATE
- YOUNG > OLD (HEREDITARY NEPHRITIS, FABRY ETC.)
- HEMATURIA > BLAND
- HEAVY PROTEINURIA > NONE .
- NORMAL KIDNEY SIZE > SMALL .
- NO EXPLANATION FOR CKD > HYPERTENSION, VASCULAR DISEASE, DIABETES .

APPROACH TO DIAGNOSIS AND TREATMENT AT THREE STAGES



FACTORS IMPLICATED IN PROGRESSION

- SYSTEMIC HYPERTENSION .
- PROTEINURIA .
- HYPERLIPIDEMIA .
- DIETARY PROTEIN .
- ANGIOTENSIN II, ALDOSTERONE .
- METABOLIC ACIDOSIS .
- HYPERPHOSPHATEMIA .
- HYERURICEMIA .

GENERAL MANAGEMENT OF CKD

- TREATMENT OF REVERSIBLE CAUSES .
- PREVENTING / SLOWING PROGRESSION .
- TREATMENT OF COMPLICATIONS .
- IDENTIFICATION, EDUCATION, PREPARATION OF PATIENTS WHO WILL REQUIRE RRT .

PREVENTING PROGRESSION

- ↓ PROTEIN EXCRETION
  - TARGET = < 0.5 TO 1 G/DAY (PCR < 60)
  - REGIMENS SHOULD INCLUDE ACEI OR ARB
  - IF TARGET IS NOT REACHED, COMBINE ACEI AND ARB
- ↓ BLOOD PRESSURE
  - TARGET = < 130/80
  - REGIMENS SHOULD INCLUDE ACEI OR ARB
  - IF TARGET NOT REACHED, ADD DIURETICS, ADDITIONAL MEDS

PREVENTING PROGRESSION

- OTHER THERAPEUTIC MODALITIES (LESS EVIDENCE)
  - ↓ PROTEIN INTAKE TO 0.8 TO 1.0 G/KG/DAY
  - TREATMENT OF HYPERLIPIDEMIA
  - TREATMENT OF METABOLIC ACIDOSIS
    - TARGET HCO_3 = 22 MMOL/L
  - SMOKING CESSATION

COMPLICATIONS OF CKD

- ECFV OVERLOAD
  - SODIUM RESTRICTION
  - DIURETIC THERAPY
- HYPERKALEMIA
  - LOW K+ DIET
  - DIURETICS
  - KAYEXALATE
- METABOLIC ACIDOSIS
  - TARGET HCO_3 = 22 MMOL/L
  - SODIUM BICARBONATE 0.5-1 G PO BID OR TID .

COMPLICATIONS OF CKD

- HYPERPHOSPHATEMIA:
  - BEGINS ~ STAGE 3 CKD
  - TARGET = 0.87 AND 1.49 MMOL/L
  - LOW PO_4 DIET
  - PO_4 BINDERS ($CACO_3$, SEVELAMER)
- RENAL OSTEODYSTROPHY:
  - PTH INCREASES ~ STAGE 2, 3 CKD
  - TARGET DEPENDS ON GFR (AVOID $\downarrow$ PTH $\rightarrow$ ADYNAMIC BONE DISEASE)
  - PO_4 BINDERS
  - VIT D_3 DECREASES WITH STAGE 3 CKD
  - CALCITRIOL 0.25 MG/DAY

COMPLICATIONS OF CKD

- HYPERTENSION
  - TARGET BP < 130/80
  - ACEI AND/OR ARB
  - LOOP DIURETIC, NON-DIHYDROPERIDINE CCB
- ANEMIA
  - COMMON WITH ≥ STAGE 3 CKD
  - TARGET HB ?
  - EXCLUDE NON-RENAL CAUSES
  - TREAT WITH ERYTHROPOIETINS AND IRON SUPPLEMENTATION

WHEN TO REFER TO A NEPHROLOGIST

- POTENTIAL BENEFITS OF EARLY REFERRAL
  - INFORMED SELECTION OF DIALYSIS MODALITY
  - TIMELY PLACEMENT OF APPROPRIATE DIALYSIS ACCESS
  - NON-EMERGENT INITIATION OF DIALYSIS
  - LOWER MORBIDITY AND IMPROVED REHABILITATION
  - LESS FREQUENT AND SHORTER HOSPITAL STAYS
  - LOWER COST
  - IMPROVED SURVIVAL
  - PREEMPTIVE TRANSPLANT

WHEN TO REFER TO A NEPHROLOGIST

- ACUTE RENAL FAILURE
- EGFR < 30 ML/MIN
- PROGRESSIVE LOSS OF RENAL FUNCTION
- PERSISTENT PROTEINURIA
  - PRESENT ON 2 OF 3 SAMPLES
  - PCR > 60 (CORRESPONDS TO > 500 MG/DAY)
- INABILITY TO ACHIEVE RECOMMENDED TARGETS FOR BLOOD PRESSURE
- INABILITY TO INITIATE RENO-PROTECTIVE STRATEGIES

DEFINITION OF LATE REFERRAL

- WHEN MANAGEMENT COULD HAVE BEEN IMPROVED BY EARLIER CONTACT WITH RENAL SERVICES.
- WITHIN ONE TO SIX MONTHS OF THE REQUIREMENT FOR RENAL REPLACEMENT THERAPY

PREPARING FOR DIALYSIS

- PRE-DIALYSIS CARE IS RECOMMENDED TO BEGIN AT STAGE 4 CKD (EGFR $\leq$ 30 MLS/MIN)
- IDEAL TIME IN PRE-DIALYSIS CARE IS 1 YEAR TO ALLOW FOR
  - MODALITY EDUCATION
    - SHOULD BE PROMOTING AUTONOMY, SELF MANAGEMENT $\rightarrow$ SELECTION OF HOME MODALITIES IN A MAJORITY OF PATIENTS
  - PLACEMENT OF BODY ACCESS
    - VASCULAR ACCESS FOR HD MUST BE PLACED ~ 3 MONTHS PRIOR TO HD INITIATION TO ALLOW MATURITY
    - PD CATHETER MUST BE PLACED ~ 1 WEEK PRIOR TO INITIATION OF PD

WHEN TO INITIATE DIALYSIS

- REFRACTORY FLUID OVERLOAD, CHF EXACERBATION
- HYPERKALEMIA (K >6) UNCONTROLLED BY DIET AND/OR KAYEXALATE
- SIGNS OF UREMIA
- METABOLIC ACIDOSIS UNCONTROLLED BY SODIUM BICARBONATE
- ?EGFR

WHAT ARE CHOICES FOR PATIENTS WITH STAGE 5 CKD?

- PRE-EMPTIVE LIVING DONOR TRANSPLANT
  - SIB, SPOUSE, PARENT, CHILD, FRIEND
- HOME-BASED DIALYSIS TREATMENT:
  - PERITONEAL DIALYSIS
  - HOME HEMODIALYSIS (NOCTURNAL)
- CENTER HEMODIALYSIS
  - HOSPITAL, CLINIC
  - SELF CARE

HEMODIALYSIS

- 3 POSSIBLE SCHEDULES
  - CONVENTIONAL – 4 H, 3 DAYS/WEEK
  - SHORT DAILY – 2-3 H, 4-6 DAYS/WEEK
  - NOCTURNAL – 6-8 H, 3-6 DAYS/WEEK
- ACCESS TO CIRCULATION
  - ARTERIOVENOUS FISTULA
  - ARTERIOVENOUS GRAFT
  - INTERNAL JUGULAR CUFFED CATHETER (UC CATHETER)

PERITONEAL DIALYSIS

- PD CATHETER
- 2 SCHEDULES
  - CAPD – 4-5 EXCHANGES OF 2-2.5 L/D
  - CCPD – CYCLER ASSISTED OVERNIGHT DIALYSIS PLUS DAYTIME DWELL

CASE

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