Diagnosis and Treatment of systemic amyloidosis, MM

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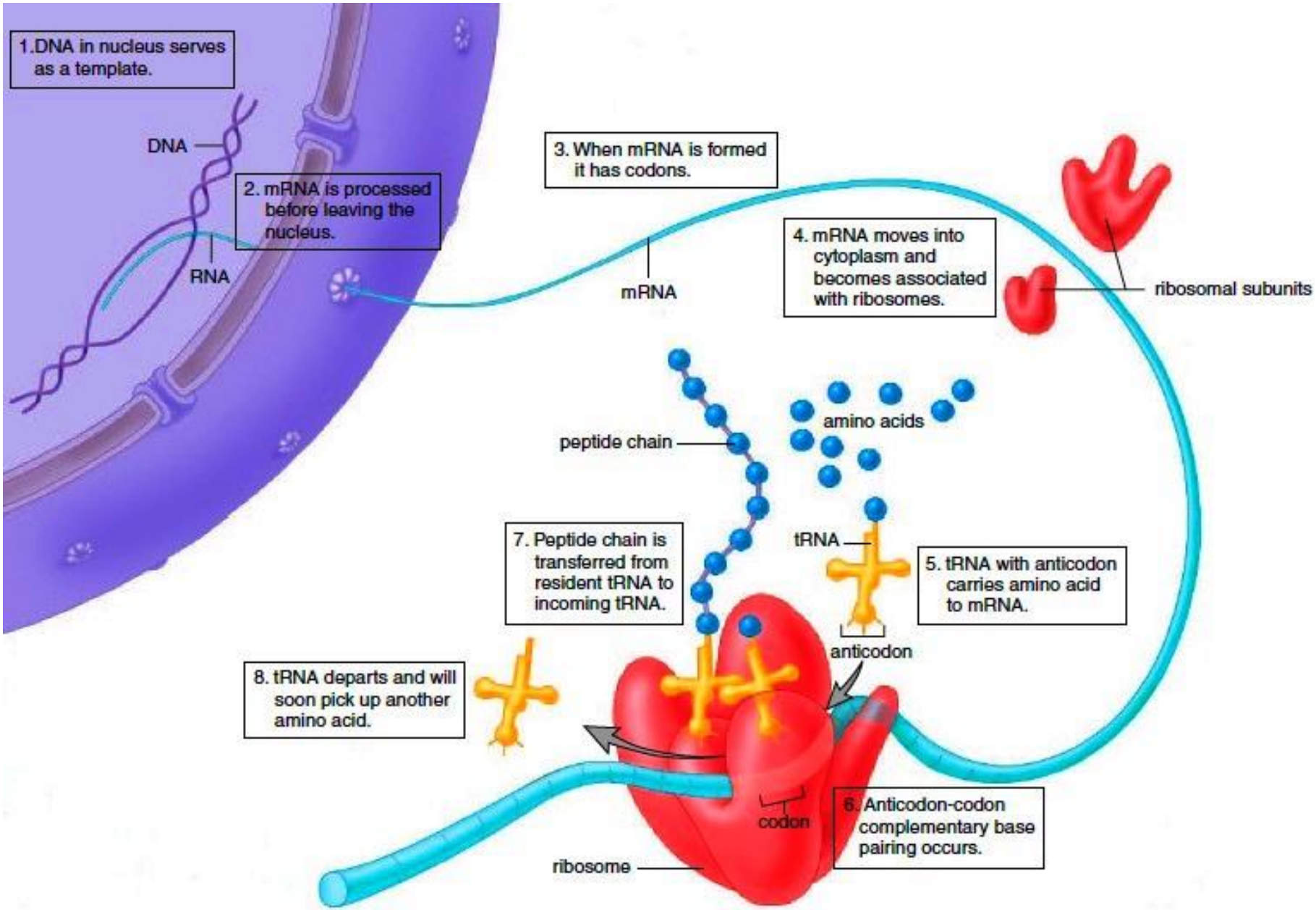
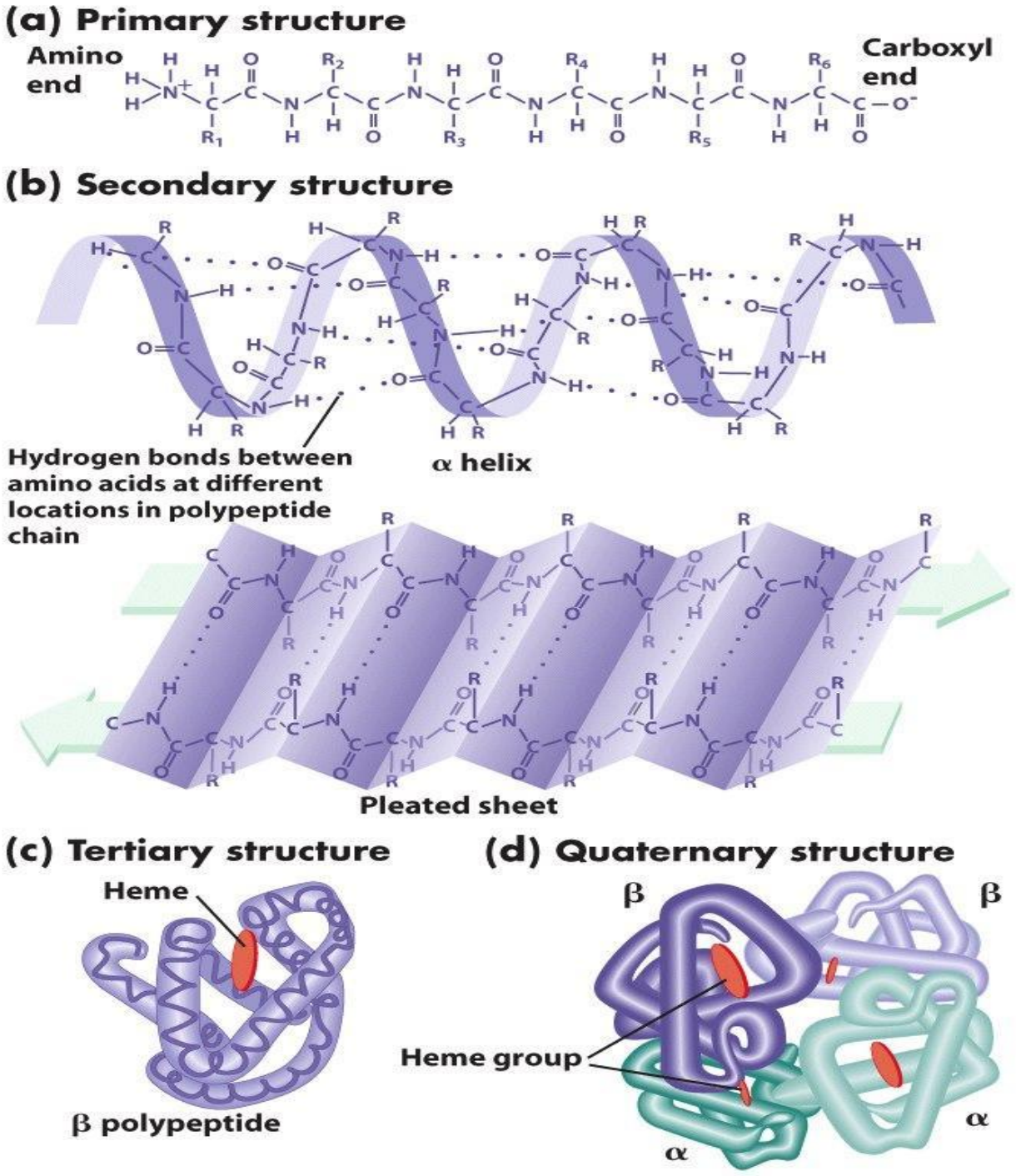
Disease of Protein misfolding

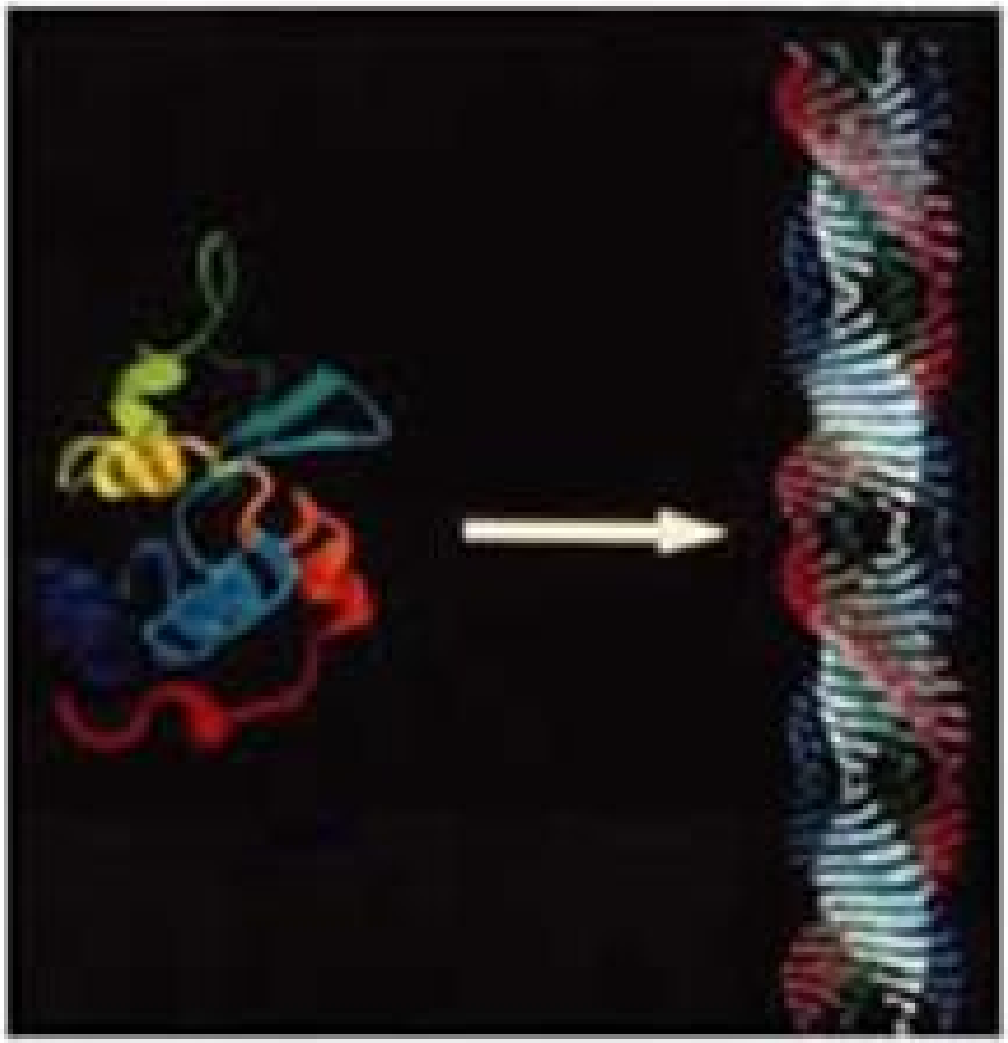
PATHOGENESIS

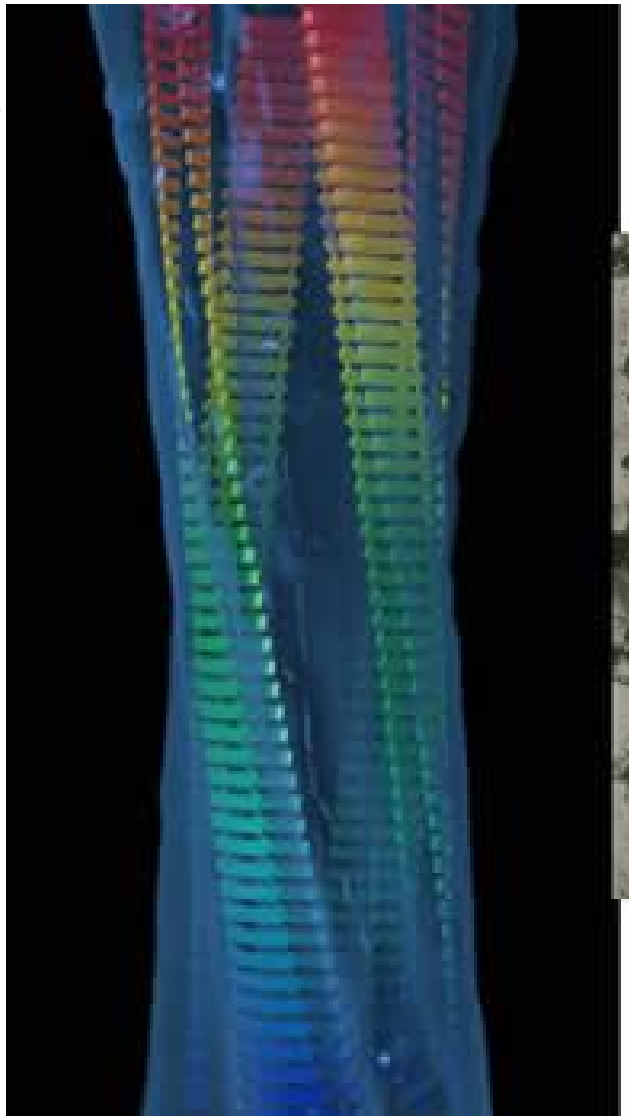
- Protein misfolding and aggregation
- insoluble fibril formation
- accumulation in extracellular space
- organ dysfunction
- death

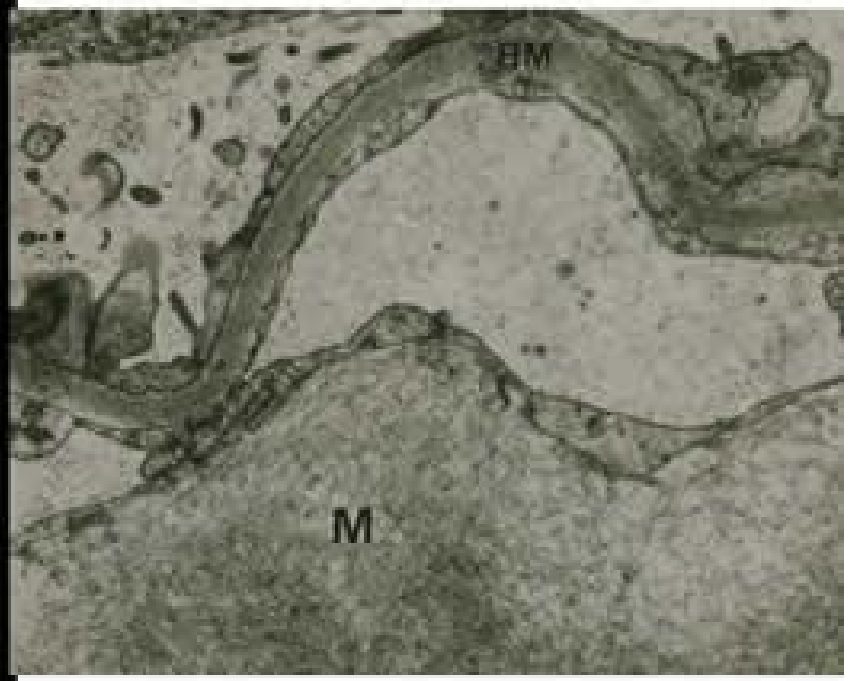
Protein Synthesis




(a) Primary structure
Amino end
Carboxyl end
(b) Secondary structure
Hydrogen bonds between amino acids at different locations in polypeptide chain
α helix
Pleated sheet
(c) Tertiary structure
Heme
β polypeptide
(d) Quaternary structure
β
β
Heme group
α
α






BM
M

- 0.8 per million per year
- Renal involvement:
  - Immunoglobulin light-chain associated (AL) in two-thirds
  - Secondary (amyloid A (AA) amyloidoses in >90%
  - In patients over the age of 60 years old as many as 10% to 20% of patients with presumed idiopathic nephrotic syndrome will have amyloidosis on renal biopsy.

- Predominant glomerular deposition:
  - proteinuria (75%, mild to massive) usually in the nephrotic range
  - benign urine sediment
  - plasma creatinine concentration normal or only moderately elevated
  - End-stage renal disease develops in approximately 20 percent of those with the nephrotic syndrome with
  - poor overall patient survival

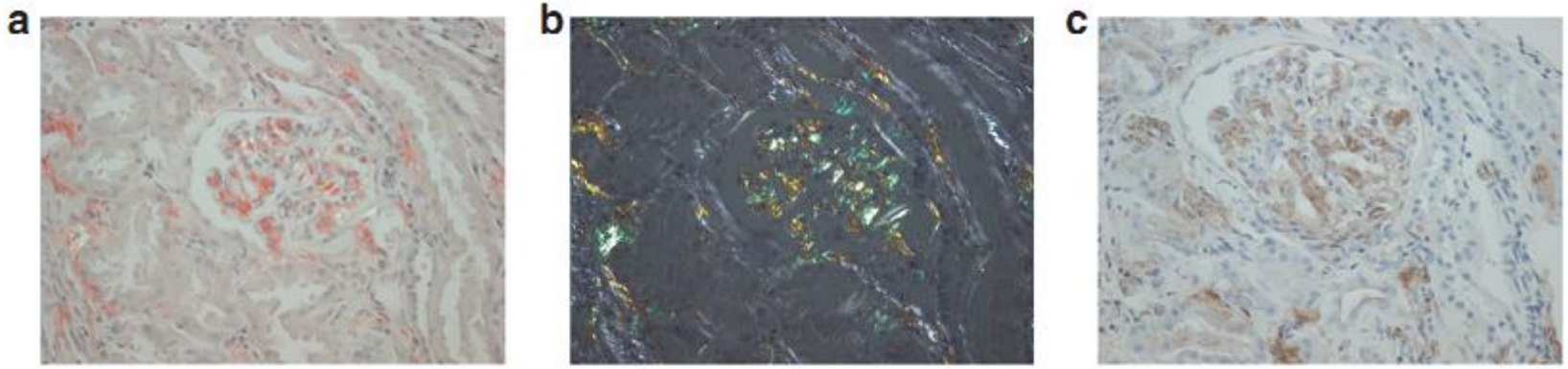
- *Vessels*:
  - slowly progressive chronic kidney disease with little or no proteinuria and more favorable prognosis

- *Heavy tubular deposition:*
  - Type 1 RTA, NDI, and acquired Fanconi syndrome in rare cases

- More than 30 different amyloid fibril precursor proteins are known in humans, but all fibril types essentially share a ***similar ultrastructure***.

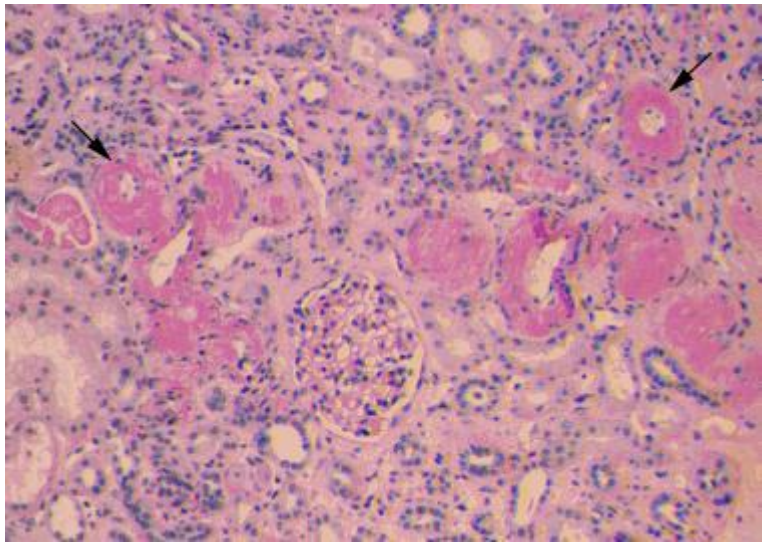
- The acquired highly characteristic b-pleated conformation of amyloid fibrils is associated with specific biophysical properties, including the ability to bind Congo red dye in a spatially ordered manner that produces diagnostic ***green birefringence*** when viewed under cross-polarized light.

- Under electron microscopy, amyloid deposits appear as randomly arranged, rigid ***nonbranching fibrils of ~10 nm*** in diameter and of indeterminate length.

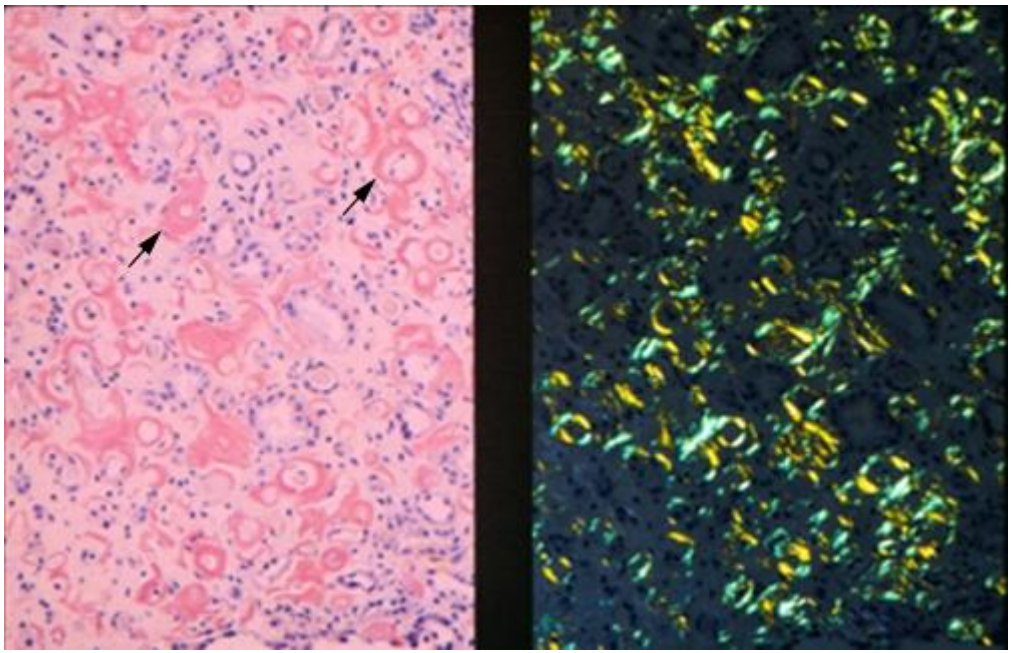


Sections of a renal biopsy sample were stained with Congo red dye and viewed at x200 magnification. (a) Amorphous deposits of eosinophilic material are visible within the glomerulus. (b) Pathognomonic green birefringence of amyloid deposits is visible when viewed under cross-polarized light. (c) Immunostaining of the amyloid deposits with anti-k antibodies was strongly positive (brown stain).

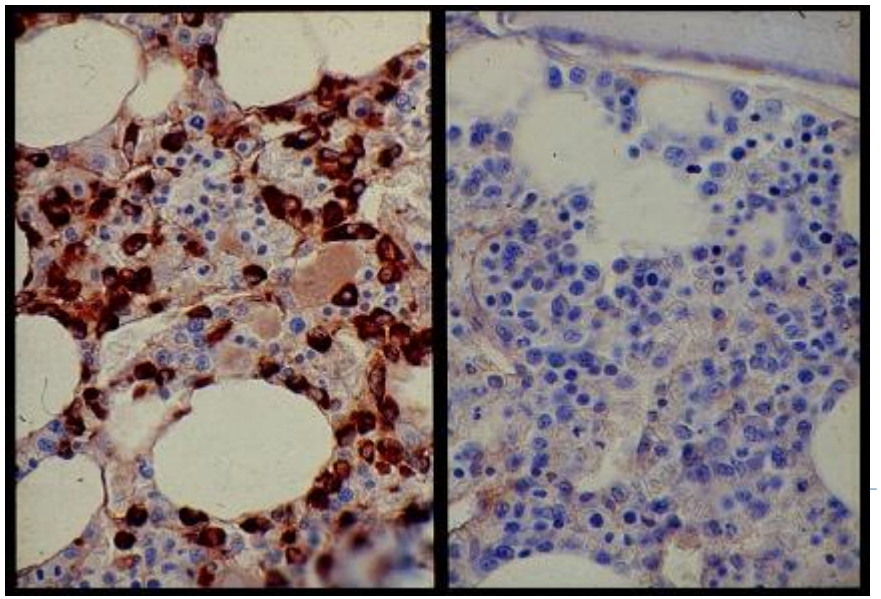
Vascular renal amyloidosis



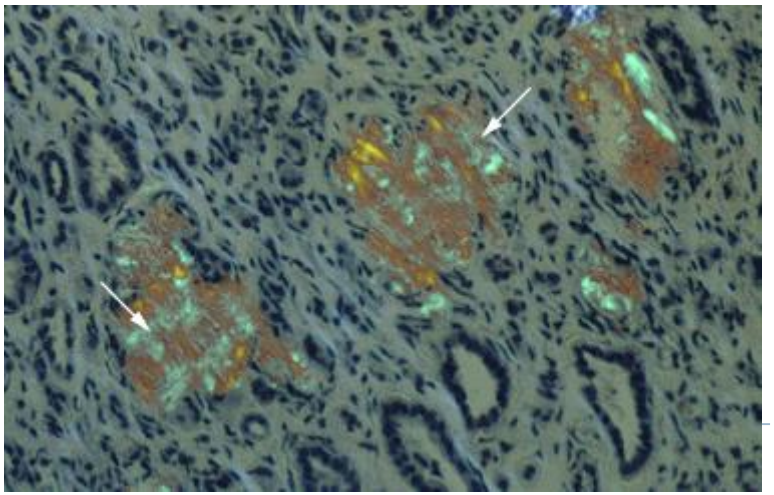
Renal tubular amyloidosis



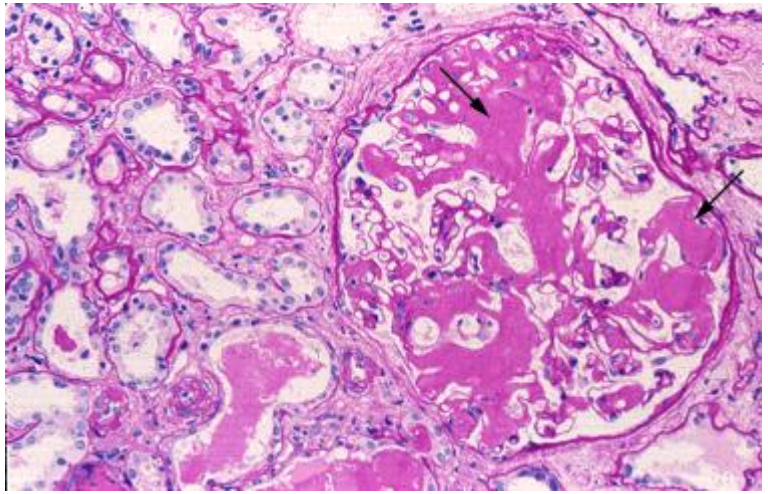
Monoclonal plasma cells in primary amyloidosis



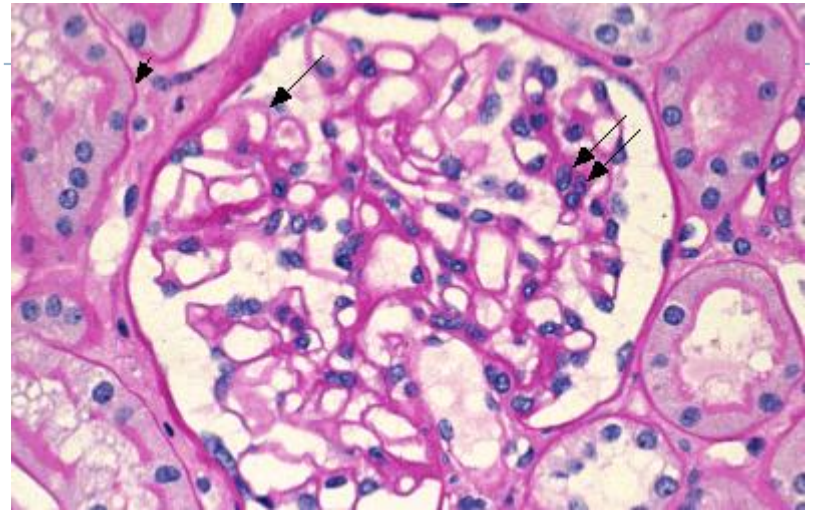
Congo red stain in amyloidosis



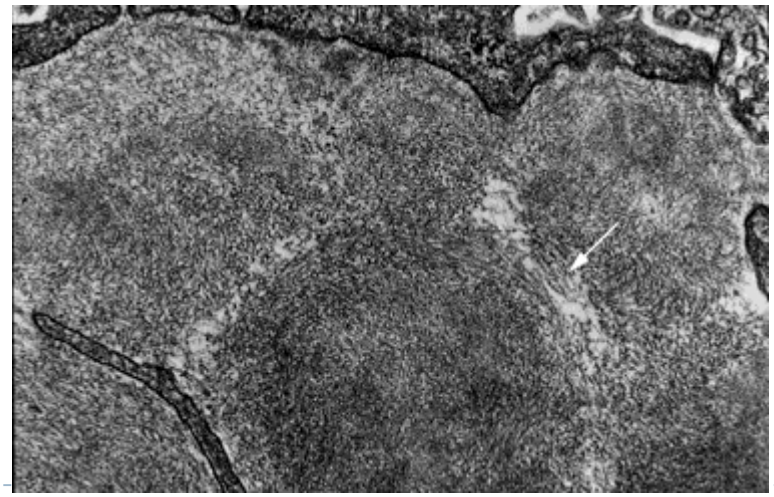
Glomerular amyloidosis



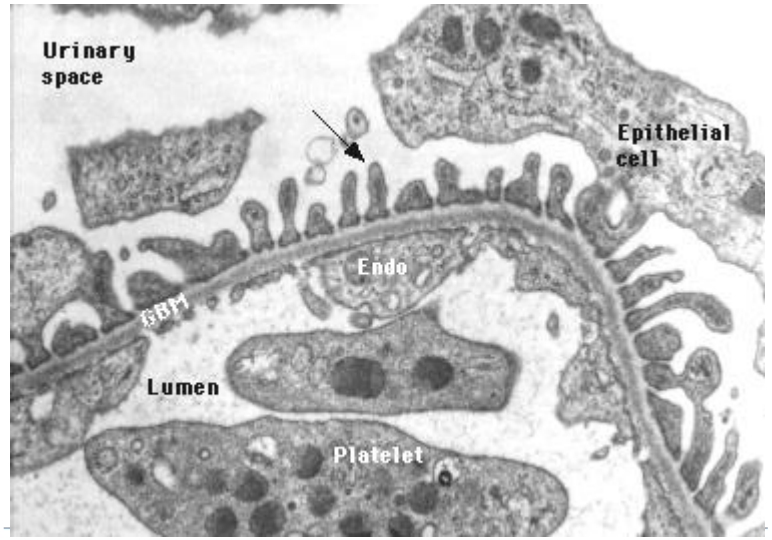
Normal glomerulus



Renal amyloidosis



Normal glomerulus



accurate identification of the protein

causing the amyloidosis is of paramount importance

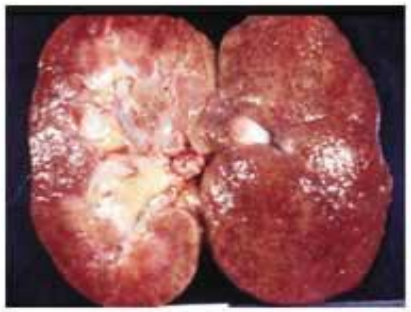
- Ideally, ***immunofluorescence on fresh tissue*** or, failing that, ***immunohistochemistry on fixed sections*** should be used to distinguish between the different types.

- ***Genetic testing*** is invaluable in diagnosing and excluding the known hereditary forms of amyloidosis

- Fibril typing by ***mass spectrometry*** is increasingly used when immunostaining fails to provide definitive results. (specific sampling by laser microdissection (LMD) and analytical power of tandem mass spectrometry (MS)–based **proteomic analysis**)

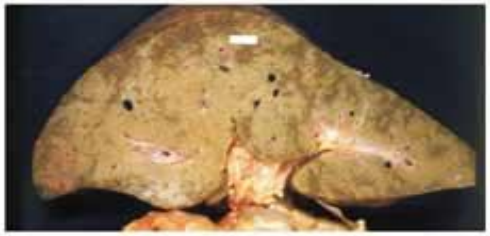
Mass spectometry only if clinically indicated (two potential amyloid precursor proteins), patients with monoclonal gammopathies who are:

- African-American
- Elderly men
- Dominant peripheral or autonomic neuropathy
- Family histories of amyloidosis
- Coexisting inflammatory disorders

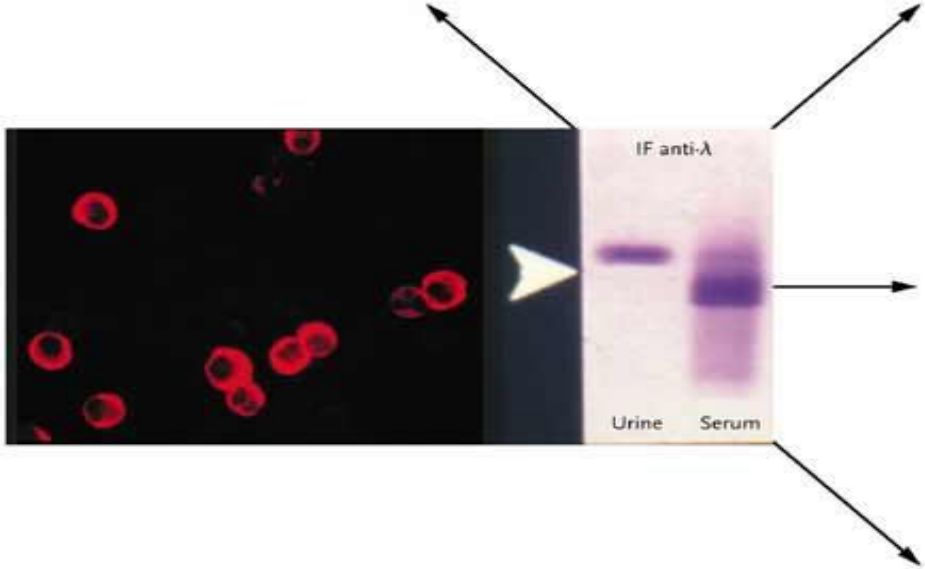


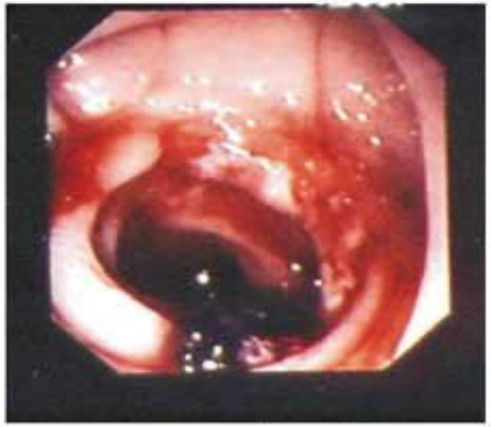
Kidney (46%)

Heart (30%)

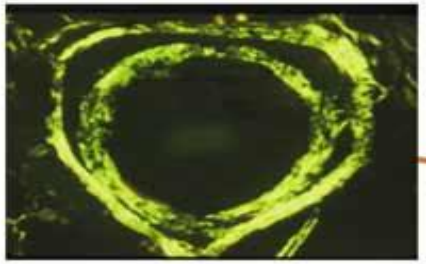


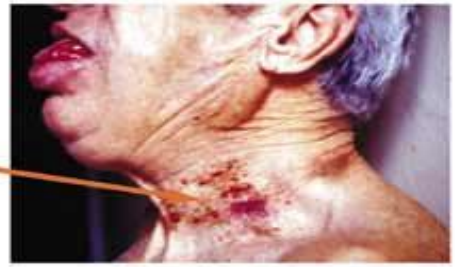
Liver (9%)





Gastrointestinal tract (7%)





Soft tissues (3%)

Peripheral nervous system (5%)

CLINICAL MANIFESTATIONS
Cardiomyopathy

- Systolic or diastolic dysfunction, heart failure
- Syncope due to arrhythmia or heart block
- Angina or infarction
  - due to accumulation of amyloid in the coronary arteries

Gastrointestinal disease

- Hepatomegaly (with or without splenomegaly)
- Bleeding
- (due to vascular fragility and loss of vasomotor responses to injury)
- Gastroparesis
- Constipation
- Bacterial overgrowth
- Malabsorption
- Intestinal pseudo-obstruction
  - resulting from dysmotility

Neurologic abnormalities

Mixed sensory and motor peripheral neuropathy and/or autonomic neuropathy :

- Symptoms of numbness, paresthesia, and pain
- Compression of peripheral nerves
  - carpal tunnel syndrome
- Symptoms of bowel or bladder dysfunction
- Findings of orthostatic hypotension
  - treatment with compression stockings, fludrocortisone, and in some midodrine

Neurologic abnormalities

- Central nervous system involvement is unusual
- **Cerebral amyloid angiopathy**
  - can cause spontaneous cortical and subcortical intracranial bleeding, primarily in the elderly

Musculoskeletal disease

- Muscles pseudohypertrophy
- Macroglossia or lateral scalloping of the tongue
  (from impingement on the teeth, characteristic of AL amyloid)
- Arthropathy
  (due to amyloid deposition in joints and surrounding structures)
- “Shoulder pad" sign

(visible enlargement of the anterior shoulder due to fluid in the glenohumeral joint and/or amyloid infiltration of the synovial membrane and surrounding structures)

Hematologic abnormalities

Bleeding diathesis :

- Factor X deficiency

(due to binding on amyloid fibrils primarily in the liver and spleen)

- Decreased synthesis of coagulation factors

(in patients with advanced liver disease)

- Amyloid infiltration of blood vessels
- Acquired von Willebrand disease

Pulmonary disease

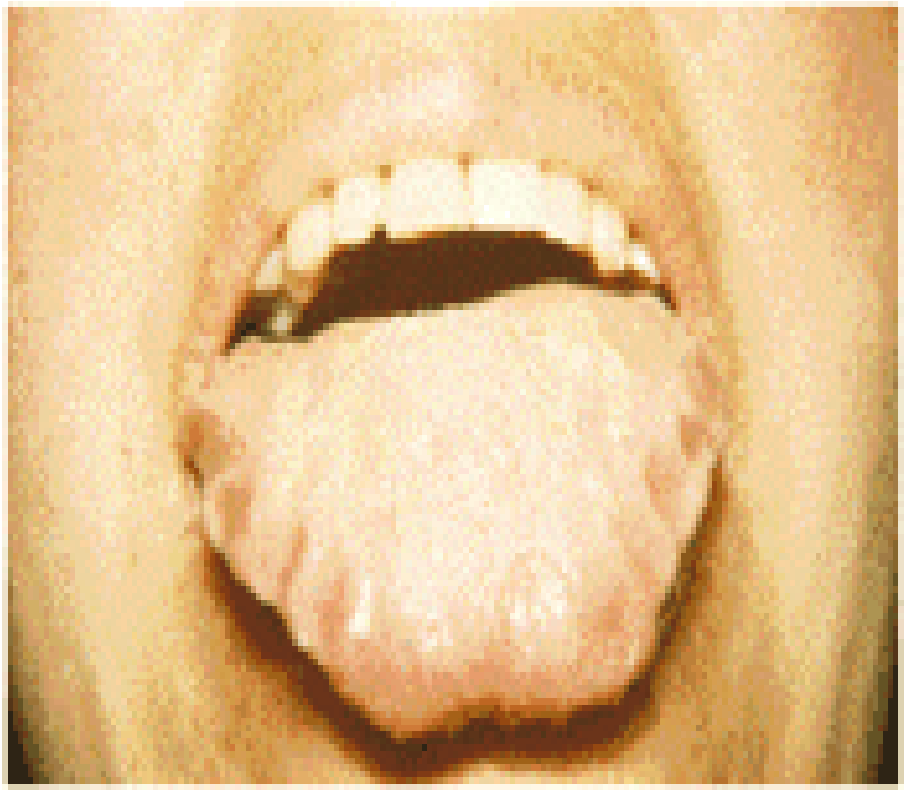
- Persistent pleural effusions
- Parenchymal nodules (amyloidomas)
- Pulmonary hypertension (rarely)
- Tracheobronchial infiltration:
  - hoarseness, stridor, airway obstruction, and dysphagia
    - bronchoscopic or surgical resection of airway abnormalities

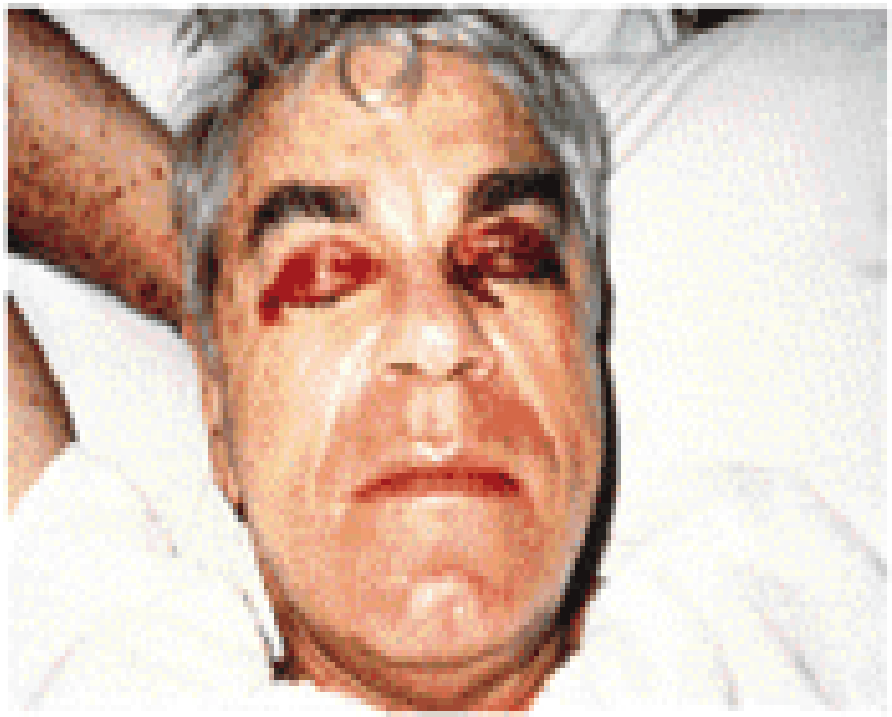
Pulmonary disease

- Persistent *pleural effusions:*
  - pleural infiltration with amyloid deposits in 1-2 percent of patients with poor prognosis
  - cardiomyopathy

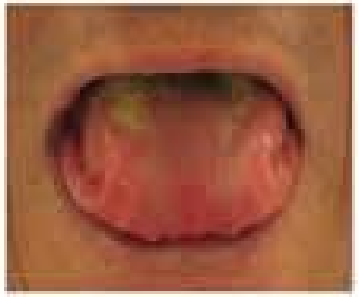
Skin involvement

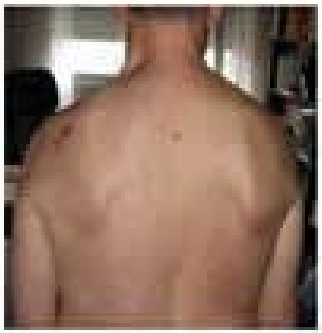
- Waxy thickening
- Easy bruising (ecchymoses)
- Subcutaneous nodules or plaques
- Raccoon eyes:
  - purpura, characteristically elicited in a periorbital distribution by a valsalva maneuver or minor trauma
  - present in only a minority of patients
  - highly characteristic of AL amyloidosis

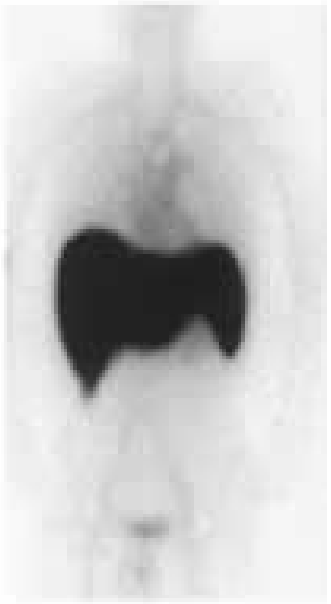


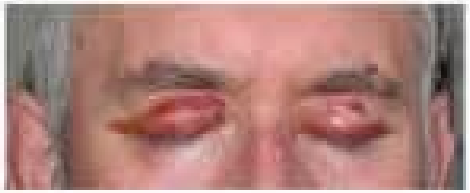


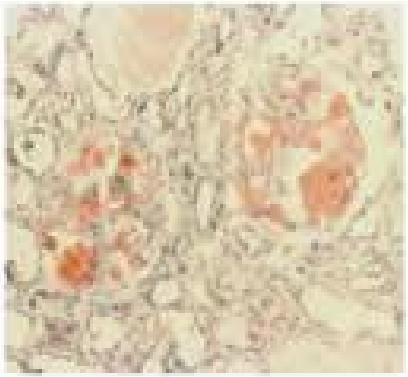
AL Amyloidosis : clinical

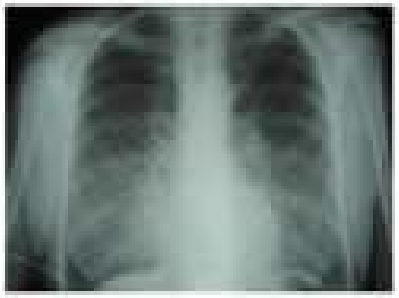


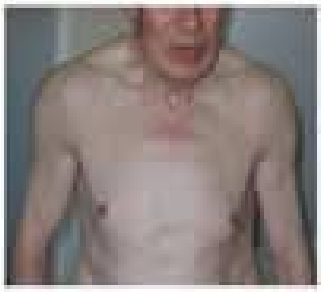












Initial Diagnostic Workup

Clinical and amyloid-related assessment

- Orthostatic vital signs
- History and physical

Laboratory evaluation (directed toward commonly affected organ systems):

- CBC and differential
- Prothrombin time (PT), Partial thromboplastin time (PTT), Factor X (if indicated)
- Hereditary amyloid testing (for African-American and Peripheral neuropathy patients at minimum)
- Electrophoresis of serum and urine
- Serum free light chains
- 24- hour urinary protein and creatinine clearance
- Blood urea nitrogen, creatinine
- Brain natriuretic peptide (BNP) or NT-proBNP, troponin
- Alkaline phosphatase, liver enzymes, bilirubin

Pathologic evaluation:

- Bone marrow aspirate and biopsy with Immunohistochemical staining for kappa and lambda and Congo red staining for amyloid
- Abdominal fat pad aspirate or involved organ biopsy as clinically indicated
- Mass spectrometry as clinically indicated

Special testing based on organ system involvement:

- *Cardiac*
  - EKG
  - Echocardiogram
  - Cardiac MRI (in certain circumstances)
  - Chest X-ray
- *Liver and GI tract*
  - Stool guaiacs
  - Gastric emptying scan (if gastroparesis present)
  - Ultrasound or CT scan to document craniocaudal Liver span
- *Peripheral nervous system*
  - EMG (if clinically significant peripheral neuropathy)
  - Nerve conduction studies
- *Other*
  - Endocrine testing: TSH, cortisol
  - Pulmonary testing: pulmonary function tests

Laboratory Tests Used to Detect M-proteins

- Serum protein electrophoresis (SPEP)
- Urine protein electrophoresis (UPEP)
- Immunofixation (IF)(quantitative immunoglobulins)
- Serum free light chain assays

- Screening by serum electrophoresis alone may be inadequate, as it does not show a monoclonal spike in nearly 50% of cases.

- Therefore, all patients should undergo ***immunofixation electrophoresis of both serum and urine***, which could detect a monoclonal (M) component.

- The measurement of circulating serum free light chain (**FLC**) is a powerful diagnostic complement as the majority of patients with light chain amyloidosis will have ***abnormalities of the kappa or lambda chains or the kappa/lambda ratio***. Additionally the FLC analysis is necessary to determine the ***hematologic response to therapy*****.**

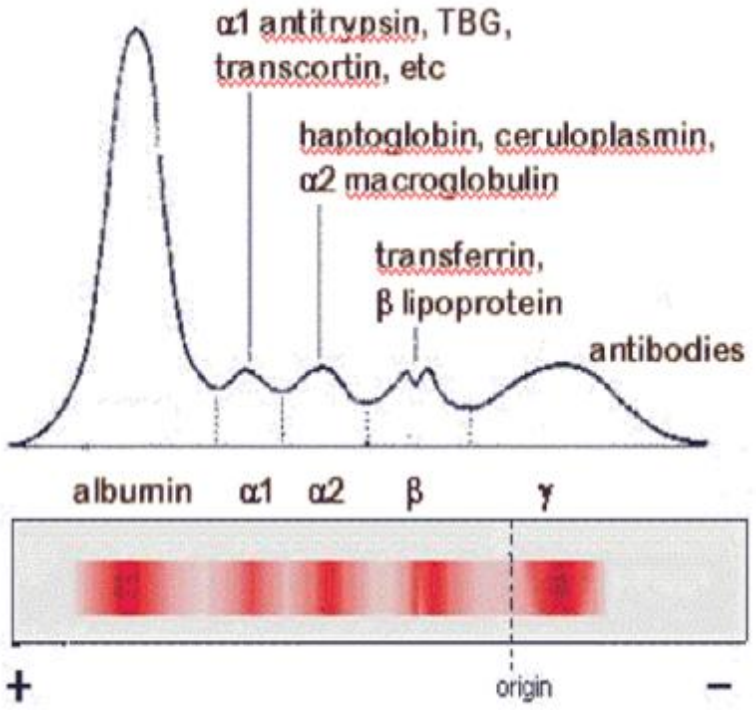
- Free light chains are cleared by the kidney therefore ***renal insufficiency*** increases the concentrations of FLC. In that case, the ***kappa/lambda ratio or the difference between involved and uninvolved free light chains*** should be monitored.

NL-SPEP

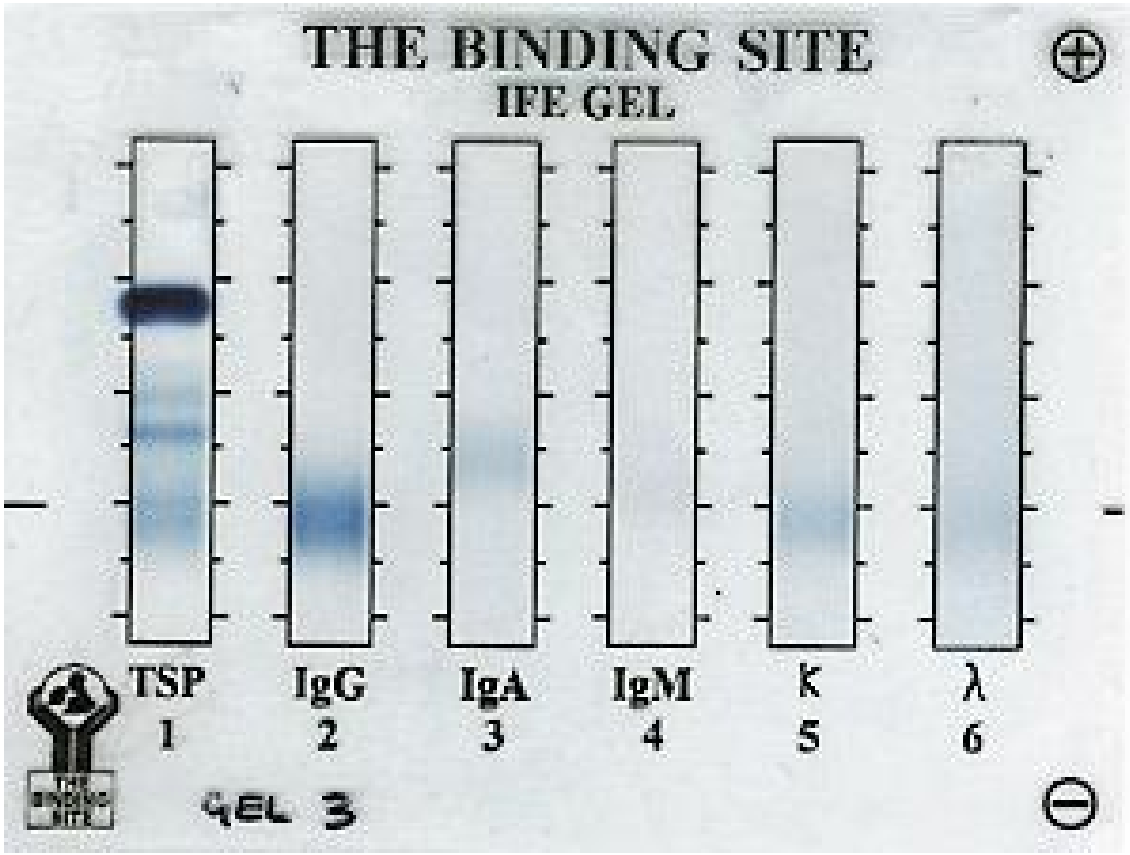
NL RANGE

- Albumin:3.3-5.7g/dl
- α-1: 0.1-0.4 g/dl
- α -2: 0.3-o.9 g/dl
- β-2: 0.7-1.5 g/dl
- gamma: o.5-1.4 g/dl

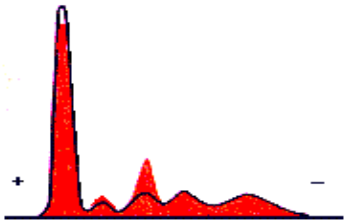
SPEP



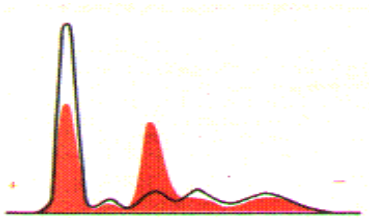
NL- IF

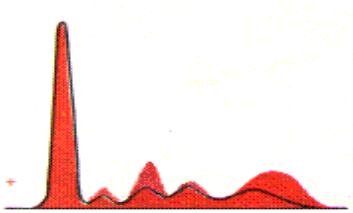


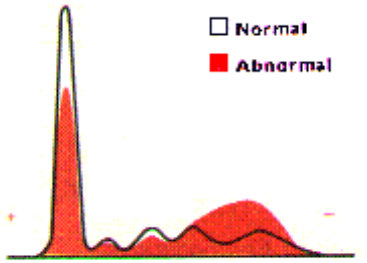
Different patterns of SPEP



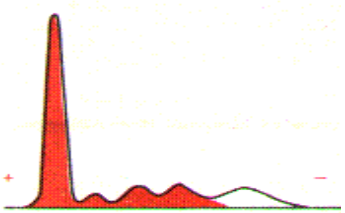
Acute Inflammation

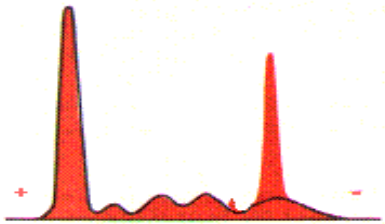

NEPHROTIC SYNDROME


Chronic Inflammation

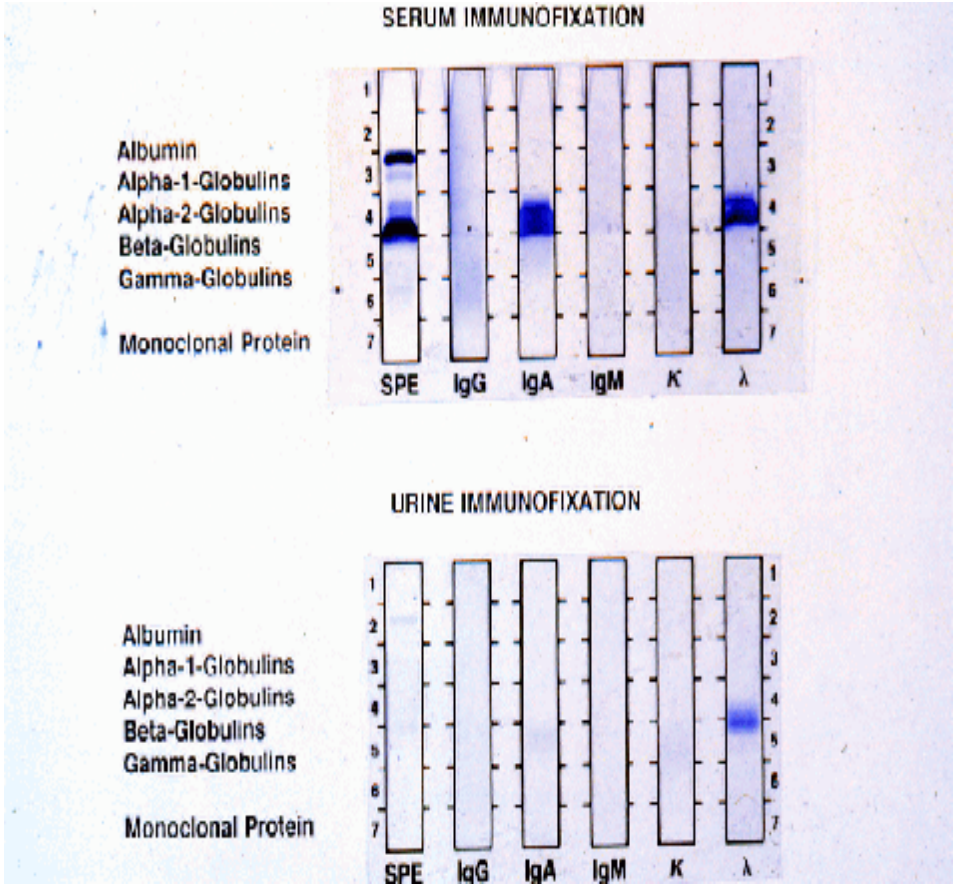


CIRRHOSIS

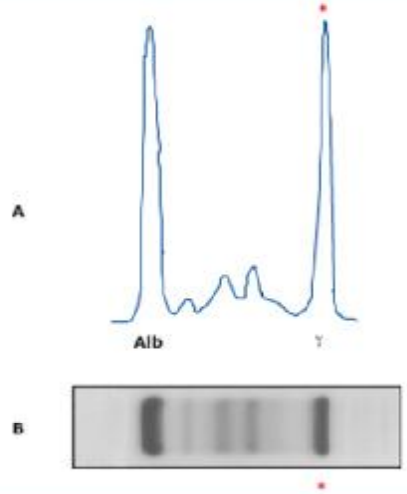

HYPOGAMMAGLOBULINEMIA


MONOCLONAL GAMMOPATHY

Monoclonal Pattern

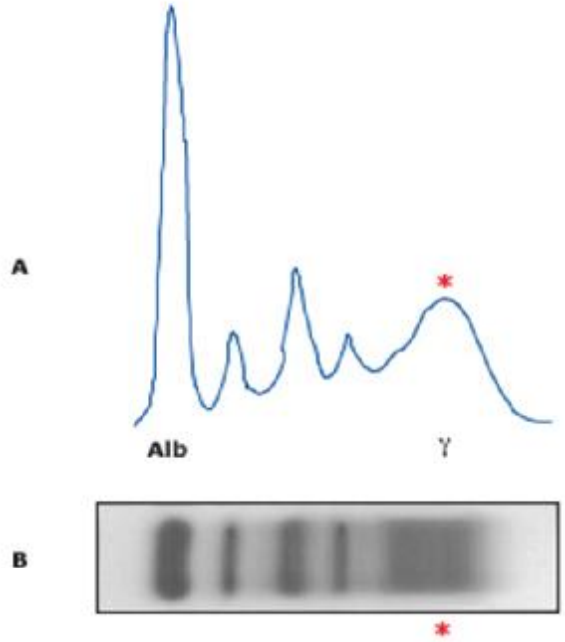


Monoclonal pattern SPEP



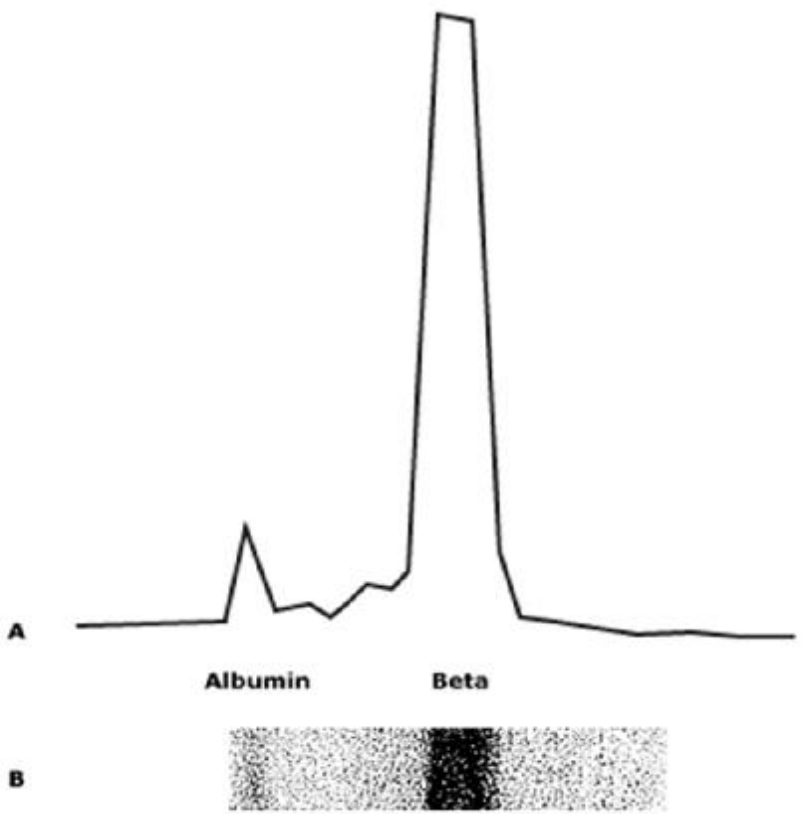
Panel B: A dense, localized band (red asterisk) representing a monoclonal protein of gamma mobility is seen on serum protein electrophoresis on agarose gel (anode on left). Panel A: Densitometer tracing of these findings reveals a tall, narrow-based peak (red asterisk) of gamma mobility and a reduction in the normal polyclonal gamma band. The monoclonal band has a densitometric appearance similar to that of albumin (alb), and has been likened to a church spire.

Polyclonal gammopathy



Panel B: A polyclonal pattern is seen on serum protein electrophoresis on agarose gel (anode on left). The band at the right (red asterisk) is broad, and extends throughout the gamma mobility area. Panel A: Densitometer tracing of these findings reveals a broad-based peak of gamma mobility. This pattern is most often due to the presence of an inflammatory or reactive process, such as chronic liver disease, connective tissue disease, chronic infection, or a lymphoproliferative disease.

Urinary monoclonal protein



Panel B: This figure illustrates the cellulose acetate electrophoretic pattern of a urine sample. It reveals a dense band of protein with beta mobility. Panel A: Densitometer tracing shows a tall, narrow-based peak of beta mobility. These findings are consistent with a urine monoclonal protein (Bence Jones protein); confirmation of the diagnosis requires demonstration that the protein contains only a lambda or kappa light chain with no heavy chain reactivity.

Normal Ranges for Serum Free Light Chains

Kappa:

3.3–19.4 mg/L

Lambda:

5.7–26.3 mg/L

Kappa/lambda ratio

0.26–1.65

Katzmann et al. *Clin Chem.* 2002;1437–1444.

Conventional assays for monoclonal immunoglobulins

Technique	Lower Detection Limit
Electrophoresis	500 - 2,000 mg/l
Immunofixation	150 - 500 mg/l

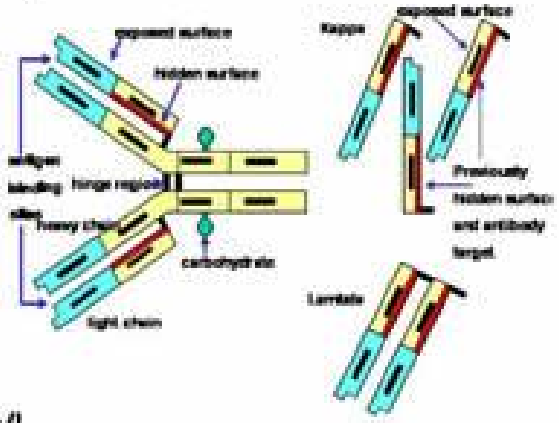
In AL amyloidosis monoclonal immunoglobulin is:

undetectable in ~ 20%

unquantifiable in > 40% of cases

Serum free light chain assay: Freelite

- Developed by The Binding Site
- Polyclonal antibodies to hidden light chain determinants

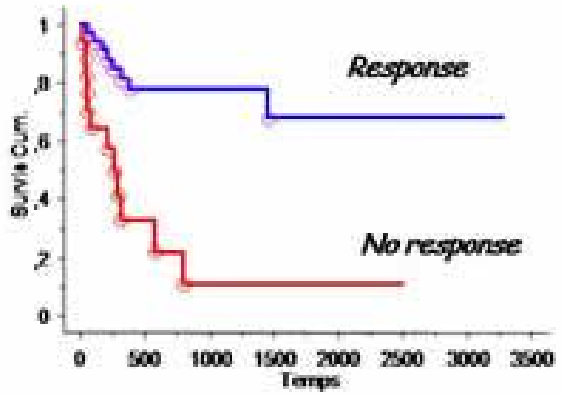


- Healthy serum:
  - polyclonal kappa < 16 mg/l
  - polyclonal lambda < 29 mg/l
- Sensitivity < 1 mg/l

Survival according to FLC response

51 patients

P<0,0001



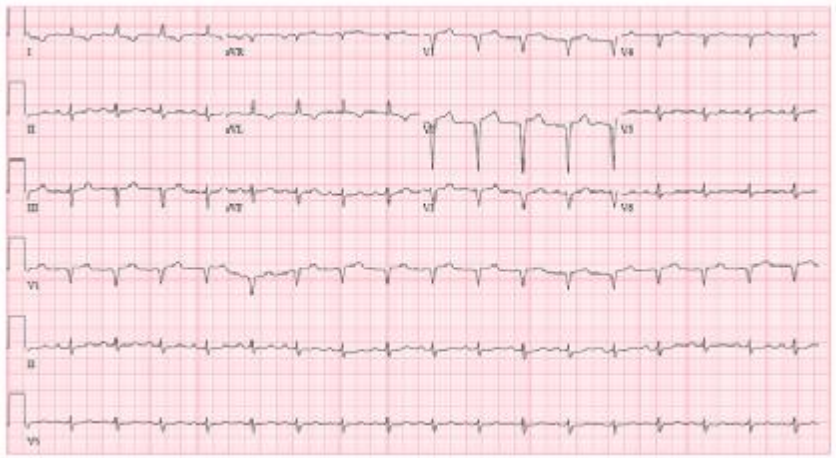
Median survival 8 mois

Median follow-up : 319 days

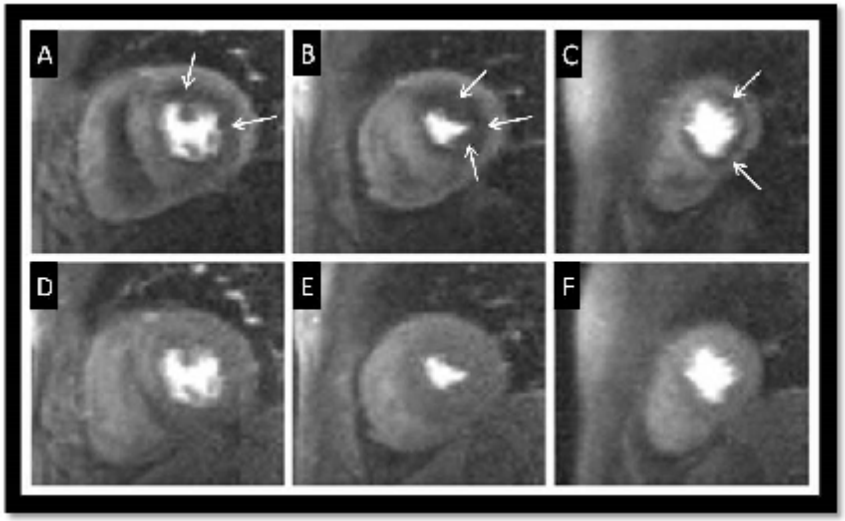
Cardiac imaging

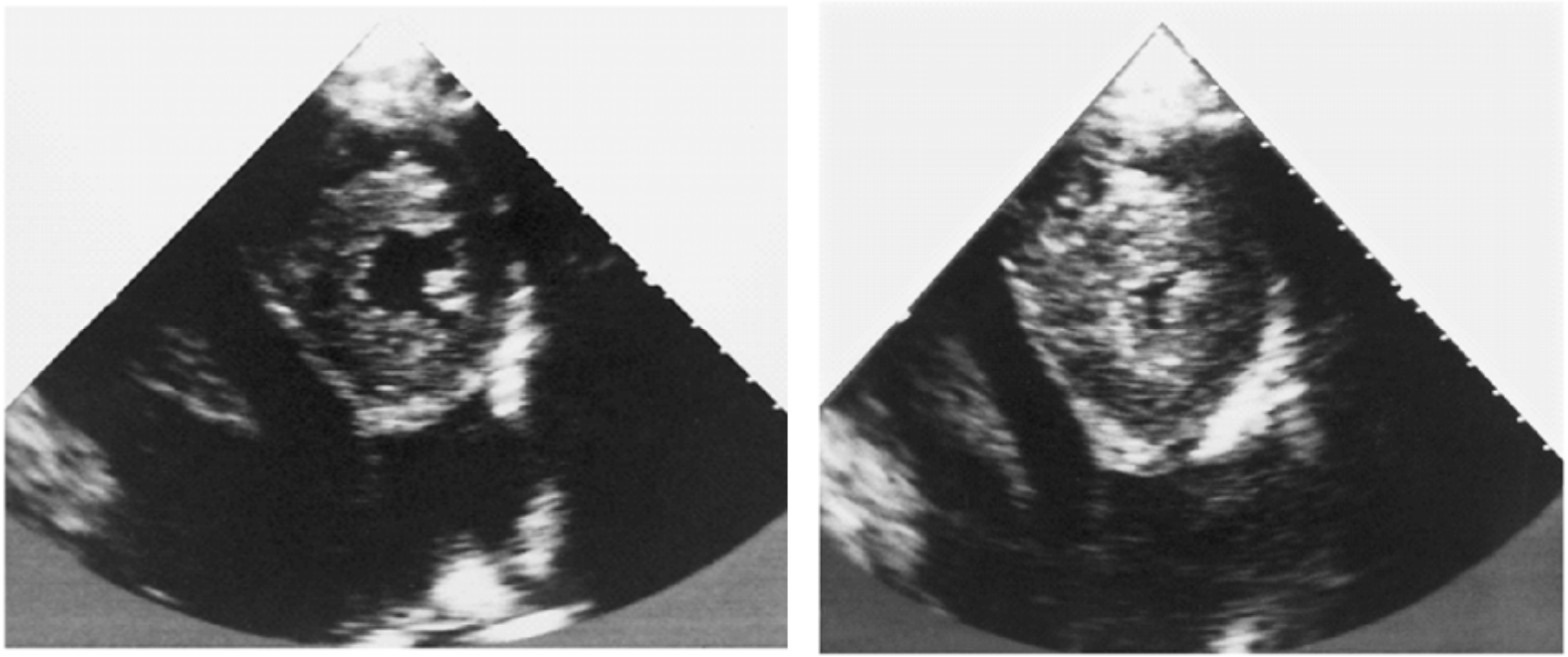
- Classical two dimensional Doppler echocardiographic:
  - concentric biventricular wall thickening with a restrictive filling pattern
- Electrocardiogram:
  - small voltages and pathological ‘Q’ waves (pseudoinfarct pattern)
- Cardiac magnetic resonance imaging (CMR):
  - subendocardial late gadolinium enhancement
  - useful in patients with LV thickening and/or hypertrophy
- Transthyretin amyloid deposits in the heart:
  - Tc3,3diphosphono1,2propanodicarboxylic acid(TcDPD) scintigraphy

ECG



CMR





Echocardiogram revealing thickened walls with small chambers

Table 1 | The major amyloid subtypes

Amyloid subtype	Fibril precursor	Treatment	Clinical involvement
AL	Monoclonal-free immunoglobulin light chains	Chemotherapy directed at the underlying plasma cell dyscrasia Potentially novel agents	Renal (50–80%), cardiac, liver, spleen, bones, GI, autonomic and peripheral neuropathy, soft tissue
AA	Serum amyloid A protein	Treatment aimed at the specific underlying inflammatory condition Potentially eprodisate	Renal (>95%), liver, spleen, adrenals, autonomic neuropathy
ATTR: wild-type	Wild-type transthyretin	Mainly supportive with optimization of fluid status	Cardiac, soft tissue
ATTR: hereditary	Variant transthyretin	Cardiac transplantation Potentially novel agents Liver ± cardiac ± renal transplantation Tafamadis Potentially novel agents	Dominant neurological ± cardiac involvement (dependent upon specific TTR variant)
β_2M	β_2-Microglobulin (associated with chronic dialysis)	Mainly supportive, for example, splints, braces, collars. High-flux dialyzer membranes, frequent hemodialysis, β_2M adsorption columns to reduce formation Renal transplantation	Osteoarticular, bone cysts, soft tissue. Late visceral deposition including cardiac, GI, and spleen
AFib (hereditary)	Variant fibrinogen Aα	Renal ± liver transplantation Potentially novel agents	Renal
Apolipoprotein AI (hereditary)	Variant apolipoprotein AI	Renal +/− liver transplantation Potentially novel agents	Renal (mainly medullary), liver, heart, skin, larynx
Apolipoprotein AII (hereditary)	Variant apolipoprotein AII	Renal transplantation Potentially novel agents	Renal
Lysozyme (hereditary)	Variant lysozyme	Renal transplantation Potentially novel agents	Renal, liver, GI, spleen, lymph nodes, lung, thyroid, salivary glands

Abbreviations: AA, amyloid A; AFib, fibrinogen Aα-chain; AL, immunoglobulin light chain amyloidosis; ATTR, amyoidogenic transthyretin; β_2M, β_2-microglobulin; GI, gastrointestinal; TTR, transthyretin.

TRANSTHYRETIN AMYLOIDOSIS (ATTR)

- Transthyretin (TTR) is a homotetrameric plasma protein that transports thyroxine and Vitamin A and is associated in its wild-type (wt) form with acquired amyloidosis, termed wild-type TTR (wtTTR) amyloidosis and formerly known as senile systemic amyloidosis.

- More than 100 genetic variants of TTR are associated with autosomal dominant hereditary amyloidosis, and these usually involve the ***peripheral and autonomic nervous system*** and/or the ***heart.***

- Notable variants include TTR Val30Met, which is the most common cause of familial amyloid polyneuropathy (FAP), and Val122Ile, which occurs in ~4% of African Americans and is associated with late-onset familial amyloid cardiomyopathy, although with quite low penetrance.

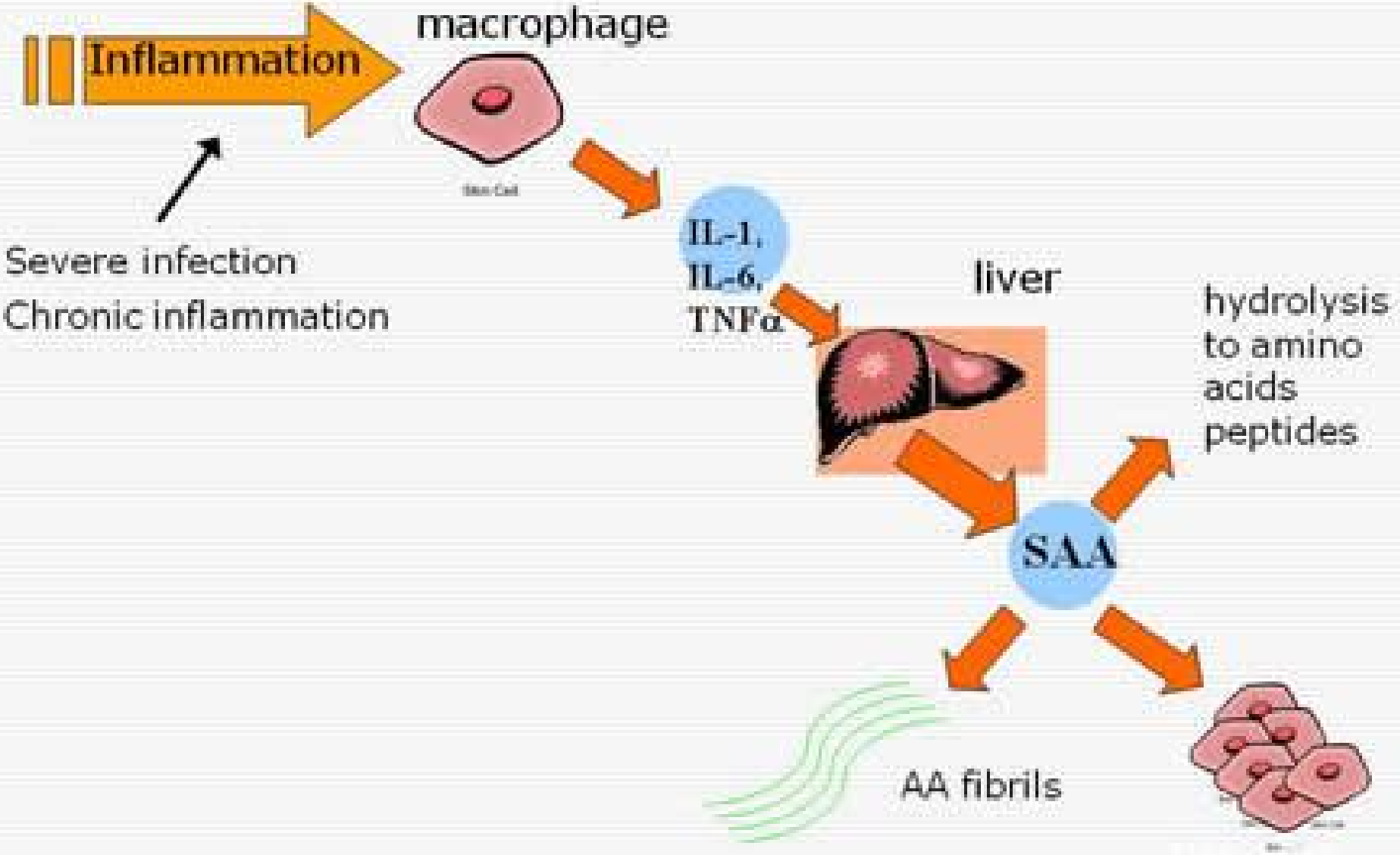
- Untreated FAP is a progressive disease resulting in death within 7–15 years; although renal amyloid deposits occur, only 34.6% develop chronic kidney disease and 10% progress to end-stage renal failure.

SYSTEMIC AA AMYLOIDOSIS

- Systemic AA amyloidosis results in organ dysfunction due to extracellular deposition of N-terminal fragments of SAA in the form of insoluble amyloid fibrils. These deposits have a predilection for the kidneys, spleen, liver, and intestines, with the kidney being the most commonly affected organ.

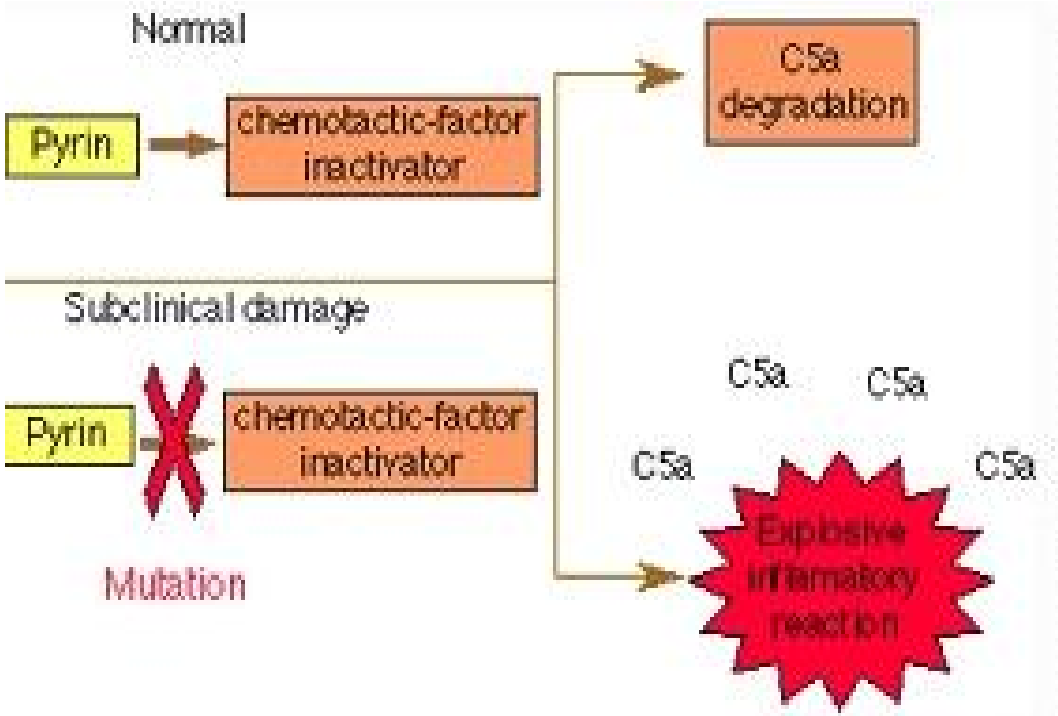
- **SAA** is a hepatic acute-phase response protein, and synthesis can be upregulated by1000-fold in response to inflammatory cytokines, particularly **interleukins 6** and **1**, and, to a lesser extent, **tumor necrosis factor-α.**

Pathogenesis of AA amyloidosis



Familial Mediterranean fever

- primarily affects populations originating in Mediterranean region
- particularly people of Armenian, Arab, Turkish, or Jewish ancestry
- 1 in 200 to 1,000 people
- Mutations in the MEFV gene
- making a protein called pyrin (marenostrin), found in WBCs
- stops inflammatory response to prevent damage to its own cells and tissues
- reduce activity of the pyrin protein:
  - inappropriate or prolonged inflammatory response leading to fever and pain in abdomen, chest, or joints
- autosomal recessive
- usually occurs in childhood or the teenage years
- episodes last 12 to 72 hours and can vary in severity
- length of time between attacks is also variable and can range from days to years
- Normal variations in the SAA1 gene may modify course of FMF
- SAA1 gene (called the alpha variant) increases risk of amyloidosis among people FMF


Normal
Pyrin
chemotactic-factor inactivator
C5a degradation
Subclinical damage
Pyrin
chemotactic-factor inactivator
Mutation
C5a
C5a
C5a
C5a
Explosive inflamatory reaction

AL AMYLOIDOSIS

- Fibrils are derived from ***monoclonal immunoglobulin light chains***, and AL amyloidosis most commonly occurs in patients with otherwise asymptomatic and low-grade clonal plasma cell dyscrasias, although 10–15% of patients have multiple myeloma.

- **Current treatment** centers on ***suppressing clonal B cells***, and hence reducing the supply of the amyloidogenic fibril precursor protein.

- This may facilitate gradual regression of amyloid deposits and stabilization or improvement in vital organ function.

Primary Treatment (AL amyloidosis)

- There are insufficient data to indicate the optimal treatment of amyloidosis, therefore, all patients should be treated in the context of a clinical trial when possible.

All current strategies include systemic therapy to destroy the plasma cells responsible for the synthesis of immunoglobulin light chain.

- Options include:
  - Bortezomib± dexamethasone
  - Bortezomib/cyclophosphamide/dexamethasone
  - Bortezomib/melphalan/dexamethasone
  - Cyclophosphamide/thalidomide/dexamethasone
  - Dexamethasone/alpha-interferon
  - High-dose melphalan with stem cell transplant
  - Lenalidomide/cyclophosphamide/dexamethasone
  - Lenalidomide/dexamethasone
  - Oral melphalan/dexamethasone
  - Pomalidomide/dexamethasone
  - Thalidomide/dexamethasone
  - Best supportive care

- newer immunomodulatory drugs
- proteasome inhibitor (bortezomib)
- more traditional regimes

- Current regimes have been modified from multiple myeloma protocols, and treatment choice depends upon the type and severity of organ involvement—for example, cardiac involvement, peripheral neuropathy, or significant hypotension may preclude particular agents.
- These drugs are commonly combined with dexamethasone and are often used in conjunction with a myelosuppressive agent, such as cyclophosphamide.

Current chemotherapy regimens for AL amyloidosis

Family	Primary agent plus adjunctive treatment	Main side effects	Comments
Alkylator	Melphalan–dexamethasone	Hematological toxicity Fatigue Peripheral edema GI side effects	Good choice for intermediate-risk and frail patients without significant cardiac involvement. IV MDex too toxic for routine use but used if poor GI absorption
Immunomodulatory	Thalidomide (with cyclophosphamide and dexamethasone)	Fluid retention Fatigue and postural hypotension Peripheral neuropathy Thromboembolism Increase in cardiac biomarkers Skin rash Teratogen	
Immunomodulatory (second generation)	Lenalidomide (with dexamethasone)	Fatigue Constipation/diarrhea Myelosuppression Thromboembolism Skin rashes Increase in cardiac biomarkers Renal dysfunction	Useful in disease refractory to alkylators and bortezomib. Response is not achieved rapidly. Addition of cyclophosphamide or melphalan has improved the CR rate but two-thirds of patients develop side effects
Immunomudulatory (third generation)	Pomalidomide (with dexamethasone)	Fluid retention Fatigue and postural hypotension Peripheral neuropathy Thromboembolism Myelosuppression Increase in cardiac biomarkers Skin rash Teratogen	Useful where disease is relapsed/refractory to lenalidomide and thalidomide including cardiac patients
Alkylator and purine analog	Bendamustine (and dexamethasone)	Cytopenias	Useful for relapsed/refractory disease
Proteasome inhibitor	Bortezomib (and dexamethasone ± cyclophosphamide or with dexamethasone and melphalan)	Peripheral neuropathy Hypotension GI disturbance Peripheral edema	Advised upfront in those with a poor prognosis where a rapid response is required

Abbreviations: AL, immunoglobulin light chain amyloidosis; CR, complete response; GI, gastrointestinal; IV MDex, intravenous melphalan-dexamethasone.

Organ Involvement

Kidney	24-hr urine protein > 0.5 g/day, predominantly albumin
Heart	Echo: mean wall thickness > 12 mm, no other cardiac cause or an elevated NT-proBNP (>332 ng/L) in the absence of renal failure or atrial fibrilation
Liver	Total liver span> 15 cm in the absence of heart failure or alkaline phosphatase >1.5 times institutional upper limit of normal
Nerve	Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Gastrointestinal tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms Interstitial radiographic pattern
Soft tissue	Tongue enlargement, clinical Arthropathy Claudication, presumed vascular amyloid Skin Myopathy by biopsy or pseudohypertrophy Lymph node (may be localized) Carpal tunnel syndrome

Hematologic and Organ Response Criteria

Response	Criteria
Hematologic CompleteResponse	Negative serum and urine immunofixation, normal kappa/lambda free light chain ratio, normal bone marrow
Very Good Partial Response	dFLC <40 mg/L
Partial Response	dFLC decrease ≥50%
No Response	Other
Kidney	50% decrease in 24-hour urinary protein excretion in the absence of worsening of creatinine clearance by ≥25% or increase in serum creatinine Of ≥0.5 g/dL
Cardiac	Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by 2 New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness and/or a decrease in NT-proBNP of ≥30% (minimum 300 ng/L) in patients with a creatinine clearance of ≥45 mL/min/1.73m^2
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm

Autologous stem cell transplantation

- The potential advantage of autologous stem cell transplantation (**ASCT**) in delivering a longer disease-free period and a relatively quick CR means that patients should be considered for this procedure from the onset.

- The depth of hematological response is associated with the degree of organ response, emphasizing the importance of **trying to achieve CR** either through chemotherapy alone or with ASCT.

- Cibeira et al. showed that a **CR**, after ASCT, confers an overall survival of 86% at 5 years and an event-free survival of 8.3 years compared with 2 years for patients not in CR.

- However, treatment-related mortality has been reported as being as high as 40% in 1999, and since then efforts have been made to risk stratify patients more rigorously.

- Gertz et al. showed that higher levels of **cardiac biomarkers** were the sole predictors of early mortality after ASCT, and treatment-related mortality was <1% if the NT-proBNP was <5000 pg/ml and troponin was <0.06 ng/ml.

- In selected low–intermediate-risk AL patients, ASCT is well established as a first-line treatment (**14% of patients**).

Table 2 | Mayo cardiac amyloid staging system

Variable	Stage I	Stage II	Stage III
cTNT	<0.035 μg/l	$\geqslant 0.035$ μg/l	$\geqslant 0.035$ μg/l
		or	
NT-proBNP	<332 ng/l	$\geqslant 332$ ng/l	$\geqslant 332$ ng/l
Median survival (months)	26.4	10.5	3.5

Abbreviations: cTNT cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide.

This staging system is widely used in studies when evaluating therapeutic efficacy. Higher stages correlate with a worse prognosis.[64]

- Carefully selected patients
- Significant treatment-related mortality
- Extent of organ involvement is predictor of outcome
- Associated with higher response rates and improved overall survival (OS)
- Best outcomes is in patients who achieve complete response (CR) to high-dose primary chemotherapy including improvement of organ-related disease
- Durability of treatment is the depth of the response to therapy measured by the lowest post-transplantation serum free light chain level

- Long-term follow-up study of the 74 patients who underwent SCT found that 32 (43%) survived greater than 10 years.

Melphalan/Dexamethasone

- In whom are ineligible for SCT
- Hematologic response in 67% (n= 31)
- Complete remission in 33% (n = 15) (in a median of 4.5 mo)
- Improvement in organ function in 48% (n = 22)
- CR maintained in 70% of the patients for up to 3 years
- Survival at a median follow-up of 5 years was about 50%

French Myeloma Collaborative Group compared melphalan and dexamethasone to high-dose melphalan followed by SCT in a randomized trial:

- no significant differences for hematologic or organ responses
- no significant differences for survival or remission duration

Immunomodulatory drugs

- **Thalidomide** (combined with cyclophosphamide and dexa):
  - 33% achieved a complete or very good partial response
  - after a median of 7 months
  - but 29% mortality
  - and 50% morbidity

- **Lenalidomide:**
  - hematological response rate ranging from 41 to 47%
  - including relapsed and thalidomide refractory cases
  - time to hematological response is longer than bortezomib

- **Pomalidomide:**
  - induce a 48% hematological response rate
  - with 3% CRs in 33 heavily pretreated patients

Proteasome inhibitors

- **Bortezomib** induces a rapid decrease in serum-free light-chain concentration in patients with myeloma.

- Purified plasma cells from amyloid patients are twice as vulnerable to bortezomib inhibition as those from myeloma patients.

- This is thought to be because amyloidogenic light chains have a greater propensity to misfold, thus **overloading the proteasome.**

- Its efficacy in achieving both a high hematological and organ response rate has led to it being adopted as a **front-line therapy in AL amyloidosis**, and it is being increasingly used in those with severe cardiac involvement whose outlook is extremely poor.

- Venner et al. reported a hematological response of 81.4% using **biweekly bortezomib, cyclophosphamide, and dexamethasone:**
  - superseding that 71% with bortezomib/dexamethasone
  - 67% with bortezomib/ melphalan/dexamethasone
  - 69% with bortezomib alone

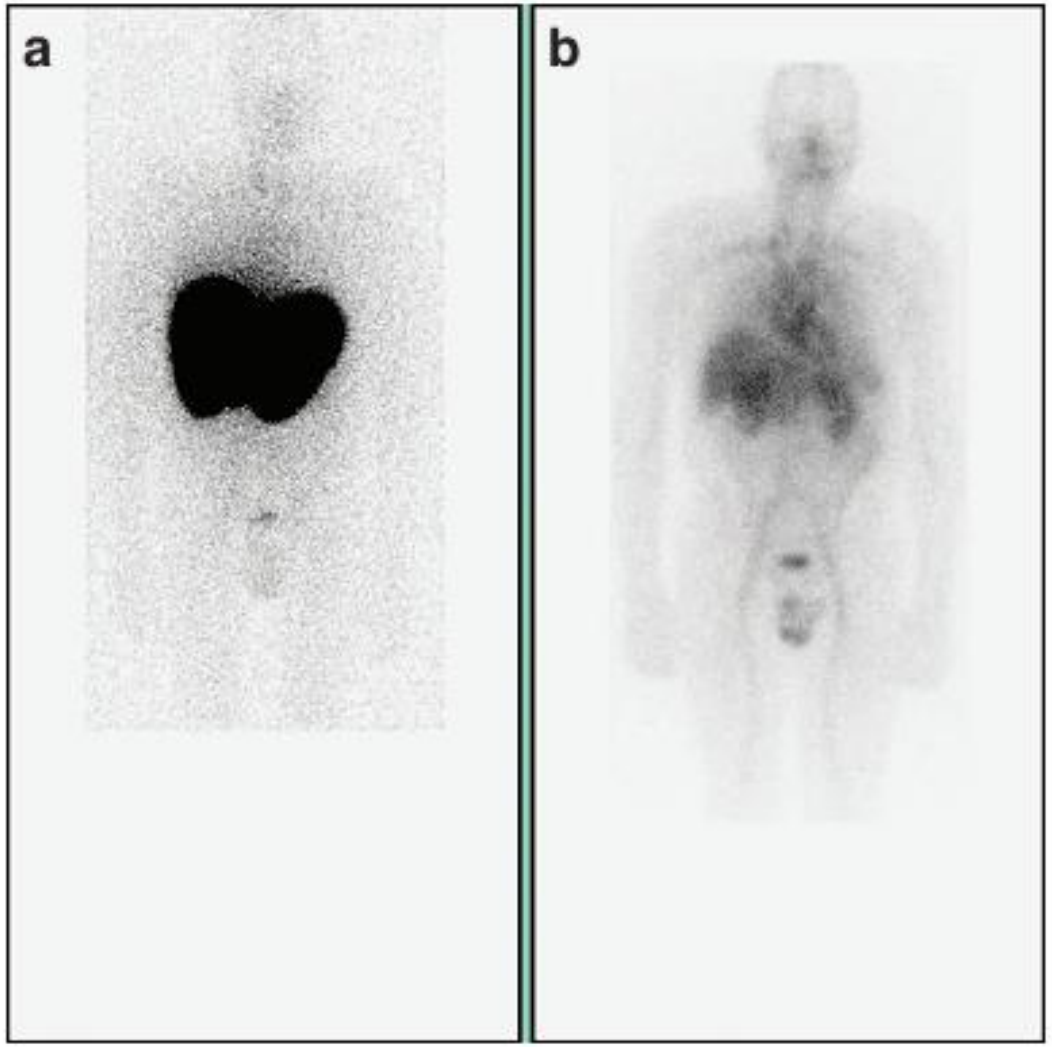
Bortezomib:

- High rates of hematologic and organ responses
- Active in untreated and relapsed amyloidosis (±dexamethasone)
- 20 relapsed or refractory patients treated with bortezomib:
  - hematologic response in 80% (n = 16)
  - CR in 15% (n = 3)
  - partial response in 65 % (n =13)

- Bortezomib was well tolerated at doses up to 1.6 mg/m2 on a once-weekly schedule and 1.3 mg/m2 on a twice-weekly schedule
- Median time to response was 1.2 months
- Once-weekly regimen associated with lower neurotoxicity

GENERIC ANTI-AMYLOID APPROACHES

- Clearance of existing deposits: (Novel agents)
  - **Immunotherapy**: fibril-specific *monoclonal antibodies* (opsonize and promote clearance of AL and AA amyloid)
  - **CPHPC and anti-human SAP antibodies:**
    - **CPHPC**: *competitive inhibitor of SAP* binding to amyloid fibrils, this drug **crosslinks pairs of SAP molecules in the plasma** that triggers their complete clearance by the liver and eventually gradually depleting SAP from the amyloid deposits, sustained and profound depletion of circulating SAP, substantial SAP depletion from the amyloid deposits
    - **anti-human SAP antibodies**: triggers a potent, complement-dependent, macrophage-derived giant cell reaction that swiftly removes massive visceral amyloid deposits
  - **Fibril disruptors**:
    - deoxyrubicin (I-DOX) and doxycycline



Iodine-123 (123I)-labeled serum amyloid P (SAP) component scintigraphy. Anterior-posterior view of an SAP scan, demonstrating (a) a large total body amyloid load with hepatic and splenic involvement (b) with regression after nine cycles of chemotherapy, resulting in a small total body amyloid load. (Unfortunately SAP scintigraphy is not informative about amyloid deposition in the moving heart)

Oligonucleotide-based therapies (Novel agents)

- **Oligonucleotide-based therapies:**
  - small interfering RNAs (siRNAs)
  - antisense RNAs (ASOs)

Oligonucleotide-based therapies:

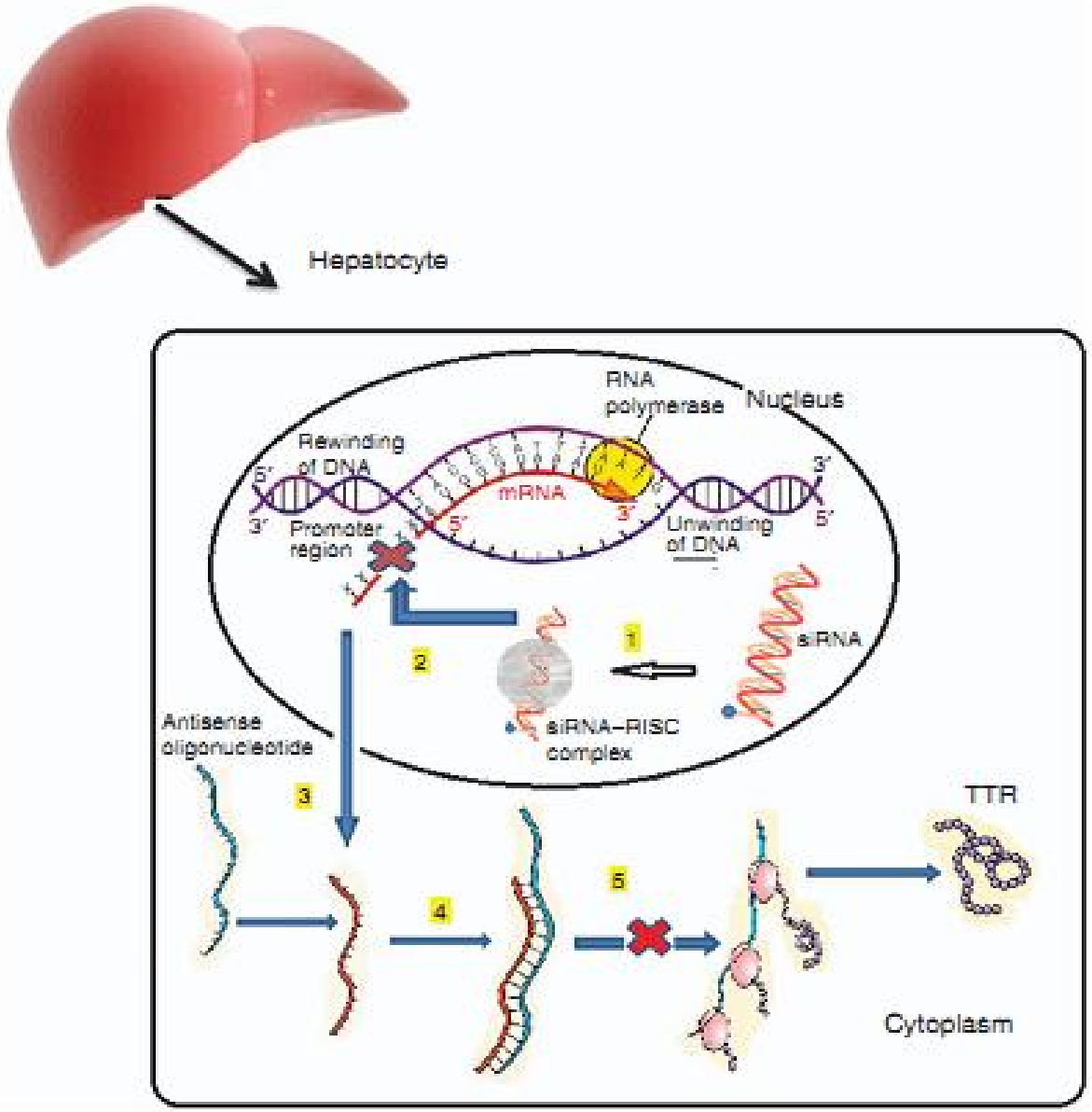
- The discovery of RNA interference by Fire and Mello, for which they were awarded the Nobel Prize in Physiology in 2006, demonstrated how the transfer of genetic information from DNA to protein can be blocked.
- Oligonucleotide-based therapies, including small interfering RNAs (siRNAs) and antisense RNAs, have the ability to cause changes *at the translational level* without becoming integrated into the human genome.

- small interfering RNAs (siRNAs) are:
  - noncoding, double-stranded molecules
  - components of the endogenous RNA interference pathway
  - serves to control gene expression
  - vary in length from 18 to 30 base pairs
  - chemically modified for drug delivery
  - to increase stability and limit immunogenicity
  - lipid nanoparticles deliver siRNAs to hepatocytes parenterally
  - resulted in a robust and durable reduction in genetic expression

- Antisense oligonucleotides (ASOs) are:
  - 13–25 nucleotide single-stranded molecules
  - hybridize to a specific messenger RNA (mRNA) sequence
  - prevent translation

- ALN-TTR01 and ALN-TTR02 (lipid nanoparticles):
  - contain an identical siRNA
  - *binds to an **mRNA** segment common to both wt and mutant TTR*
  - rapid, dose-dependent, and durable **reduction in transthyretin levels**
  - in 32 patients with TTR amyloidosis

- ISIS-TTRRX (chimeric antisense inhibitor of TTR):
  - binds selectively and with high affinity to human TTR **mRNA**
  - results in its degradation
  - preventing production of both wt and variant TTR protein
  - **twice-weekly subcutaneous injections** well tolerated
  - in both TTR transgenic mouse models and monkeys
  - with a reduction in hepatic TTR mRNA and plasma wt TTR protein levels by ~80%
  - currently under evaluation in a phase I clinical trial in normal healthy volunteers
  - beneficial in other types of amyloidosis
  - SAA levels in ASO-treated mice were 63% lower, resulting in reduced AA amyloid deposition.



Hepatocyte schematic demonstrating the mechanism by which small interfering RNAs (siRNAs) block the transcription process and antisense oligonucleotides interfere with the translation process, ultimately preventing transthyretin (TTR) formation. (1) The siRNAs bind to the RNA-inducing silencing complex (RISC) in an ATP-dependent manner. (2) This multisubunit protein complex migrates toward messenger RNA (mRNA). At some point, the siRNA unwinds and the antisense strand remains bound to the RISC and blocks transcription by the direct degradation of the target mRNA sequence through the use of both endo- and exonucleases.(3) The mRNA migrates into the cytoplasm where (4) hybridization with the antisense oligonucleotide prevents protein translocation (5).

STABILIZATION OF THE TTR TETRAMER

- **Diflunisal:**
  - a NSAIDs stabilizes tetrameric TTR by binding via the thyroid hormone receptor sites (apply in FAP)
- **Tafamadis:**
  - an orally administered drug that acts to stabilize the TTR tetramer through its affinity for the T4-binding site, and it does not carry the risks associated with NSAIDs (apply in FAP)
- **Epigallocathechin-3-gallate:**
  - most abundant catechin in green tea(GT), efficiently inhibits fibril formation from amyloid TTR and converts existing fibrils into nonfibril conformers. TTR tetramer stabilization is observed when epigallocathechin-3-gallate binds to recombinant wt and variant TTR tetramers at three sites different from the thyroxine-binding site. (apply in cardiac)
- **Oligonucleotide-based therapies:**
  - small interfering RNAs (siRNAs)
  - antisense RNAs (ASOs)

Treatment of AA Amyloidosis

- Current treatment is aimed at reducing **SAA** production to **healthy normal levels (3mg/l)** through control of the respective underlying inflammatory disease. Sustained suppression of SAA production results in amyloid regression.

- Proteinuria may diminish substantially, although gradually over months and even years, in patients with AA amyloidosis when the underlying inflammatory disease remains quiescent.

Kidney transplantation (in AA amyloidosis):

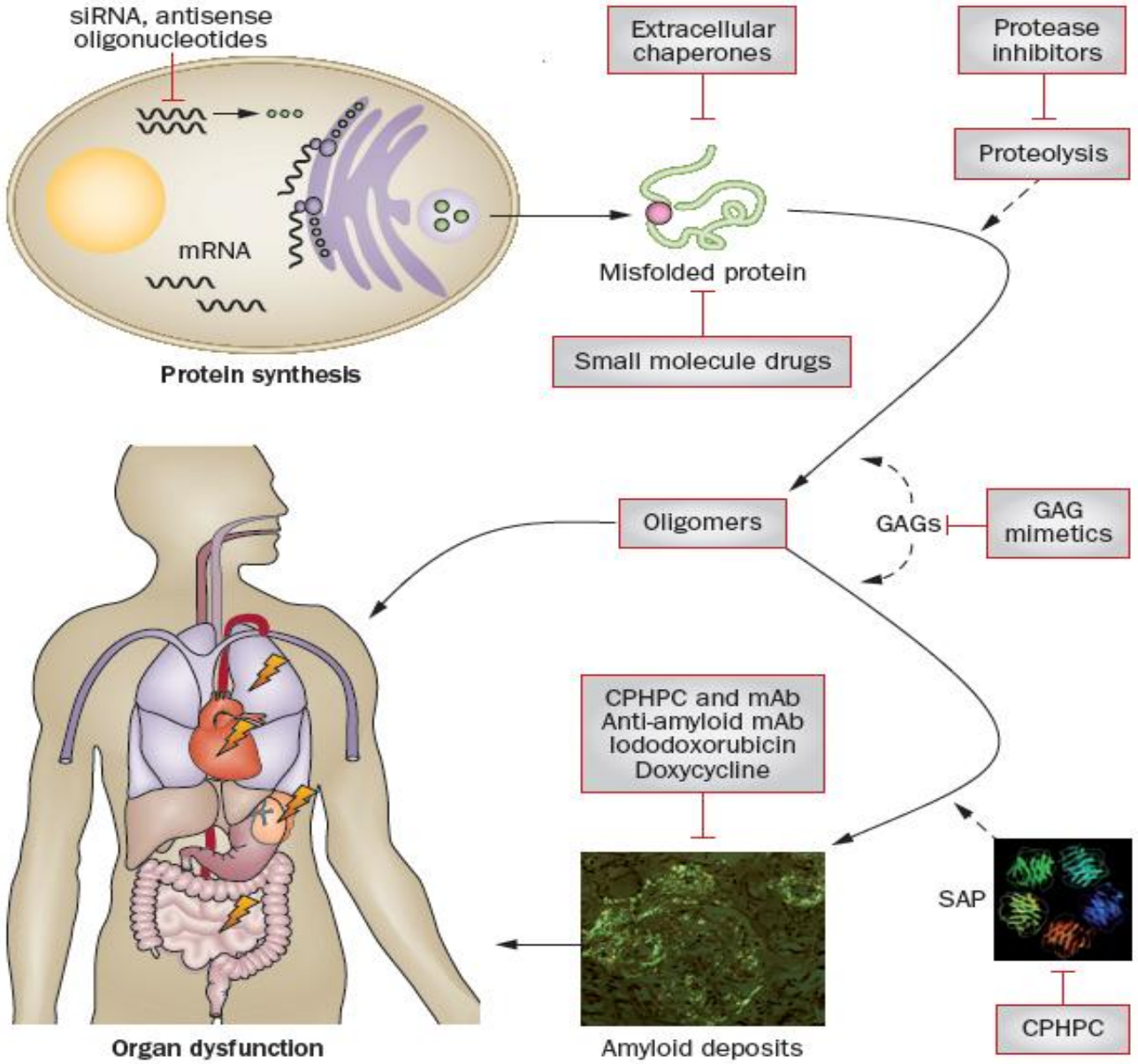
- Pinney et al. described 43 patients with AA amyloidosis and renal transplants:
  - Graft loss due to recurrent amyloid occurred in only 4.6% of cases and predicted median graft survival was 10.3 years.
  - **Lower SAA levels** were associated with an improved outcome, with graft survival (noncensored for death) of 14.5 years in patients with a median SAA value of <10mg/l and 7.8 years in those with a median SAA value of >10mg/l.

- Kofman et al. showed that their cohort of 59 transplanted AA patients:
  - Patient survival was less good compared with the outcome of 179 age-matched renal transplant recipients, although graft survival was not statistically different.
  - A total of 72.3% developed at least one infection, and 43% of patient deaths were due to severe sepsis.

Eprodisate (in AA amyloidosis):

- Glycosaminoglycans, such as heparin sulfate, promote fibril assembly by acting as chaperones during early stages of protein refolding and amyloid formation.

- Eprodisate (Kiacta, Neurochem) is a negatively charged, sulfonated molecule that is structurally similar to heparin sulfate and works by competitively inhibiting the interaction between SAA and glycosaminoglycans.


siRNA, antisense oligonucleotides
mRNA
Protein synthesis
Extracellular chaperones
Misfolded protein
Small molecule drugs
Protease inhibitors
Proteolysis
Oligomers
GAGs
GAG mimetics
CPHPC and mAb
Anti-amyloid mAb
Iododoxorubicin
Doxycycline
Amyloid deposits
SAP
CPHPC
Organ dysfunction

In summary

- Disease of protein misfolding
- Tissue diagnosis by congo red stain and EM (8-10 nm nonbranching fibrils)
- Diagnosis of amyloidosis subtype:
  - AL amyloidosis (light chain)
  - Secondary amyloidosis (SAA)
  - Wild type TTR (senile) and variant TTR amyloidosis (FAP, cardiac)
  - Other hereditary amyloidosis (Apolipoprotein A1, Apo AII, Lysozyme, Fibrinogen Aα, Gelsolin)
  - Dialysis-related (β2M)
- Accurate identification of the protein causing amyloidosis:
  - IF on fresh tissue, IHC, mass spectrometry (genetic testing)
- Serum and urine protein electrophoresis and immunofixation, FLC

Summary

- Al amyloidosis treatment:
  (suppressing of clonal plasma cells)
  - **ASCT**: longer disease-free survival, OS in 43% > 10 years, relatively quick CR, higher treatment-related mortality, in low–intermediate-risk AL patients (14% of patients)
  - **Melphalan/dexamethasone**
  - **Bortezomib, cyclophosphamide, dexamethasone**: ***front-line therapy in AL amyloidosis***, ***severe cardiac*** involvement, high hematological (81%) and organ response rate, rapid response
  - **Immunomodulatory agents** (***linalidomide, pomalidomide***) + Dexa + Cyc or Mel

Summary (Novel agents)

- **Immunotherapy**: fibril-specific *monoclonal antibodies*
- **CPHPC and anti-human SAP antibodies**
- **Fibril disruptors**: deoxyrubicin (I-DOX) and doxycycline
- **Diflunisal, Tafamadis,** Epigallocathechin-3-gallate: (TTR stabilizer)
- **Oligonucleotide-based therapies:**
  (blocking of genetic information from DNA to protein)
  - ***small interfering RNAs (siRNAs)***
  - ***antisense RNAs (ASOs)***
- **Eprodisate:**
  (competitively inhibiting interaction between SAA and GAGs)

Diagnosis and Treatment

- Malignant neroplasm of plasma cells which accumulate in BM
- Leading to bone destruction and marrow failure
- 24,050 new cases MM in US in 2014
- with 11,090 deaths
- Mean age 62 for men (75%> 70 years), 61 for women (79%> 70 years)
- 5-year survival 25% in 1975 to 34% in 2003

- MM is sensitive to a variety cytotoxic agents
- Unfortunately, responses are transient, and not curable
- Diverse cytogenetic abnormalities indicates that MM is a heterogeneous disease thus risk-adapted approaches and individualizing treatment will help refine patient management

Initial Diagnostic Workup and Clinical Presentation

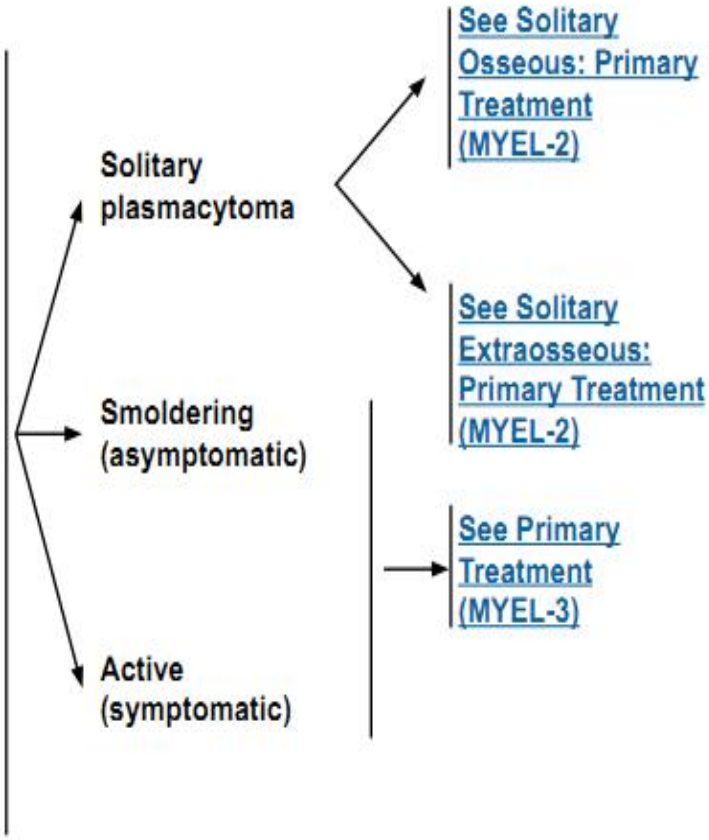
INITIAL DIAGNOSTIC WORKUP

- H&P
- CBC, differential, platelet count
- BUN/creatinine, electrolytes
- LDH
- Calcium/albumin
- Beta-2 microglobulin
- Serum free light chain (FLC) assay
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24 h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 amplification]

Useful Under Some Circumstances

- MRI
- CT scan (avoid contrast)
- PET/CT scan
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Bone densitometry
- Plasma cell labeling index
- Staining of marrow and fat pad for amyloid
- Serum viscosity
- HLA typing

CLINICAL PRESENTATION



- LDH and **β2M** access the tumor burden
- 20% of MM patients have secretory urine proteins and 3% have neither serum nor urinary proteins (non-secretory myeloma)

- Several subtypes of MM at the genetic and molecular level
- Chromosome analysis by conventional karyotyping (cytogenetics) and fluorescence in situ hybridization (FISH) on plasma cells obtained from BMA

- PET/CT and MRI scans are more sensitive than plain radiographs and are only indicated when symptomatic areas show no abnormality on routine radiographs

Definition of Multiple Myeloma (Smoldering and Active)

Smoldering (Asymptomatic) Myeloma	Active (Symptomatic) Myeloma
M-protein in serum *IgG ≥3 g/dL *IgA > 1 g/dL Or *Bence-Jones protein >1 g/24h And/or Bone marrow clonal plasma cells ≥10% No related organ or tissue impairmrnt (no end organ damage, including bone lesions) or symptoms.	Requires one or more of the following: *Calcium elevation (>11.5 mg/dL) *Renal insufficiency (creatinine>2 mg/dL) *Anemia (hemoglobin <10 g/dL or 2 g/dL <normal) *Bone disease (lytic or osteopenic)

Staging Systems for Multiple Myeloma

Stage	Durie-Salmon Criteria	ISS Criteria
I	All of the following: *Hemoglobin value >10 g/dL *Serum calcium value normal or ≤12 mg/dL *Bone X-ray, normal bone structure or solitary bone plasma only *Low M-component production rate *IgG value < 5 g/dL *IgA value <3 g/dL *Bence Jones protein <4 g/24h	Serum beta-2 microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
II	Neither stage I nor stage III	Neither stage I nor stage III
III	One or more of the following: *Hemoglobin value <8.5 g/dL *Serum calcium value >12 mg/dL *Advanced lytic bone lesions *High M-component production rate *IgG value >7 g/dL *IgA value >5 g/dL *Bence Jones protein >12 g/24 h	Serum beta-2 microglobulin ≥5.5 mg/L
Subclassification Criteria A Normal renal function (serum creatinine level <2 mg/dL) B Abnormal renal function (serum creatinine level ≥2 mg/dL)		

Myeloma Therapy (1)

MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

	Preferred Regimens	Other Regimens
Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/doxorubicin/dexamethasone (category 1) • Bortezomib/lenalidomide /dexamethasone • Bortezomib/thalidomide/dexamethasone (category 1) • Lenalidomide /dexamethasone (category 1)	• Carfilzomib .lenalidomide /dexamethasone • Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Thalidomide/dexamethasone (category 2B)
Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)	• Bortezomib/dexamethasone • Lenalidomide/low-dose dexamethasone (category 1) • Melphalan/prednisone/bortezomib (MPB) (category 1) • Melphalan/prednisone/lenalidomide (MPL) (category1) • Melphalan/prednisone/thalidomide (MPT) (category 1)	• Dexamethasone (category 2B) • Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B) • Melphalan/prednisone (MP) • Thalidomide/dexamethasone (category 2B) • Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance Therapy	• Bortezomib • Lenalidomide (category 1) • Thalidomide (category 1)	• Bortezomib + prednisone (category 2B) • Bortezomib + thalidomide (category 2B) • Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

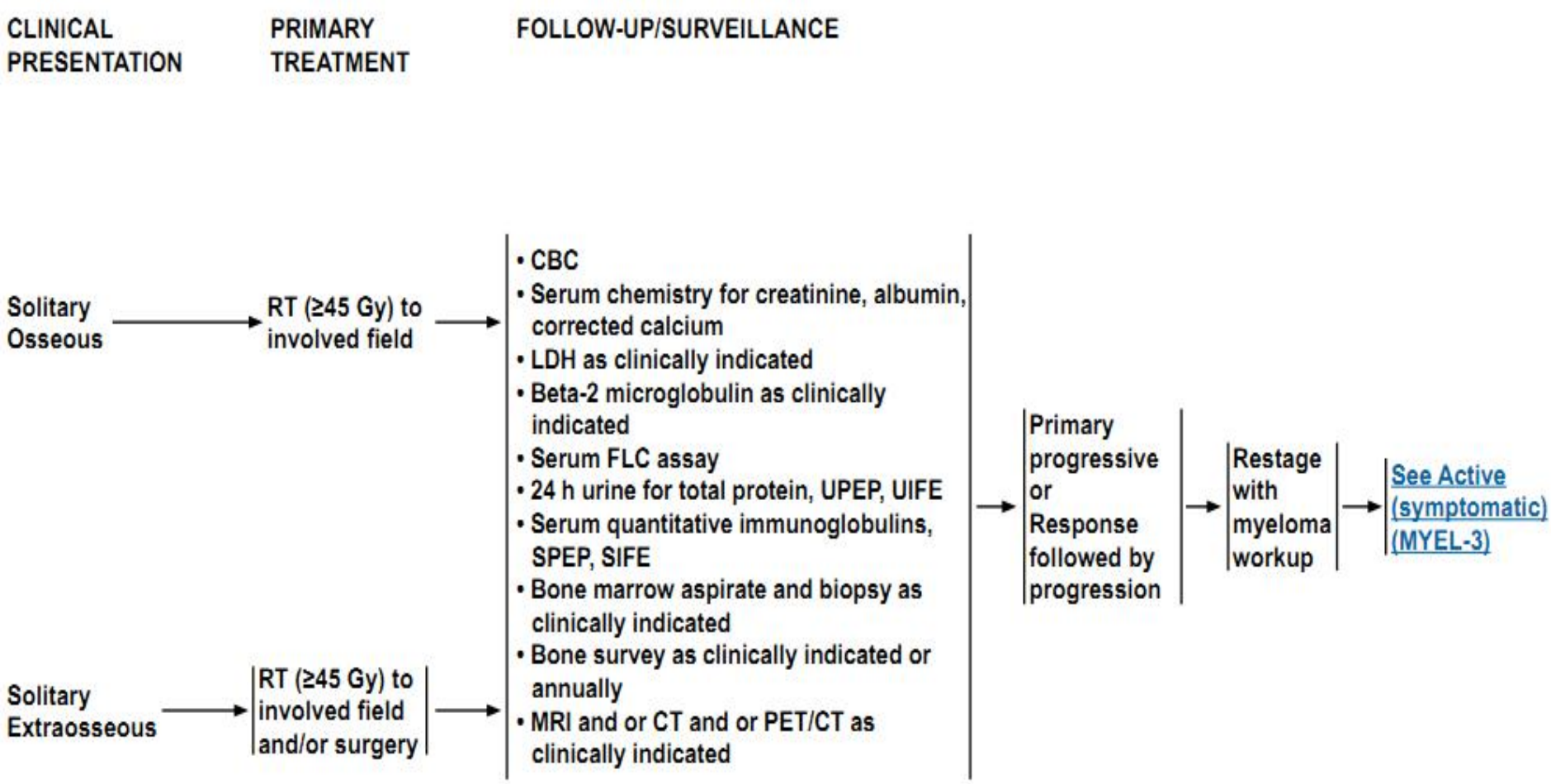
Myeloma Therapy (2)

MYELOMA THERAPY

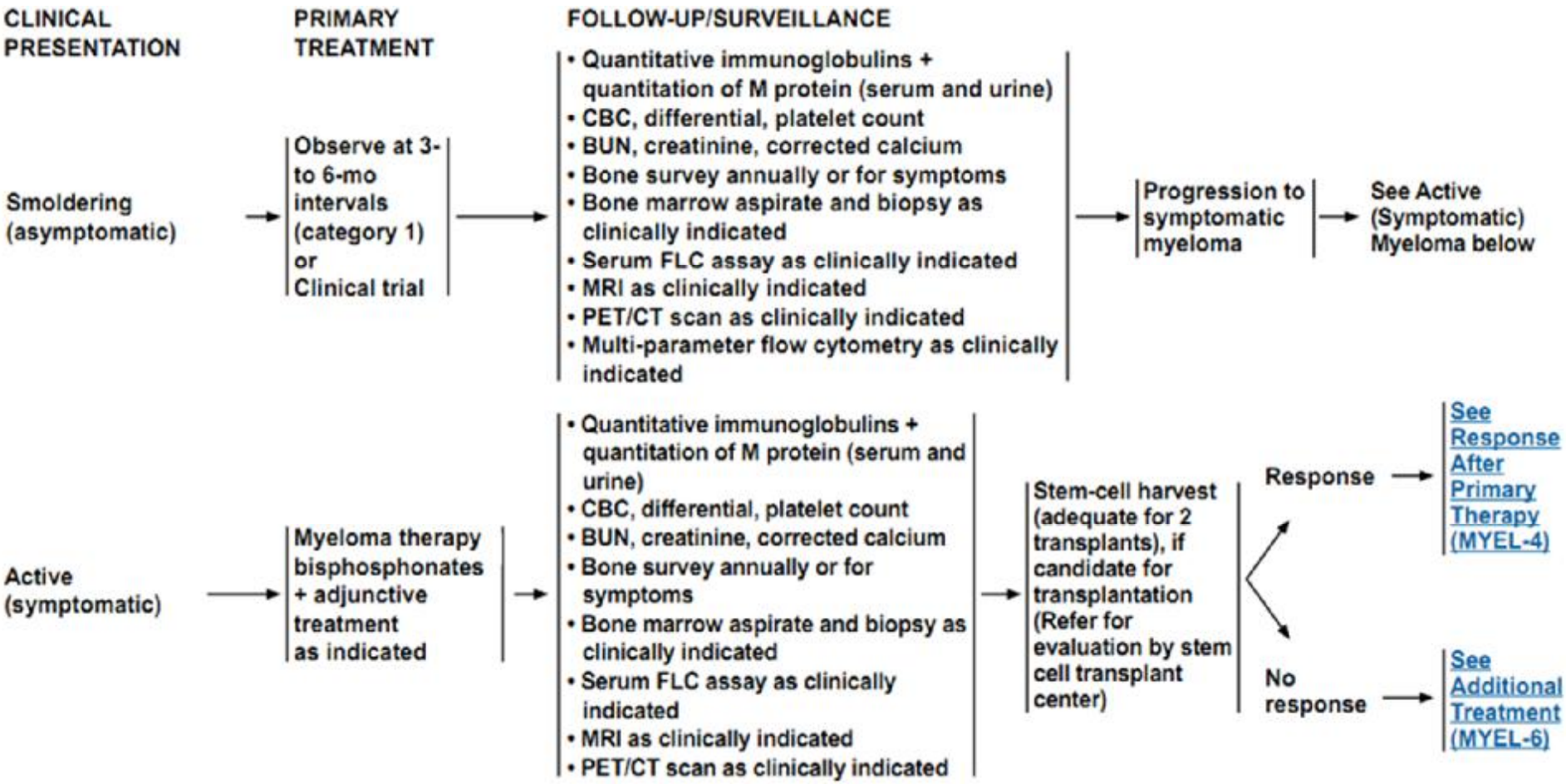
Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

	Preferred Regimens	Other Regimens
Therapy for Previously Treated Multiple Myeloma	• Repeat primary induction therapy (if relapse at >6 mo) • Bortezomib (category 1) • Bortezomib/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin (category 1) • Bortezomib/thalidomide/dexamethasone • Carfilzomib • Cyclophosphamide/bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • High-dose cyclophosphamide • Lenalidomide/dexamethasone (category 1) • Pomalidomide /dexamethasone • Thalidomide/dexamethasone	• Bendamustine • Bortezomib/vorinostat • Lenalidomide/bendamustine/dexamethasone

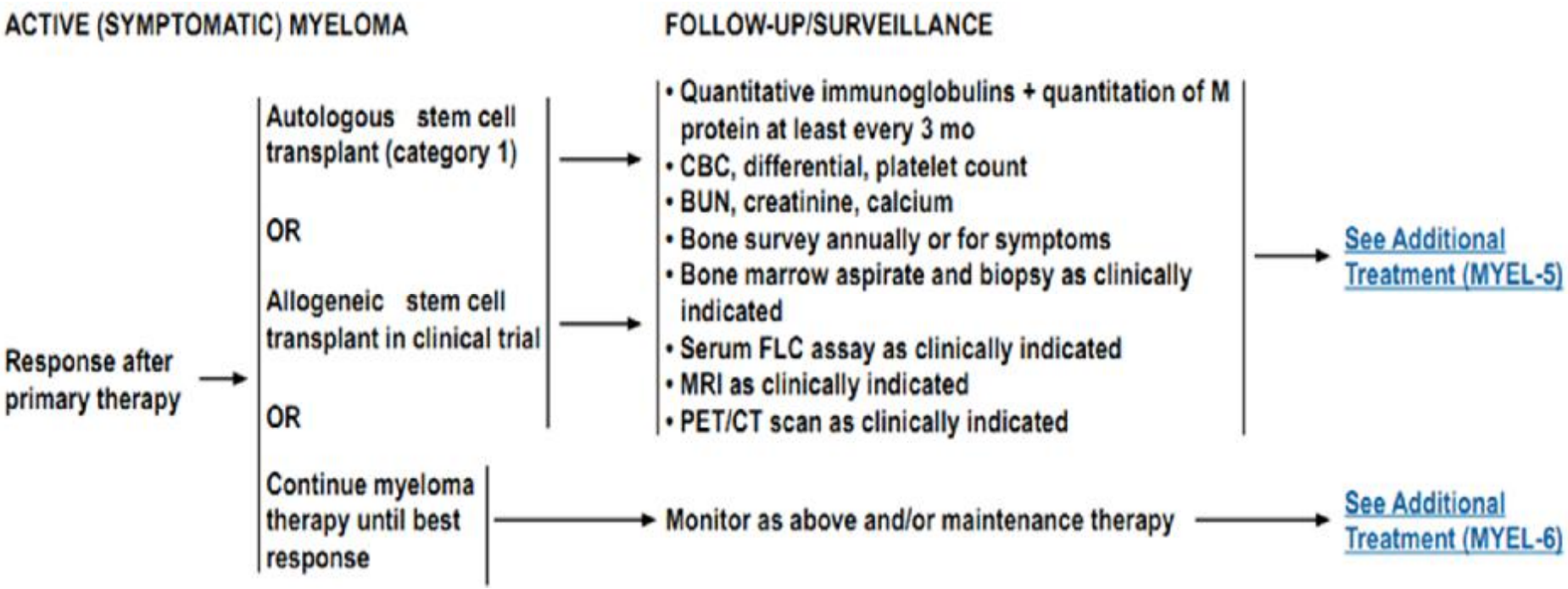
Solitary Plasmacytoma (Osseous or Extraosseous) Primary Treatment



Multiple Myeloma: Primary Treatment and Follow-Up/Surveillance



Active (Symptomatic) Myeloma Follow-Up/Surveillance



Adjunctive Treatment

Bone Disease

Bisphosphonates (pamidronate and zoledronic acid)

*All patients receiving primary myeloma myeloma therapy should be given bisphosphonates (category 1)

*Use of bisphosphonates in smoldering or stage I disease preferably in the context of a clinical trial. These patients should have bone survey annually and if symptomatic

*Monitor for renal dysfunction with use of bisphosphonates

*Monitor for osteonecrosis of the jaw

RT

*Low-dose RT (10-30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture or impending cord compression

*Limited involved fields should be used to limit the impact of irradiation on stem cell harvest or impact on potential fracture treatment

*Orthopedic consultation should be sought impending or actual long-bone fractures or bony compression of spinal cord or vertebral column instability

*Consider vertebroplasty or kyphoplasty for symptomatic vertebral compression fractures

Hypercalcemia

*Hydration/furosemide, bisphosphonates (zoledronic acid preferred), steroids, and/or calcitonin

Hyperviscosity

*Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity

Anemia

*Guidelines for Cancer and Chemotherapy Induced Anemia

*Consider erythropoietin for anemic patients

Infection

*Guidelines for Prevention and Treatment of Cancer Related Infections

*Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection

*Consider pneumovax and influenza vaccine

*PCP, herpes, and antifungal prophylaxis if high-dose dexamethasone regimen

*Herpes zoster prophylaxis for patients treated with bortezomib

Renal Dysfunction

*Maintain Hydration to avoid renal failure

*Avoid use of NSAIDs

*Avoid IV contrast

*Plasmapheresis (category 2B)

*Not a contraindication to transplant

*Monitor for renal dysfunction with chronic use of bisphosphonates

Coagulation/thrombosis

*Prophylactic anticoagulation recommended for patients receiving thalidomide-based, or lenalidomide with dexamethasone therapy

*Guidelines for Venous Thromboembolic Disease

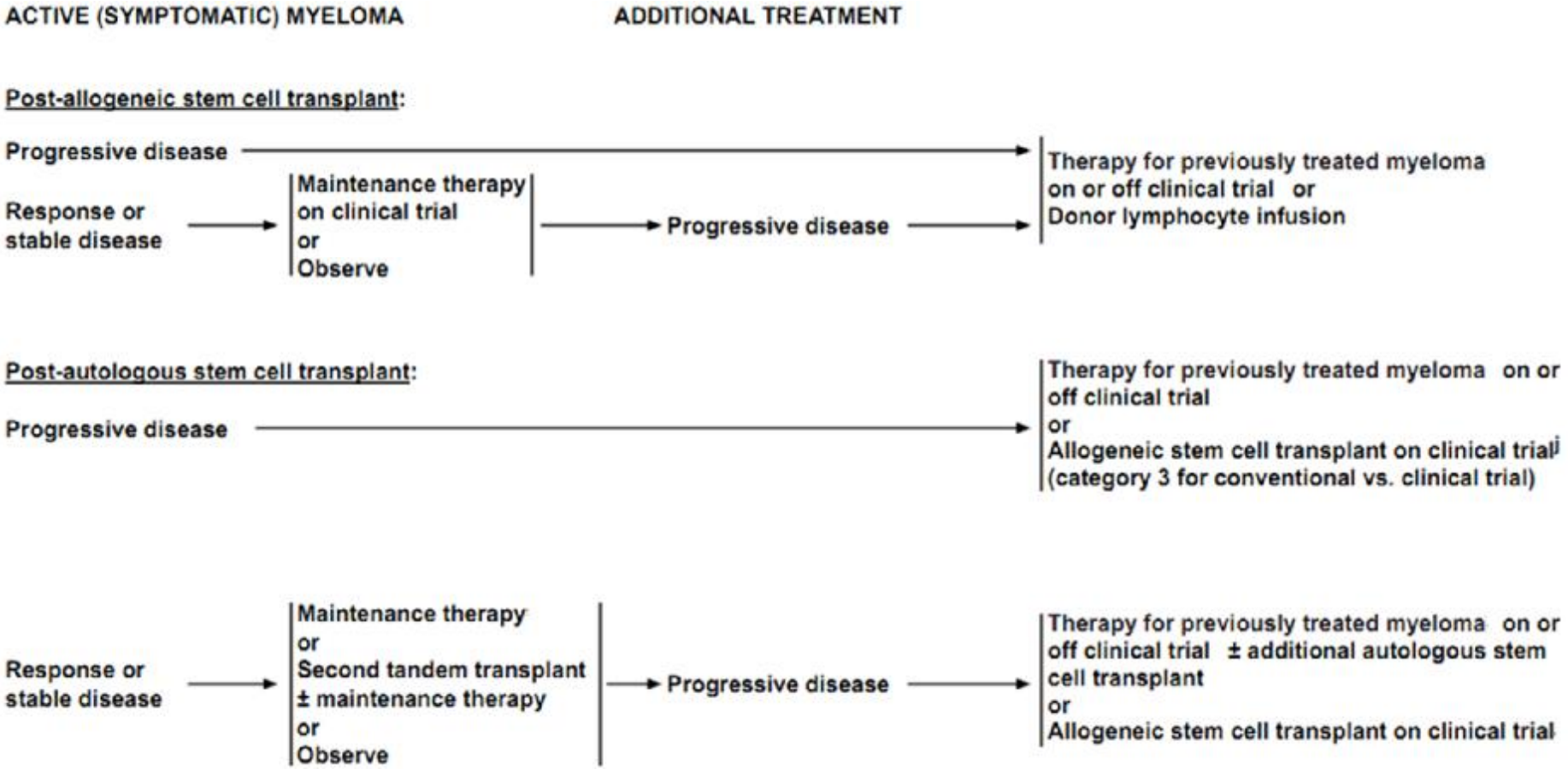
Response Criteria for Multiple Myeloma (1)

Response Category	Response criteria
CR, complete response	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma clls in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessment are needed
sCR, strigent complete response	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessment of laboratory parameters are needed
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with >four colors)
Molecular CR	CR as defined plus negative allele-specific pligonucleotide polymerase chain reaction (sensitivity 10^5)
VGPR, very good partial response	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M component plus urine M component <100 mg/24h; in patients for whom only measurable disease is by serum FLC level, >90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessment are needed
PR, partial response	≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was≥30%; In addition, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytoma is required. Two consecutive assessment are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed.
MR, minimal response for relapsed refractory myeloma only	≥25% but ≤49% reduction of serum M protein and reduction in 24-hour M protein by 50% to 89%; In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytoma is also required; No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD, stable disease	Not meeting criteria for CR, VGPR, PR or progressive disease; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD, progressive disease	Increase of 25% from lowest response value in any of following: Serum M component with absolute increase ≥0.5 g/dL; serum M component increases ≥1 g/dL are sufficient to define relapse if starting M component is ≥5 g/dL and/or; Urine M component (absolute increase must be ≥200 mg/24 h) and/or; Only in patients without measurable serum and urine M protein levels: differences between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥10%); Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytoma; development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder; Two consecutive assessment before new therapy are needed

Response Criteria for Multiple Myeloma (2)

Relapse Subcategory	Relapse Criteria
Clinical relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice *Development of new soft tissue plasmacytomas or bone lesions *Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion *Hypercalcemia (>11.5 mg/dL) *Decrease in hemoglobin of ≥2 g/dL *Rise in serum creatinine by 2 mg/dL or more
Relapse from CR (To be used only if the end point studied is DFS, disease free survival)	Any one or more of the following: *Reappearance of serum or urine M-protein by immunofixation or electrophoresis *Development of ≥5% plasma cells in the bone marrow *Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

Additional Treatment Post Stem Cell Transplant




Thank you for
your attention