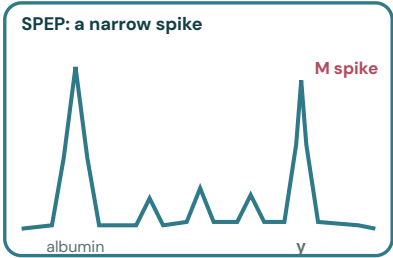


Multiple myeloma: tests, treatment by setting, options and problems during treatment

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A. Diagnosis and staging tests and what they change

Finding the monoclonal protein: four tests, each with a blind spot



- SPEP**
Finds and measures the spike
Misses small and light-chain-only proteins
- Immunofixation**
Confirms clonal; names it (IgG κ ...)
Does not measure the amount
- Serum free light chains**
κ/λ ratio (normal 0.26–1.65); light-chain myeloma
Ratio drifts up in kidney disease
- 24-h urine PEP + IFE**
Bence Jones protein; baseline
Urine dipstick does not detect it

Screen with SPEP + immunofixation + serum free light chains (+ quantitative immunoglobulins, CBC, calcium, creatinine). If a protein is found or the ratio is abnormal, add 24-hour urine electrophoresis and immunofixation. Follow a patient on the same free-light-chain assay throughout: results differ between manufacturers.

Monoclonal protein tests (UpToDate laboratory methods for monoclonal proteins review). Schematic drawing, not to scale.

Table A. Diagnosis and staging tests and what they change

Test	When	What it changes	Pitfalls
SPEP + serum immunofixation	Every suspected plasma cell disorder	Size and type of M protein; MGUS vs SMM threshold (3 g/dL)	SPEP misses small or light-chain-only proteins
Serum free light chains (κ, λ, ratio)	Screening, light-chain myeloma, follow-up	Ratio ≥100 (involved ≥100 mg/L) = myeloma; MGUS risk	Ratio rises in kidney disease; use one manufacturer for follow-up
24-h urine electrophoresis + immunofixation	Protein found or ratio abnormal; baseline	Bence Jones protein; nephrotic albuminuria (AL, deposition disease)	Urine dipstick does not detect light chains
CBC, calcium, creatinine, albumin, LDH, B2M	Every case	CRAB; R-ISS; high-risk (B2M ≥5.5 with normal creatinine)	Check ionised calcium if high calcium without symptoms

Test	When	What it changes	Pitfalls
Marrow aspirate + biopsy (CD138 or flow); FISH ± NGS	All except low-risk MGUS	≥10% clonal cells; 20/2/20; IMS/IMWG risk	Focal disease: a low count does not exclude myeloma
Whole-body low-dose CT (or PET-CT, MRI)	Every non-IgM protein except low-risk MGUS	Lytic lesions = myeloma; PET for extramedullary disease	Bone scans miss lytic lesions; X-rays are insensitive
Whole-body or spine-pelvis MRI	Suspected SMM or solitary plasmacytoma	>1 focal lesion = myeloma; rules out more lesions	Equivocal lesions: repeat in 3–6 months
Kidney biopsy	Albuminuria, or kidney injury without very high light chains	Cast nephropathy vs AL, deposition disease, MGRS	Correct bleeding risk first
HBV, HCV, HIV; echocardiogram, pulmonary function	Before anti-CD38, HCT or CAR-T	Antiviral prophylaxis; transplant fitness	Daratumumab interferes with blood-bank cross-matching

B. Treatment by setting

First-line treatment: by transplant eligibility and risk

Confirm active myeloma → FISH risk → fitness, kidneys, neuropathy, clot risk → transplant opinion (no fixed age limit)

Transplant eligible

- Induction 3–6 cycles: D–VRd or Isa–VRd (VRd if a quadruplet is not possible)
- Collect stem cells (G–CSF ± plerixafor)
- Early HCT (high-dose melphalan), or store cells for first relapse
- Maintenance: lenalidomide (± anti-CD38) ~2 years; high risk: lenalidomide + bortezomib until progression

Not transplant eligible

- D–VRd or Isa–VRd for most; DRd or VRd if frail
- VCd if lenalidomide unsafe (kidney, clots)
- 8–12 cycles, then lenalidomide-based maintenance
- Frail: dose-reduced DRd, IsaRd or Rd

Limited resources

- Bortezomib triplet: VTd or VCd (VRd if lenalidomide affordable)
- No bortezomib: CTd or MPT
- Transplant if possible (no melphalan before collection)
- After HCT: thalidomide or lenalidomide maintenance

With every regimen: osteoclast inhibitor if bone disease or osteopenia; aspirin or anticoagulant with IMiDs; levofloxacin for the first 3 months; aciclovir with bortezomib or anti-CD38; vaccines; dental check; weekly dexamethasone; subcutaneous bortezomib.

First-line pathways (UpToDate initial treatment, HCT, overview and resource-limited settings reviews). D = daratumumab; Isa = isatuximab; V = bortezomib; R = lenalidomide; T = thalidomide; C = cyclophosphamide; d = dexamethasone; MP = melphalan–prednisone.

Table B. Treatment by setting

Setting	Standard choice	Key evidence	Notes
MGUS, low risk	Observe; tests at 6 months, then every 2–3 years	Rajkumar 2005	Bone drug only for osteoporosis
MGUS, other	Observe; yearly tests	Kyle 2018	Report new symptoms at once
SMM, low or intermediate risk	Observe closely	Lakshman 2018	MRI to exclude focal lesions
SMM, high risk (20/2/20)	Daratumumab for up to 3 years (or lenalidomide ± dexamethasone); trial	AQUILA	OS 93% vs 87% at 5 years
Solitary plasmacytoma of bone	RT 35–50 Gy; observe	ILROG 2018	RT even after complete excision
Extramedullary plasmacytoma	Incomplete excision: RT 40–50 Gy; complete: observe	Ozsahin 2006	Doses <40 Gy did worse
Myeloma, transplant eligible	D–VRd or Isa–VRd × 3–6 → collect → HCT → maintenance	PERSEUS , GMMG-HD7	High risk: early HCT; two-drug maintenance

Setting	Standard choice	Key evidence	Notes
Myeloma, not transplant eligible	D–VRd or Isa–VRd; DRd or VRd if frail; then maintenance	CEPHEUS, IMROZ, MAIA	Frail: dose–reduced, dexamethasone–sparing
Limited resources	VTd or VCd (VRd if possible); CTd or MPT without bortezomib	IFM2013–04	Thalidomide maintenance after HCT
Maintenance, standard risk	Lenalidomide ~2 years (± anti–CD38)	ENDURANCE	Indefinite: same OS, more toxicity
First relapse	BCMA–directed (cilta–cel, teclistamab + daratumumab, BVd) or a triplet of unused classes	CARTITUDE–4, MajesTEC–3	Triplet if infection–prone or no access
Later relapse	BCMA if unused; talquetamab; selinexor; venetoclax for t(11;14)	MonumenTAL–1	Trials encouraged

C. Treatment options: evidence and best fit

Relapse: check what the disease is refractory to, then target BCMA

Refractory = progression on, or within 60 days of, a drug. Re-check FISH, kidneys, marrow reserve, infection risk, access.

First relapse

- BCMA CAR-T: cilta-cel (CARTITUDE-4: OS benefit)
- Teclistamab + daratumumab (MajesTEC-3)
- BVd: belantamab + bortezomib (DREAMM-7)
- Or a triplet with unused classes (DPd, DKd, KPd, PVd, IsaKd)
- Stored cells: second HCT is an option

Second or later

- BCMA if not yet used: CAR-T, bispecific (teclistamab, elranatamab, linvoseltamab) or belantamab
- After BCMA: talquetamab (GPRC5D)
- Selinexor-based, alkylators
- Venetoclax only with t(11;14)

Safety with T-cell therapies

- CRS and neurotoxicity (ICANS): step-up dosing, monitoring
- Infections: IVIG if IgG low, PJP and antiviral prophylaxis
- Belantamab: eye examinations
- Frail or infection-prone: a triplet may be wiser

Relapsed myeloma (UpToDate relapsed disease and administration reviews). D = daratumumab; P = pomalidomide; K = carfilzomib; V = bortezomib; Isa = isatuximab; d = dexamethasone.

Table C. Treatment options: evidence and best fit

Option	Best for	Evidence	Watch for
D-VRd (daratumumab + VRd)	Fit patients, standard or high risk, ± HCT	PERSEUS : 48-month PFS 84% vs 68%; CEPHEUS : 54-month 68% vs 50%	Cytopenias, infections; plerixafor more often
Isa-VRd	As D-VRd	IMROZ : 5-year PFS 63% vs 45%; GMMG-HD7	Infusion reactions, infections
VRd	When a quadruplet is not possible	SO777 : median OS NR vs 69 months vs Rd	Neuropathy (use subcutaneous, weekly)
DRd	Older, frail, pre-existing neuropathy	MAIA : 5-year OS 66% vs 53%	Neutropenia, pneumonia
VCd / VTd	Kidney injury, clot risk, limited resources	IFM2013-04 : VTd more responses	Thalidomide: neuropathy, clots, constipation
Autologous HCT	Fit patients (age is not a bar)	DETERMINATION : PFS 68 vs 46 months; OS same	Mucositis, infection; second myeloid cancers
Lenalidomide maintenance	After HCT or induction	Myeloma XI	Second cancers, cytopenias, diarrhoea
Cilta-cel (BCMA CAR-T)	Lenalidomide-refractory, 1–3 prior lines	CARTITUDE-4 : 30-month OS 76% vs 64%	CRS, ICANS, delayed neurotoxicity, cytopenias
Teclistamab + daratumumab	1–3 prior lines, not anti-CD38-refractory	MajesTEC-3 : 36-month OS 83% vs 65%	CRS, infections (IVIG, prophylaxis)
Belantamab + bortezomib (BVd)	Relapse (outside the US mainly)	DREAMM-7 : median PFS 37 vs 13 months	Corneal toxicity: eye checks
Talquetamab (GPRC5D)	After BCMA therapy	MonumentAL-1	Taste, skin and nail changes; weight loss

D. Managing problems during treatment

Preventing the complications that kill: infection and clots

Infection

- Levofloxacin for the first 3 months (TEAMM: fewer fevers or deaths, 19% vs 27%)
- Aciclovir/valaciclovir with bortezomib, anti-CD38, carfilzomib
- Pneumococcal, influenza and recombinant zoster vaccines, ideally before treatment
- PJP prophylaxis with prolonged T-cell suppression (CAR-T, bispecifics)
- HBV screen before anti-CD38; IVIG for recurrent infection with low IgG

Clots (with IMiDs)

- IMiDs: thalidomide, lenalidomide, pomalidomide
- Score the risk: SAVED ≥ 2 or IMPEDE VTE ≥ 8 = high
- Standard risk: aspirin (with gastric protection)
- High risk: LMWH, a DOAC or warfarin
- Maintenance on a single IMiD: aspirin
- After a clot on an IMiD: anticoagulate until 1–3 months after the IMiD stops

SAVED: surgery in 90 days (+2), Asian population (–3), previous VTE (+3), age ≥ 80 (+1), high-dose dexamethasone (+1 or +2). It was derived in US registries: how the "Asian" point applies to Indian patients is untested.

Supportive care (TEAMM, Drayson 2019; SAVED, Li 2019; IMPEDE VTE, Sanfilippo 2019; UpToDate infections and VTE reviews).

Table D. Managing problems during treatment

Problem	Prevent	Recognise	Act
Bacterial infection	Levofloxacin first 3 months; vaccines	Fever, cough, burning urine	Same-day assessment; IVIG if IgG low and recurrent
Herpes zoster	Aciclovir/valaciclovir with PIs and anti-CD38	Painful band-like rash	Treatment-dose antiviral
Venous thrombosis	Aspirin or anticoagulant with IMiDs (SAVED, IMPEDE VTE)	Leg swelling, breathlessness	Anticoagulate; continue until 1–3 months after IMiD
Peripheral neuropathy	Subcutaneous, weekly bortezomib; avoid in pre-existing neuropathy	Numbness, burning, unsteadiness	Reduce or hold bortezomib/thalidomide
Kidney injury	Fluids; no NSAIDs or contrast if avoidable	Less urine, rising creatinine	Urgent anti-myeloma therapy; correct calcium
Hypercalcaemia	Effective therapy; avoid dehydration	Thirst, vomiting, confusion, constipation	Fluids, steroids, zoledronic acid (denosumab if refractory)
Jaw osteonecrosis	Dental clearance before; avoid extractions	Exposed bone, jaw pain	Stop the bone drug; dental/oral surgery care
Cord compression	Imaging for new back pain	Back pain, leg weakness, bladder change	MRI within 24 h, dexamethasone, RT; surgery if retropulsed bone

Problem	Prevent	Recognise	Act
CRS / ICANS (CAR-T, bispecifics)	Step-up dosing; trained centre	Fever, low BP, low oxygen; confusion, writing change	Tocilizumab, steroids per grade
Cardiac events (carfilzomib)	Blood pressure control	Breathlessness, chest pain	Hold drug; cardiology