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Citation: EMJ. 2026;11[3]:58-63. https://doi.org/10.33590/emj/IC6RV098

Q1 Your career has spanned a period of remarkable progress in the diagnosis and treatment of amyloidosis. What inspired you to specialise in this field, and which milestones stand out as having most fundamentally changed the way clinicians care for patients today?

I went into amyloidosis research in 1999 as a very naïve nephrologist who wanted to do clinical-based research in multisystem diseases. I was very lucky to coincide with a period of huge advances spanning the understanding of pathogenesis to innovations in treatment. Amyloidosis moved from a disease that very few had heard of, and even fewer could spell, to a high-profile disease with a number of innovative specific treatments, and hopefully more on the way.

This was such a productive period that I have struggled to keep the milestones down, but I believe they are as follows (since 1999):

1999: The UK National Amyloidosis Centre (NAC) was founded by Philip Hawkins and Mark Pepys, University College London, UK. The centre pioneered routine serum amyloid P component scintigraphy for quantifying whole-body amyloid burden.

2001: Serum free light chain assays are validated,[1] transforming diagnosis and monitoring of amyloid light chain (AL) amyloidosis.

2002: Genetic screening shows that hereditary amyloidosis is commonly misdiagnosed,[2] establishing the importance of routine genetic testing in the diagnosis of amyloidosis.

2004: The Mayo cardiac biomarker staging for AL amyloidosis is published and becomes the global prognostic standard, which has subsequently been updated but not replaced.[3]

2005: First description of the characteristic cardiovascular MRI appearance of cardiac amyloidosis, establishing a diagnostic pattern.[4]

2005: First major description of ^{99m}Tc-DPD bone scintigraphy in transthyretin (TTR) cardiac amyloidosis,[5] the basis of the 'Perugini grade' later formalised by Gillmore et al.[6] in 2016 into a non-biopsy diagnostic pathway for TTR amyloid cardiomyopathy.

2007: In amyloid AA amyloidosis, normalising circulating serum amyloid A protein levels is defined as the treatment target,[7] confirming that fibril precursor supply predicts outcome.

2008: Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is identified,[8] a new systemic amyloid type.

2009: Mass spectrometry-based amyloid typing from routine biopsies is found to be more reliable for typing than immunohistochemistry.[9]

2012: Tafamidis is approved for hereditary TTR amyloidosis (ATTR) polyneuropathy,[10] this is the first specific agent for hereditary amyloidosis and the first precursor protein stabiliser.

> **The way modern healthcare is structured is not always helpful in recognising multisystem disease**

2015: Wild-type ATTR is recognised as a common cause of heart failure with preserved ejection fraction.[11]

2015: Trial of birtamimab, an anti-fibril monoclonal antibody targeting misfolded light chain deposits, in AL amyloidosis;[12] Phase 3 VITAL trial later suggested survival benefit confined to Mayo Stage IV patients.[13]

2018: The first gene silencers are approved for hereditary ATTR polyneuropathy: patisiran, the first small interfering RNA therapeutic,[14] and inotersen, the first antisense oligonucleotide.[15]

2019: Tafamidis is approved for ATTR cardiomyopathy (ATTR-CM);[16] first treatment for ATTR-CM.

2021: The combination drug treatment of daratumumab, cyclophosphamide, bortezomib, and dexamethasone is approved for AL amyloidosis,[17] and is the first monoclonal antibody regimen in AL amyloid.

2021: First-in-human systemic CRISPR-Cas9 gene editing study in hereditary ATTR.[18]

2022–3: Second-generation gene silencers approved for hereditary ATTR polyneuropathy.[19,20]

2024: Acoramidis is approved as second-generation oral TTR stabiliser for ATTR-CM.[21]

Q2 Despite growing awareness and improved diagnostic tools, many patients with amyloidosis still experience significant delays before receiving a diagnosis. What do you see as the main barriers to earlier recognition, and how can clinicians across different specialties improve diagnostic pathways?

For patients, delayed diagnosis is a huge issue. Behind the 'average 2.7 years to diagnosis' statistic is an individual who felt something was very wrong long before; the patient surveys are devastating on this point.[22]

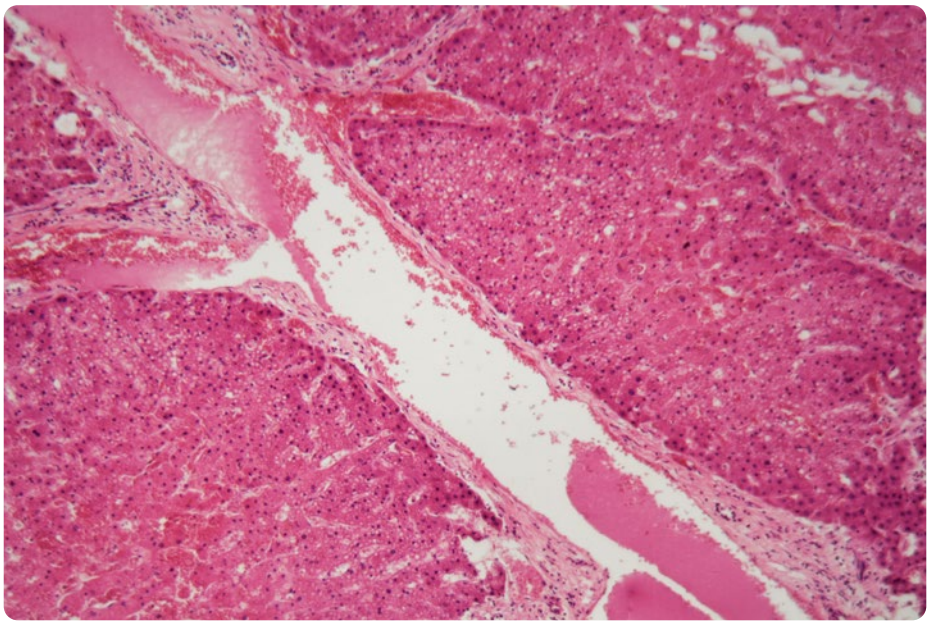
The way modern healthcare is structured is not always helpful in recognising multisystem disease. Tingling hands go to the neurologist or surgeon, breathlessness to the cardiologist, and fatigue gets blamed on getting older. All too often, each specialist offers a reasonable but wrong explanation, and that leaves the patient trying to connect the pieces.

The best solution should not ask any one clinician to become an expert in all rare multisystem diseases. There are real, systematic opportunities to support diagnosis. Examples of this include routine Congo red staining of carpal tunnel tissue in older adults, AI-assisted recognition of unusual echo strain patterns, or collation of a paraprotein alongside biomarkers of renal or cardiac disease. None of it should need anyone to be cleverer, just a supporting system that helps physicians spot the red flags for rapid onward referral.

Q3 Your research has focused extensively on the phenotypic characterisation of amyloidosis. How has a better understanding of disease heterogeneity changed the way clinicians diagnose, monitor, and manage patients, and what important questions remain unanswered?

The most important message is that amyloidosis is not a complete diagnosis. It is vital to recognise that, although all types of amyloid share physiochemical properties and many share a broadly similar clinical picture, current management relies on precise typing and treatment targeting the fibril precursor protein. Consequently, expert centres that can provide definitive typing have become the recognised standard of care.

There is a lot we still do not really understand. The biggest issues, in my mind, include a better understanding of the determinants of organ trophism, and whether it will become possible to predict organ involvement for individual



patients; understanding the mechanisms underlying variable penetrance and expressivity in hereditary amyloidosis; and, most importantly, understanding how amyloid is cleared. We know from clinical observation that some patients appear able to clear more than half their amyloid load within a year, whereas others with apparently equivalent suppression of precursor protein show no detectable clearance. The hope is that better understanding of how aberrantly folded protein deposits are handled might result in novel therapies enhancing clearance mechanisms.

Q4 Amyloidosis often requires input from multiple specialties, including cardiology, nephrology, neurology, haematology, and rheumatology. What are the key ingredients of an effective multidisciplinary approach, and how can we improve coordination of care for these patients?

A multidisciplinary team only really works when it meets regularly with shared time and space. The team has to be able to see and discuss patients together. Coordinated care works best if there is a single referral pathway and a clear definition of responsibilities and #of the individual taking overall responsibility for care.

In my view, healthcare systems should cover designing pathways specifically for a multisystem disease, including shared clinics, shared access to clinical records and investigations, and well-attended regular multidisciplinary meetings. It should also ensure a single point of contact for patients, and enough system resources to allow rapid reassessment and additional investigations when required.

Q5 The therapeutic landscape for amyloidosis has evolved rapidly in recent years, with advances ranging from gene-silencing therapies and TTR stabilisers to emerging amyloid-targeting approaches. Which recent advances do you believe have been the most transformative, and which research directions hold the greatest promise for further improving patient outcomes over the next decade?

If you'd asked this question 15 years ago, the honest answer would have been "not much." Now it's almost an embarrassment of riches, which is a much better problem to have.

The single most transformative change, I think, has been simply having anything at all approved for TTR amyloid. Previously, a diagnosis of ATTR-CM was essentially treated supportively, with management of cardiac failure and arrhythmias. The recognition of highly suggestive features on cardiac imaging, combined with specific treatments, has changed the disease landscape and enormously increased awareness and diagnosis.

Close behind that is gene-silencing: patisiran, then inotersen, then their successors that are dosed every few months instead of every week. Turning off the liver's production of the TTR protein at its source, rather than just mopping up after it, was a genuinely different way of thinking about treatment, and is proving effective.

And for AL amyloidosis, adding daratumumab to standard chemotherapy has been transformative in a less glamorous way: not a new mechanism exactly, but deeper, faster clonal responses that translate into organ recovery, which is what patients care about.

Looking ahead, the thing I find most exciting is the shift from stabilising or slowing amyloid deposition to clearing it away via therapeutic antibodies that target the fibrils already in the heart or nerves. If that works reliably, it changes the conversation from "let's try to stop this getting

worse" to "let's see some of that damage recover," which is a lovely conversation to be able to have with a patient.

The other direction worth watching is gene editing as a single treatment. It's early days, but it looks promising as a route to long term cure in hereditary TTR amyloidosis.

If I had predict what will matter most over the next decade, it's probably not a single new drug, it's working out how to combine these tools sensibly, and catching the disease early enough that organ function and quality of life is protected.

Q6 The development of effective therapies for rare diseases depends not only on scientific advances, but also on well-designed clinical trials and appropriate regulatory pathways. Drawing on your experience with the Medicines and Healthcare products Regulatory Agency (MHRA), what do you see as the biggest challenges and opportunities when it comes to translating promising amyloidosis research into routine clinical practice?

Rare disease drug development is a reminder that science solving a problem is less than half the battle. The other half is convincing a regulator, with a disease too rare to run the trials that medicine normally insists on, that you can demonstrate an effect.

The central headache is simply numbers. A trial big enough to prove a drug saves lives needs patients that amyloidosis, mercifully, doesn't have in abundance. So, the field has had to get rather inventive, using organ response and biomarkers as early markers of benefit rather than waiting years for a mortality signal, borrowing statistical strength from natural history registries instead of insisting on a fresh placebo arm for every trial, and running master protocols that test several ideas across several amyloid subtypes under one umbrella rather than starting from scratch each time.

That last point raises an ethical issue that's rather particular to this field: now that effective treatments exist, putting a newly diagnosed patient on placebo starts to feel genuinely uncomfortable, which pushes trials towards active comparators or "add-on" designs, which are trickier to run and analyse.

The regulatory side has been good to this field lately. Accelerated pathways (e.g., orphan designations, rolling review, early scientific advice) mean a promising therapy doesn't have to queue behind the ordinary process, and having UK, European, and American regulators each running their own path means more than one door to knock on, if occasionally more paperwork behind each one.

But honestly, the part that trips things up the most in practice isn't the licencing, it's what happens after. A drug be approved and still take years to reach a patient because the health economics case for an ultra-rare, high-cost therapy is hard to build. That gap between 'licensed' and 'actually prescribable' is, in my view, the bit that deserves far more attention than it currently gets.

The nicest opportunity, I think, is international collaboration by pooling patients, sharing registries, and treating a rare disease trial as a genuinely global project.

Q7 Many clinicians associate AA amyloidosis with a historical disease burden, yet advances in biologic therapies have dramatically changed outcomes for patients with systemic autoinflammatory disorders. How has the management of AA amyloidosis evolved during your career, and what lessons from this field might inform the treatment of other forms of amyloidosis?

Over my career, AA amyloidosis has changed from being a relatively frequent finding to becoming a genuinely rare cause of renal amyloid. This reflects advances in the control of chronic inflammation in general, particularly the widespread introduction of highly effective biologic therapies into rheumatology practice. As a result, we now see very few cases of AA amyloidosis complicating inflammatory arthritis or autoinflammatory disease. There has been a shift in epidemiology so that the major underlying causes are now long-term substance use disorder in people who inject drugs, chronic inflammation of unknown aetiology, and metabolic inflammation related to obesity.

"AA amyloidosis has changed from being a relatively frequent finding to becoming a genuinely rare cause of renal amyloid"

The lessons from this are both highly applicable to other types of amyloid and specific to AA amyloidosis. The broadly applicable finding is that, if fibril precursor proteins are suppressed from the outset, amyloidosis does not develop. The more specific observation is that, as a complication of chronic inflammation, the treatment advances that have dramatically changed the epidemiology of AA amyloidosis have been driven by advances in the treatment of the underlying disorders. Because these conditions require treatment in their own right, there have not been the same challenges regarding the detection of subclinical amyloid and the timing of interventions that we are now facing, particularly in ATTR.

Q8 Are there important sex differences in the presentation, diagnosis, or progression of amyloidosis that clinicians should be more aware of? Do women face particular challenges in recognition or access to diagnosis, and what further research is needed to better understand these differences?

That 'more common in men' pattern holds in almost all types of amyloidosis, but ATTR takes it to an extreme: wild-type cardiac ATTR cohorts are approximately 90% male. The underlying mechanisms for this are not yet clear, although increased mechanical stress and hormonal effects have both been considered.

We know that in hereditary ATTR, penetrance can be affected by sex, and in some cohorts of those with the V30M mutation, men seem to be affected earlier and more severely than their female relatives. In addition, in some populations, maternal inheritance has been associated with higher penetrance and earlier onset.

A third of patients with AL amyloidosis wait over a year and see five or more physicians

What's much better documented is that when women do get wild-type ATTR, they tend to be older at diagnosis and have more advanced disease, which raises concerns around ascertainment bias and systematic under-referral and under-investigation of women. This has already translated into bias in the treatment data, as the pivotal ATTR drug trials were approximately 90% male.

Sex-stratified re-analyses of existing registry and trial data, and of referral patterns for ^{99m}Tc-DPD scanning and cardiac MRI, may help us understand how much of this is cultural rather than biological.

Q9 As clinical lead of the NAC, you have helped shape one of the world's leading specialist services. What lessons from the centre's model of care could be applied more broadly to improve outcomes for patients with amyloidosis and other rare diseases?

The NAC model has benefited from central funding by NHS England Highly Specialised Services, and over the last 25 years this has supported both clinical care and research, with innovations in diagnostics and treatments, the building of large-scale cohorts with long-term follow-up, and specialist training. Co-location of the NAC laboratory facilities for diagnosis and typing of amyloid with university space encourages translational and reverse-translational research.

The mixed-specialty setup is essential for a multisystem disease, as is the weekly multidisciplinary team. Planned visits with all investigations done at a single time in one site support prompt decision-making, and the current development of a national networked hub-and-spoke model will improve local care provision and reduce unnecessary patient travel for follow-up visits.

The lessons for other rare diseases: concentrate expertise for the whole disease pathway in a specialised and well-funded centre, commit to following patients for decades, and support a network with shared experience, research, and training opportunities.

Q10 Beyond scientific advances, what do you see as the greatest unmet needs for people living with amyloidosis today, and where should future research and healthcare policy focus to achieve the greatest impact?

Earlier diagnosis tops every patient survey; a third of patients with AL amyloidosis wait over a year and see five or more physicians before they are diagnosed, and nearly two-thirds say the diagnostic process needs serious improvement.

Access without prolonged travel is a real need. Concentrating expertise in a handful of national

centres makes rigorous diagnosis possible, but it also means patients face a long round trip for every review. In the UK, we are addressing this with the setup of a network with designated regional centres with central funding.

Recognition of the burden amyloidosis inflicts on patients and families deserves more attention. This is a lifelong, life-shortening diagnosis, and a caregiver survey found people spending 6 hours a day on practical care and another 4 hours on emotional support, with impact on their own quality of life. We measure organ function pretty well, but we measure what the diagnosis does to the person sitting next to the patient in clinic very badly.

Q11 Finally, what advice would you give to clinicians and researchers entering the field of amyloidosis, and what discoveries or developments do you hope to see over the next decade?

If I can borrow rather than invent the best advice, my father gave an interview more than 20 years ago, and two things he said have stuck with me. The first he got from his own father: be sceptical, especially of the received wisdom of the rich and powerful; coming with a fresh eye and questioning existing dogma is immensely valuable. The second: it matters what you discover, not where you publish it.

Don't, meanwhile, let the recent wave of approved treatments make it feel like the interesting questions all have answers. If anything, they highlight the harder ones: we still struggle with why the misfolded protein deposits in one organ over another, how identical mutations produce different outcomes in the same family, and how amyloid regression occurs and how this can translate into reversal of organ damage.

As for the next decade, I'd hope that we get a more sophisticated understanding of the risk factors for amyloidosis, that diagnostic delay becomes a historical embarrassment, and that we move into an age of individually tailored treatment, combining different treatment strategies with hope of long-term cure.

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