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# Hertfordshire Journal Of Medicine

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### **Publisher: University of Hertfordshire**

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**Cover Image:** Cyberknife

Another year is drawing to a close and it is time to reflect and plan for the next year. Much has happened and there are several new developments which merit attention. The result of the GMC National Training Survey 2011 has now been released. This is an important source of regulatory evidence and an essential read for anyone involved with postgraduate medical training.

There are some national trends prominent in the GMC National Training Survey 2011. It is heartening to see that satisfaction with training continues to grow and nearly eighty percent of trainees rate their training as excellent. However, there are areas which raise concern. Nearly a third of trainees do not get any feedback from supervisors, a quarter feel ill prepared for their next post and two thirds work over and above the European Working Hours limit of forty eight hours a week. There are also concerns regarding supervision, handover and intensity of work. Medical educators and managers will need to work together and look at ways of improving the educational experience for our trainees.

There have been several prominent trends in medical education with focus on accountability and professionalisation with the result that there are calls for accreditation and professional development of medical supervisors. There is scant national guidance on the competencies or training required of postgraduate medical supervisors. No agreed standards exist across the United Kingdom and there is no consensus on minimum acceptable training required to fulfil this role. Lack of defined quality markers and curriculum makes the situation more complicated.

Some deaneries have taken the initiative and have produced a professional standards framework. The minimum requirements include training in workplace assessments, educational supervision, equal opportunities and familiarity with the educational programmes, curriculum and learning portfolios.

GMC Education Strategy 2011 – 13 document concludes that there should be a framework for regulating all stages of medical education. Standards, outcomes and a quality assurance will be the main focus and surveys will be an important source of regulatory evidence. From 2013, it will apply to clinical supervisors and educational supervisors.

It is well recognised that effective supervision of trainees involves skills that are different from other more general competencies expected of a trainer.

Hence it is widely accepted that trainers with additional postgraduate educational roles should be selected, appropriately trained and be able to demonstrate their ability as effective trainers.

A framework for the Professional Development of Postgraduate Medical Education has been proposed by the Academy of Medical Educators. The framework is designed around seven key areas of activity, all of which relate to the role of the postgraduate medical supervisor. Educational supervisors are expected to meet the requirements of all seven areas. This project has been commissioned by the Department of Health. Preparatory reports and supporting evidence is available at [www.medicaleducators.org](http://www.medicaleducators.org).

This proposed framework recommends a portfolio-based process where evidence is collected in the seven domains listed. It is also recommended that performance review of an educational supervisor should be considered at their annual appraisal along with other clinical and non-clinical activity. Formal appraisal should be conducted every five years to accredit and re-approve educational supervisors. Multisource feedback and GMC trainees survey results for the supervisors clinical area will become important documentary evidence for supervisor appraisal.

Over the next year we will be hearing more from the GMC regarding its responsibility for defining regulatory standards and for quality assurance. On the other hand we need to be prepared and supervisors should maintain a portfolio of evidence. A suitable job plan with appropriate workload and time to develop trainees is imperative in developing a well trained workforce.

HJM has had an exceptional year and we have received a record number of articles. This is reflected by the diversity and quality of articles published in this edition. There is a thought provoking editorial by Mr James Quinn, Medical Director East & North Herts NHS Trust. The outstanding editorial by Professor Peter Hoskin is an essential read for anyone even remotely associated with oncology services. There are several excellent reviews and interesting case reports which will be of interest for colleagues working in general practice as well as in secondary care.

**Shahid A Khan**  
Editor HJM

## **The Changing Face of Medical Education – A Personal Perspective**

Some believe that the quality of medical training is deteriorating. I disagree, from what I can see; it is the best it has ever been.

I trained in London in the 1980's and while the standard of my training was good for its time, it wasn't fit for purpose. Drunk on the technological advances of the mid 20th century we in the health service had forgotten the hard earned lessons of the pre-antibiotic era that the careful application of technique could and would save lives. I could give numerous examples but the most striking to me is the introduction of simple infection control measures which would have been familiar to Florence Nightingale and which have been devastatingly effective with many lives saved as a result.

In our glee at the armamentarium of potent drugs available to rescue the sick we lost our way and the improvements in healthcare which could potentially have been ours in the 70's and 80's have been delayed until the very end of the last century and the first decade of this.

We all know that fluid resuscitation saves lives but why was it done so badly for so many years? Our adherence to well tested fluid resuscitation algorithms is now much improved (although not perfect) and this improvement is down to advances in medical education along with better teamwork and better focussed clinical audit.

This loss of focus in doing the right thing every time was reflected in the focus of our medical education. We were taught about how these new drugs worked but not how to use them safely. We were imbued with the success of new surgical techniques but less emphasis was placed on considering the risks. It was ok to have 'a go'. If you succeeded that was great, if you failed well at least you had tried. The apprenticeship system for junior doctors was 'watch and learn'. There was little formal training. Training was focussed on developing the independent professional able to deal with the unexpected but left one less well equipped to deal with the expected.

You may think that I exaggerate but what could be more expected than a cardiac arrest on a medical ward? Yet formal cardiac resuscitation training for junior doctors was not common practice in the 80's.

This generation of junior doctors surveys a very different landscape. You will see ever more importance being placed on teamwork, safe practice and the correct use of treatment algorithms proven scientifically to lead to the best medical outcome. You will have closer supervision and will work many fewer hours per week although the intensity of that work will be high.

To some extent these changes will threaten the medical autonomy of doctors. Freedom of action will be curtailed by better knowledge of what works and what doesn't, and what doesn't will no longer be tolerated.

The goal will however be that medical outcomes will continue to improve in the absence of new wonder drugs and surgical techniques. You will be carefully taught procedures but some of you may be frustrated at the pace of progress of your practical experience.

As trained consultants you will have less experience than earlier generations did and you may be less prepared for the unexpected. You will however be much better equipped to deal with the expected which makes up the majority of medical practice and the consistency of practice that you will apply will make you better doctors and lead to better outcomes for your patients.

**James Quinn**  
Medical Director  
East & North Herts NHS Trust

## **Regional Developments in Non-Surgical Oncology**

Peter Hoskin, Mount Vernon Cancer Centre. Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex HA6 2RN UK

### **Developments in Clinical Oncology**

Mount Vernon Cancer Centre which is part of East and North Hertfordshire NHS Trust, is one of the country's largest non-surgical Cancer Centres. The management of patients with malignant disease has changed dramatically in recent years with improved outcomes in many areas where in the past few treatment options were available. The main modalities for the treatment of cancer remain surgery, radiotherapy and systemic treatment which may span a range of options including chemotherapy, biological agents and hormone manipulation. In all of these areas, substantial advances have been made and the clinicians at Mount Vernon have played an important role.

### **Radiotherapy**

Radiotherapy is the treatment of disease with ionising radiation, typically in the form of high energy x-rays produced by linear accelerators. The accuracy and precision with which radiation is delivered in the clinical setting has changed considerably in recent years with the advent of more complex beam shaping devices, called multi-leaf collimators and the ability to take diagnostic x-ray images on the high energy linear accelerator to ensure the accuracy of treatment delivery each day across a lengthy course of treatment. Intensity modulated radiotherapy (IMRT) is now emerging as a standard for the delivery of high dose curative radiotherapy in many sites of the body. At Mount Vernon, most patients with head and neck cancer and cervical cancer receive this treatment as well as selected patients with prostate cancer. IMRT is a complex means of radiation delivery in which the intensity of the beam varies across its profile and between five and seven individual beams are used to produce a three dimensional volumetric dose distribution. This can be tailored to virtually any shape within the body and equally important shaped to avoid surrounding normal structures, thus not only increasing the accuracy of radiation delivery to the cancer, but also reducing significant radiation-induced side effects.

Even greater precision can be achieved using a technique called stereotactic radiotherapy. In 2010, Mount Vernon was the first cancer centre in the United Kingdom to install a Cyberknife machine for NHS patients. The first patient was treated on the 31<sup>st</sup> August 2010, and since then, over 70 patients have received stereotactic radiotherapy with this equipment. The principle of Cyberknife

is to deliver radiation to a very small precise volume using multiple 'beamlets'. Each beamlet may have a diameter of only 10 to 20 mm and 200 or more of these small beamlets will be directed onto the site to be treated to enable a high radiation dose to be concentrated there. Equally important, whilst doing so it will avoid delivering excessive dose to normal critical structures with highly complex planning algorithms which can define the areas through which radiation will pass and weigh the importance of radiation delivery to different structures. This technology allows us to deliver potentially curative doses of radiation to sites which have previously been difficult to access safely and to do so with either single treatment episodes or a short course of 3 to 6 treatments compared to a lengthy course of 7 to 8 weeks using conventional techniques. It also provides the opportunity for some patients to have re-treatment to previously irradiated areas which has previously not been a realistic proposal in the curative setting. One of the important features of Cyberknife is the ability to track tumours during treatment. This is achieved by two tracking x-ray beams which feed data back to the control and enable the beam to be adjusted for movement of the target because of changes in the body's shape or function. This is particularly important when treating lung tumours and those in the upper abdomen where respiratory and cardiac movement has a significant impact on tumour position and shape.

An alternative means of delivering radiation is using brachytherapy. This does not use external beams of x-rays, but directly places a radiation source into the body. The brachytherapy unit at Mount Vernon is one of the most active in the country and has been at the forefront of developments in this field. The use of CT and MR Imaging to adjust dose delivery during brachytherapy has been a major advance in recent years and we are fortunate in having a dedicated open bore MR to enable our brachytherapy patients to have MR-guided dose delivery which both increases the accuracy and allows us to treat more extensive areas than previously. Prostate cancer is one of the largest areas of brachytherapy activity and at Mount Vernon we have pioneered the use of high dose rate brachytherapy using only one or two treatments. Thus curative treatment can be delivered over 24 hours with an overnight stay in the hospital, replacing a lengthy course of 7 to 8 weeks external beam radiotherapy.

### Chemotherapy

New chemotherapy drugs often grab the headlines in the press, being heralded as a major advance in the treatment of cancer. The development of a new cancer drug reflects many years of endeavour from the first biochemical and laboratory experiments to the final clinical trials confirming the superiority of a new agent over current practice. At Mount Vernon there is considerable activity in the research of new drugs with early phase trials evaluating toxicity and early efficacy alongside phase 3 trials comparing new agents with standard treatment. Eligible patients treated for all the major organ types and some of the rarer cancers at Mount Vernon will be offered entry into these studies. In doing so many patients are able to receive new drugs ahead of their general release, and at no cost to the local health economy.

One of the new areas of interest is the development of drugs which do not specifically damage the cancer cells, but target their blood supply and its development, which is essential for a new tumour colony to be able to survive and grow. Bevacizumab is now widely available and has been shown to improve results in many of the common solid tumours including colorectal cancer, ovarian cancer and breast cancer. This drug is a monoclonal antibody which works by targeting vascular development within the tumour, blocking vascular endothelial growth factor. Thalidomide once used with notoriety in early pregnancy has had a rebirth as an effective anti-vascular agent in malignant disease and is now one of the standard drugs used in the treatment of multiple myeloma. A newer derivative lenolidamide is also now available with greater activity. Another new drug which has greatly improved the outcome in myeloma is bortezomib which is a proteasome inhibitor. Proteasomes regulate protein expression and function within the cell, and present a new target for anti-cancer drugs. Bortezomib, thalidomide and lenolidamide are now also widely used in multiple myeloma and with these new drug combinations, the outlook for patients with this disease has improved considerably, adding many years to the prognosis.

A greater understanding of the genetic changes in malignancy have led to two important new drugs for melanoma, another cancer with a dire prognosis once it has metastasised. One of the mechanisms by which signals from the growth factor receptor on the cell surface are passed to the nucleus is through the BRAF kinase pathway. BRAF is a member of this family of kinases and a mutation in BRAF is found in 30 to 60% of melanomas. The mutated form activates a signal transduction pathway (MAPK-ERK) which enhances the proliferation and metastatic potential of tumour cells. A new drug called vemurafenib has been developed which

is a selective inhibitor of the mutated BRAF. Melanoma patients who have this specific mutation have a response rate approaching 70% using this drug and significant improvements in survival have been found compared to conventional chemotherapy using dacarbazine.

Whilst the immune system is known to be critical in the regulation of malignant cells and their ability to develop into clinically significant cancer, manipulations of the immune system to date have been disappointing. A new drug however, ipilimumab, has been shown to have a dramatic effect in melanoma. This drug works through cytotoxic T lymphocytes binding to PDL-1 which is an antigen on the cell surface playing a critical role in regulating natural immune responses. Again compared with conventional treatment, this drug has been shown to improve survival in patients presenting with metastatic melanoma.

These above are few examples of the ever increasing and improving options for drug treatment in cancer, and whilst each make only a small incremental gain, the overall effect may result in a substantial improvement in both quality and quantity of life for many patients.

### Hormonal Manipulation

Certain cancers, in particular breast cancer, uterine cancer and prostate cancer are regulated by the hormonal environment. Thus oestrogen suppression is effective in breast and uterine cancer; androgen deprivation results in dramatic responses in prostate cancer. Unfortunately however, most hormone responses are maintained for a limited period. In prostate cancer the concept of hormone resistant prostate cancer (HRPC) is well recognised with most patients achieving an excellent initial response to withdrawal of testosterone only to relapse 2 to 3 years later. The management of HRPC is unsatisfactory with only one modestly effective chemotherapy agent available to date, taxotere. To this has recently been added a new chemotherapy drug cabazitaxel which shows improved activity compared to other second line chemotherapy agents including an improved survival. The major recent advance in the management of HRPC however has been the development of new drugs which target the androgen hormone system through different processes to the conventional LHRH agonists and peripheral antiandrogens. One of these, abiraterone, has recently been licensed for patients who have progressive disease despite androgen deprivation followed by first line chemotherapy. This drug targets intracellular testosterone production which is thought to be one of the main mechanisms of

resistance developing in the prostate cancer cell. Many Mount Vernon patients have already been fortunate enough to receive this drug as the clinical trials in which it was evaluated were active at the Cancer Centre over the last 2 years.

### Summary

The field of non surgical oncology continues to expand. With the increasing incidence of cancer and an ageing population, the demand for these treatments will increase year by year. The challenge for us is to provide state of the art treatment in a resource limited health setting where the new drugs showing survival advantage may

prove too expensive for approval by NICE and the new complex technology required for modern radiation delivery is beyond the means of NHS providers. Notwithstanding these difficulties treatment for our cancer patients continues to improve and develop year by year with consequent increases in survival and quality of life.

### Peter Hoskin

Consultant Clinical Oncologist  
Mount Vernon Cancer Centre  
Professor of Clinical Oncology, University College  
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Dear Editor,

May I make some comments with regards to the case report by Drs. Das and Ghosh "An Unusual Barrier to Effective Rehabilitation Following Critical Illness Neuropathy".<sup>1</sup>

The authors state that "the radiographs show myositis ossificans, which is often termed heterotopic ossification". They correctly comment that there is ossification in the gluteal muscles. However, in the discussion, they state that heterotopic ossification occurs between muscle planes and not in muscle itself. This is incorrect. There are many types of heterotopic ossification of which myositis ossificans is one. This is ossification of the muscle and is confirmed by CT in this case.

In the discussion on the radiological investigations, some of the views expressed are misleading. Scintigraphy is very sensitive to the deposition of calcium phosphate, either as calcification or ossification. It is not however specific for myositis ossificans. CT is also very sensitive and tends to be more specific as the condition progresses. MR can also be helpful. If the condition is suspected, CT is the investigation of choice.

The condition is currently most commonly seen following traumatic amputation. It is a frequently encountered problem in servicemen who have lost a limb in Afghanistan. The Americans like to use radiotherapy to limit the progression but surgery is the norm in the UK. This is an interesting case report. I hope my comments clarify some minor points.

**Peter Brooks**

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**References**

- 1 Das S, Ghosh P. An unusual barrier to effective rehabilitation following critical illness neuropathy. *HJM* 2011;6:11-13.

**Authors' Reply**

Dear Editor,

We thank Dr Brooks for his letter which clarifies a few points relating to our article.<sup>1</sup> Due to the limited text for the 'case report', we have not been able to discuss the pathogenesis in detail.

Heterotopic Ossification (HO) is formation of bone within soft tissue. However, this morbid soft-tissue ossification has a pathogenesis distinct from metastatic and dystrophic soft-tissue calcification. The transformation of primitive cells of mesenchymal origin, present in the connective tissue septa within muscle, into osteogenic cells is thought to be the pathogenesis of HO.<sup>2</sup>

With regards to radiological investigations, the focus was on early detection. The review articles by Luc Vanden Bossche et al<sup>3</sup> and Dia Shehab et al<sup>2</sup> both suggest three phase bone scintigraphy as the most sensitive method for the early detection of HO. However, we do agree that local protocols may be different and CT may be more widely used and be the imaging modality of choice in our Trust at present.

A detailed discussion on management is again beyond the scope of our text. Table 2 of the review article by Dia Shehab et al<sup>2</sup> highlights the criteria for recommending surgical removal of HO.

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**PSA as a Biomarker for Prostate Cancer and the Great Screening Debate**

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In Western societies prostate cancer represents the commonest solid tissue malignancy and the second leading cause of cancer death in men (after lung cancer). With over 20,000 new cases diagnosed in the United Kingdom every year (and 134,000 in Europe as a whole) the disease has a significant impact on the health of the nation.<sup>1</sup> For an individual man the estimated lifetime risk of developing clinical prostate cancer is approximately 10% with the risk of death from it approaching 3%.<sup>2</sup> It is a large and growing problem with the annual cost of treating prostate cancer in England and Wales alone being around £100 million a year. Synonymous with prostate cancer and its management is the prostate specific antigen (PSA). There are many controversies surrounding the role of PSA. For a start it is neither prostate specific nor an antigen. Nevertheless it is a test that vast numbers of patients are aware of and (for some across the Atlantic) the right to PSA screening for prostate cancer ranks alongside life, liberty and the pursuit of happiness. The role of PSA testing in the United Kingdom however (and Europe beyond) is much more circumspect. Nevertheless, patient surveys appear to consistently report a broad-based approval for screening efforts. One such study reported in the British Medical Journal revealed that the vast majority of patients with suspected or confirmed prostate cancer were keen that friends and family undergo routine testing. Significantly however their reasoning included a belief that early diagnosis would reduce mortality and improve quality of life – evidence that is to date clearly lacking.<sup>3</sup> There is however a very real difference between the role of PSA testing in men with lower urinary tract symptoms (LUTS) - which is widely acknowledged - and that of its role in an asymptomatic group.

Fundamentally, PSA represents a glycoprotein (its official name is human Kallikrein 3 or hK3) whose principal function is to liquefy the seminal coagulum and dissolve the cervical cap (thus releasing spermatozoa to continue their journey to fertilise the ova after ejaculation). PSA can be detected in the serum of healthy individuals (both male and female) and is found at low levels in amniotic fluid, urethral glands, breast and salivary glands. It is normal for a small amount of PSA to enter the circulation in most individuals and as a result it can routinely be detected - a fact exploited in the Hybritech Tandem-R PSA test - the first commercially available test for PSA. The precise level depends on a number of factors not least of which are age, prostate size and the presence of pathology (either benign or malignant). Certainly

an underlying prostatic malignancy may disrupt barriers between parenchyma and the circulation such that higher levels of PSA can be detected in serum samples. All prostatic epithelial cells whether hyperplastic, cancerous or normal synthesise PSA. As a result PSA testing is far from perfect - the main problem being that PSA levels may be raised in the absence of pathology and be normal in the presence of disease. Additionally, PSA levels are also inherently variable and as such affects the interpretation of any one single result. Whilst many would accept a normal range for a PSA value to lie somewhere between 0-4ng/ml, the reality is that large numbers of patients with prostate cancer would remain undetected within this range. About 15% of men with a normal digital rectal examination (DRE) and a PSA of less than 4ng/ml have prostate cancer. That said there is no evidence to suggest that lowering the PSA threshold to less than 4ng/ml improves long-term survival. More significantly it also risks increasing the detection of 'insignificant' cancers. The converse of course is also true of PSA levels at the other end of the spectrum in that raised levels of PSA may incorrectly assign individuals to high-risk groups despite the fact that many go on to have negative biopsies and no evidence of disease.

As a result a number of refinements have been suggested to PSA testing. In addition to the often quoted normal range, there are now age specific ranges. In themselves they may provide an early indication of future problems. They have not however been universally endorsed. The FDA, National Academy of Clinical Biochemists (NACB) and the Laboratory Medicine Practice Guidelines (LMPG) have failed to validate age specific ranges in contradistinction to the American Urological Association (AUA) which has embraced them. Rather than a PSA of less than 4ng/ml being regarded as normal for a 45 year old man (for example) the age specific normal value would suggest a range of between 0-2.5ng/ml. as normal. Clearly a significant difference. Certainly it feels intuitive to consider at least the value of age-specific ranges without necessarily regarding them as dogma. Likewise it is clear that larger prostates are associated with higher PSA readings. Benson (1992) presented original data on so-called PSA density, which suggested that PSA levels were adjusted (and divided by) TRUS volume measurements. Values above 0.15 (or 15%) in the 4-10ng/ml range were more likely to suggest a benign cause for the raised PSA. More recently

specific TRUS measurement of transition zone volumes have been suggested to improve accuracy further. The rate of change of PSA has also been suggested as another important tool in assessing PSA levels. Rises of 0.07-0.27ng/ml appear acceptable on the background of benign prostatic hyperplasia whilst rises of greater than 0.75ng/ml per year are considered more suspiciously. Finally improvements in measuring PSA isoforms have allowed the measurement of free PSA and its ratio to total PSA. The percentage of free PSA [(fPSA/tPSA)x100] is an adjunct to total PSA in men with a total PSA concentration between 4-10ng/ml. A higher percentage of free PSA suggests a lower probability of finding prostate cancer on biopsy. In the presence of prostate cancer a greater proportion of circulating PSA is complexed but no current commercially available assay is available to measure the complex of  $\alpha$ 2-macroglobulin (although current research efforts are currently focussed on complexed PSA measurements).

Whilst all these modifications will undoubtedly play a role in the management of patients with suspected prostate cancer, the question of their role in screening remains a controversial one. Prostate cancer screening is a sensitive and emotional subject with strong views held on both sides. The reality is however that (and regardless of the merits of any of the currently available serum biomarkers) the evidence for a formal screening program (for an otherwise asymptomatic population) is lacking. Controversy has been fuelled by two recently published trials (ERSPC and PLCO), which failed to provide the assumed and overwhelming endorsement for a screening program.<sup>4,5</sup> Methodological failures were sighted and explanations made but the end result is that the controversy continues. The studies provided contradictory results. There was no benefit in the PLCO study although the ERSPC study did reveal fewer prostate cancer deaths in the screened population than the unscreened (a significant reduction of 20% fewer men dying from prostate cancer). The devil is however always in the detail. The study identified that there was a need to screen 1410 men (with another 48 men needing to be treated) to prevent just one prostate cancer death. It has been estimated that the over detection rate (that is the identification of men who would not have had clinical symptoms within their lifetime if it had not been for screening) could be as high as 50%. This over-diagnosis and over-treatment were important adverse effects of the screening program. The problem is that PSA has not the specificity to determine a prostate biopsy indication resulting in large numbers of unnecessary biopsies (and continuing to miss those with low PSA values).

More recently however results from the Goteborg screening trial have been published. With longer follow-up the numbers needed to treat (NNT) to prevent one prostate cancer death were much reduced (from 48 to 12) and 44-56% reduction in prostate cancer mortality. These results are more palatable. The future for screening will depend on lowering this NNT further whilst placing increasing efforts (with the selective use of innovative biomarkers etc) to increase its selectivity to achieve an acceptable risk-benefit ratio. Current UK-based NICE guidelines (alongside guidelines from the British Association of Urological Surgeons) do not recommend screening but advise health practitioners to counsel patients about the inaccuracies associated with PSA screening and the substantial risk of over-diagnosis, such that patients (who might not otherwise have been troubled by their disease in their lifetime) are subjected to radical curative interventions with an inevitable risk of side-effects and complications.

A number of other blood based biomarkers hold out the hope of further improvements for both prostate cancer detection and prognostication. Human Kallikrein-2 (hK2) is a serine protease (and the younger brother of PSA). There is some 80% sequence homology between them. hK2 serum levels however are less than 2% of that of total PSA.<sup>6</sup> It circulates (as with PSA) in bound and unbound forms and there is hope amongst researchers that its combination with total, free and intact PSA will further aid selection of patients for further invasive investigation. The urokinase plasminogen activation (uPA) axis is intricately linked with prostate cancer pathogenesis and in particular to the degradation of extracellular matrix proteins. uPA (a serum protease) binds its receptor (uPAR) and consequently allowing plasminogen to plasmin conversion and consequently initiates protease action resulting in the degradation of extracellular matrix proteins.<sup>7</sup> Measurement of uPA and uPAR have both found utility in improving selection of patients for biopsy as well as potentially offering further prognostic indices. Pre-operative levels were associated with aggressive biochemical recurrence in a radical prostatectomy series. Transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) has an essential role in cellular proliferation and has been associated with tumour progression and metastases.<sup>8</sup> Increased levels were associated with prostate cancer progression. Interleukin-6 (IL-6) is a cytokine, which (alongside its receptors) is associated with prostate cancer. Elevated levels of both have been associated with metastatic and hormone refractory disease.<sup>9</sup> A combination of the latter two markers have been included in nomograms to predict biochemical recurrence after

surgery. Endoglin (or CD 105) is a transmembrane glycoprotein which is involved in the responses of cells to TGF- $\beta$ 1. It may identify patients pre-operatively who are at high risk of recurrence. Significantly it may select patients for neo-adjuvant or adjuvant therapies and even perhaps represent a measure for occult metastatic disease. Of course each of these putative biomarkers is unlikely to threaten the present role of serum PSA testing. Nevertheless, taken together as a panel (and with the addition of VEGF and CD -106) there appears to be an improved predictive accuracy of the Kattan pre-operative nomogram (a process by which clinicians try to predict whether patients have localised disease suitable for radical intervention) by as much as 15%. If verified and extended into routine practice it would improve the counselling process in which patients are appraised of the risks of recurrence following radical intervention.<sup>10</sup>

There is currently one other important biomarker (a urine based biomarker) which is increasingly being relied upon by clinicians: the PCA-3 test. PCA-3 (or DD-3) was first discovered in Nijmegen (Netherlands) and Baltimore (USA). Marion Bussemaker (a post-doctoral researcher) studied prostate tissue and found an mRNA transcript highly specific for prostate cancer. The mRNA (a non-coding segment of mRNA) was eventually mapped to the long arm of chromosome 9 (at the 9q21-22 position). The fact that this could be detected in urine has increased its acceptability as a biomarker further. In fact, the PCA-3 test involves an estimation of not only PCA-3 mRNA but also of PSA mRNA (because the latter estimates the amount of prostate-specific nuclear material in the urine specimen – normally post-prostatic massage). The result therefore provides an assessment of PCA-3 expression corrected for normal or benign epithelial cells (which express PCA-3 at low levels). Its utility has been initially in those men with raised PSA levels despite a normal biopsy. A recent European multi-centre study revealed that the PCA-3 assay may not only have a good predictive value in patients undergoing repeat biopsy but also in biopsy-naïve patients (with a PSA value of 2.5-10ng/ml). It is very likely to become an increasingly routine part of the diagnostic armamentarium.<sup>11</sup>

Richard Ablin (credited with the discovery of PSA) has asserted that the role of PSA in screening has been a 'hugely expensive public health disaster' explaining that - in his opinion at least - 'financial motives have spurred a tsunami of testing'. Many will have sympathy with this view. Nevertheless,

used judiciously it continues to have a significant role in the day-to-day management of patients with established or suspected prostate cancer. The PSA test is clearly flawed but this does not mean that it is without utility. What is apparent however is that its use has to be more judicious and its role in screening (in contradistinction to its use in the management of men with LUTS or suspected pathology) more critically examined given the lack of evidence that it leads to a reduction in patient mortality. The use of PSA testing in a symptomatic patient group will continue to offer utility and with those refinements outlined above, further enhance its role in the management of patients with suspected or established prostate cancer. Alongside these refinements the search for new and improved biomarkers for the disease continues. And for the first time in a generation there does genuinely appear to be candidate markers, which will allow a focus onto a sub-group of patients who need further investigation.

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**Tumour Markers - Appropriate Testing**

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A tumour marker refers to any substance or molecule produced by a tumour or the host in response to the tumour used to differentiate between a tumour and normal tissue.<sup>1</sup> The substance may be one that is not usually present in normal individuals or, if present, the concentration is much higher in the presence of tumours. Tumour markers may be detected in serum, urine, other fluids or in tissues in patients with cancer. If used appropriately, tumour markers may assist in determining the diagnosis, prognosis, treatment choice, monitoring, and screening of various cancers. However, various studies have demonstrated ineffective use of tumour markers, with significant financial and clinical implications.<sup>2-4</sup>

This article aims to alert the reader regarding the potential pitfalls of using tumour markers in isolation to diagnose or screen for malignancies.

**Specificity of Tumour Markers**

The specificity of a diagnostic test is the certainty of the presence of disease when the test is positive. It is important to note that many molecules are produced in excess in malignant as well as non

malignant states. Table I lists various non-malignant states that may cause a rise in some commonly requested tumour markers highlighting the fact that most tumour markers are not very specific. Thus, measuring tumour markers in a patient with non-specific symptoms and a low risk of malignancy may lead to unwarranted stress for the patient in addition to increased expenses. Furthermore, this may also lead to other additional unnecessary special investigations.

**Sensitivity of Tumour Markers**

The sensitivity of a diagnostic test is the certainty of absence of disease when the test is negative. Many tumour markers may not be elevated in the early stages of disease and thus may not be sensitive enough to be used as a screening or diagnostic tool in isolation. For example, a CEA level of >5 ug/l is found in only 3% of patients with Dukes' Stage A disease.<sup>6</sup> Indeed, some tumour markers may not be expressed by a subgroup of patients. For example, CA-19.9 is not expressed in patients who are negative for the Le<sup>a</sup> blood group antigen, thus these patients may *never* have a raised CA19.9 in spite of having pancreatic cancer.<sup>1</sup>

Tumour marker	Benign conditions that may cause a rise in serum tumour marker levels
α fetoprotein (AFP)	Liver regeneration, pregnancy.
Cancer antigen 125 (CA125)	Acute hepatitis, acute/chronic pancreatitis, acute urinary retention, arthritis, chronic liver diseases, chronic renal failure, colitis, congestive heart failure, cystic fibrosis, diabetes, diverticulitis, endometriosis, heart failure, irritable bowel syndrome, leiomyoma, menstruation, non-malignant ascites, ovarian hyperstimulation, pericarditis, pregnancy, sarcoidosis, systemic lupus erythematosus.
Cancer antigen 15-3 (CA15-3)	Acute hepatitis, chronic liver diseases, chronic renal failure, colitis, dermatological conditions.
Cancer antigen 19-9 (CA19-9)	Acute cholangitis, acute/chronic pancreatitis, cholestasis, diabetes, irritable bowel syndrome, jaundice.
Carcinoembryonic antigen (CEA)	Chronic liver diseases, colitis, diverticulitis, irritable bowel syndrome, jaundice, respiratory diseases, smoking.
Human chorionic gonadotrophin (HCG)	Chronic renal failure, menopause, pregnancy.
Prostate specific antigen (PSA)	Acute urinary retention, prostatitis, urinary tract infection.

**Table I:** Benign conditions associated with raised tumour markers.<sup>5</sup>

### Tumour Markers as a Screening Tool

The use of tumour markers as a screening tool in an asymptomatic population is contentious, as exemplified by the case of prostate cancer screening with PSA.<sup>7,8</sup> This is discussed in a separate paper also in this issue of the Journal. Various studies have shown a wide range of outcomes regarding the benefit, or the lack of, screening. The European Randomised Study of Screening for Prostate Cancer, comprising about 162,000 patients with a median follow up of 9 years, showed an absolute difference of only 0.71/1000 between the screening and control group. Implying that 1410 (95% CI, 1142 to 1721) people would need to be screened and 48 additional people would need to be treated to prevent one death from prostate cancer. Notably, the additional benefit was restricted to the age group of 55-69 years. However the improvement in mortality came at the expense of significant over-diagnosis (about 50%) of prostate cancer (defined as the diagnosis of cancer in patient who would not have any clinical symptoms during their lifetime). This study effectively demonstrates both the benefit and risks associated with screening in an asymptomatic population, highlighting the importance of appropriate pre-test counselling in this situation.

In females, ovarian cancer is currently associated with a very high mortality rate despite the availability of improved treatment modalities. This has been attributed to delayed diagnosis / late detection. However, a trial comprising about 72,000 women randomised to screening with transvaginal ultrasonography with or without CA125 or no screening, failed to show any mortality benefit from screening asymptomatic women.<sup>9</sup>

Notably, the recent 2010 NICE guidelines recommend screening with CA125 in patients (especially those over 50 years) with the symptoms of abdominal pain or bloating, urinary frequency or urgency, IBS like symptoms, loss of appetite or early satiety occurring more than 12 times per month.<sup>10</sup> Interestingly, the diagnosis pathway in primary care recommends that if a patient has a CA125 value of <35 IU/l and no cause of her symptoms is apparent, an urgent referral is not required; however, a value of >35 IU/l is only present in 50-60 % of the patients with Stage 1 disease. Also, patients with ascites and raised CA125 with an RMI (risk of malignancy index) score of  $\geq 250$  are required to be referred urgently. As CA125 is raised in ascites due to any cause, in patients with cirrhosis, nephrotic syndrome and congestive cardiac failure, the search for the tumour that does not exist might be rather distressing, both for the patient and the doctor; a problem encountered locally. The NACB (National

Academy of Clinical Biochemistry) therefore recommends CA125 along with transvaginal ultrasonography for screening for ovarian cancer in symptomatic patients.<sup>11</sup>

### Tumour Markers as a Diagnostic and Prognostic Tool

A clinical presentation suggestive of a diagnosis of a particular cancer would be an appropriate prompt for the request of the relevant serum tumour marker. The measurement of one tumour marker is usually sufficient, except in a few important exceptions, such as germ cell tumours (alpha fetoprotein and HCG). Requesting of panels of tumour markers and inappropriate requests such as CA125 in men or PSA in women is both ill-advised and ill-received.

There are various examples where the use of tumour markers can assist in diagnosis and assessing prognosis as outlined in Table II. In patients with a high risk of malignancy, substantially raised tumour markers may provide useful information especially if they are unwilling to have invasive investigations.

The use of tumour markers as a diagnostic tool is best exemplified by germ cell tumours, in which HCG, AFP and LDH measurement in conjunction with radiological testing is mandatory.<sup>11</sup> The pre-treatment value of these tumour markers is known to be an important prognostic indicator and is thus used for risk stratification, determination of treatment modalities and surveillance protocols.

### Use of Tumour Markers for Surveillance

The most appropriate use of tumour markers is serial monitoring of patients after treatment to determine response and relapse. Tumour markers may be elevated before the onset of symptoms and thus enable early detection of relapse. Benefits of intensive surveillance have been demonstrated in patients with colorectal cancer, where monitoring of CEA measurements has improved survival compared to a cohort with less intensive follow-up. Currently three-monthly intervals are recommended for measurement of CEA in those patients with stage II or III colorectal cancer who are candidates for active management.<sup>11</sup>

It is important to note however, that the timing and intervals of measurement are extremely important in certain cases. For example, in the absence of disease, AFP has a half life of about five days; thus a half-life of more than seven days during chemotherapy is a predictor of poor prognosis and recurrence. Weekly measurement of AFP after the first week would therefore assist in determining the intensity of treatment. Measurement of AFP within

Tumour marker	Relevant cancer	Screening or early detection	Diagnosis or case finding	Prognostic (with other factors)
$\alpha$ fetoprotein	Germ cell/testicular tumour	No	Yes	Yes
	Hepatocellular carcinoma	Yes (high risk groups)	Yes (with liver imaging)	Yes
Calcitonin	Medullary thyroid carcinoma	No	Yes	Yes
Cancer antigen 125	Ovarian cancer	No	Yes	Yes
Cancer antigen 15-3	Breast cancer	No	No	No
Cancer antigen 19-9	Pancreatic cancer	No	Yes (if cancer strongly suspected)	Yes
Carcinoembryonic antigen (CEA)	Colorectal cancer	No	No	Yes
Human chorionic gonadotrophin (HCG)	Germ cell and testicular cancers; gestational trophoblastic neoplasia.	No	Yes	Yes
Paraproteins (also measured in urine)	B cell proliferative disorders	No	Yes	No
Prostate specific antigen	Prostate cancer	No	Yes	No
Thyroglobulin	Thyroid cancer (follicular or papillary)	No	No	No

**Table II:** Ten most frequently requested serum tumour markers and recommendations for their use as per the current National Academy of Clinical Biochemistry. Adapted from.<sup>5</sup>

the first week of treatment may be misleading due to an initial surge as a result of chemotherapy. Another example would be PSA measurement in post treatment monitoring of prostate cancers, wherein serial measurements rather than a single measurement must be used to determine recurrence. Although PSA is a sensitive tool to determine recurrence in patients with radical prostatectomy and those on hormonal treatment, it is less so in patients who have undergone radiation therapy. It is also important to be aware that certain treatments may interfere with the actual measurement of the analyte. For example, treatment with CA125 antibodies will interfere with CA125 measurement by immunoassay because the analytical technique involves using CA125 antibodies.

**Preanalytical, Analytical and Postanalytical Considerations**

As with any test, it is important to consider the influence of biological and analytical variation, analyte stability and assay interference when interpreting a result. Whilst the list is not exhaustive, a few examples are mentioned here.

For example interpretation of a single AFP for diagnosing a tumour in a newborn, when the AFP is physiologically high would be incorrect. Instead, measuring the half-life might be more appropriate in this instance. Another important phenomenon

encountered when the levels of a tumour marker are exceptionally high is the ‘hook effect’. This occurs in one step ‘sandwich’ immunoassays. Here the analyte is ‘sandwiched’ between a capture antibody (attached to the tube) and a detection antibody (attached to a form of signal generator), when all three are placed together in a ‘tube’. Following a wash step to remove the unbound antibody, the signal in the ‘tube’ is measured; the amount of signal being directly proportional to the concentration of the analyte. However, in case of high analyte levels, the analyte binds independently with the capture and detection antibody, preventing the formation of the ‘sandwich’. As the detection antibody is no longer tethered to the capture antibody, it is lost in the wash step resulting in a low signal and a spurious low result.

Reducing the analyte concentration by diluting the sample is an effective way to overcome this problem. An example would be a normal or minimally raised prolactin in a patient with a large prolactinoma. Operating on this tumour would be incorrect as this tumour is highly responsive to treatment with dopamine agonists. In this case, it would be advisable to request a prolactin result ‘in dilution’ before assuming that the tumour is a ‘non-secreting’ macroadenoma and subjecting the patient to surgery.

In addition, most assays for tumour markers are immunoassays and are therefore prone to interference by heterophilic antibodies or those used therapeutically as mentioned previously. Lastly, it is important to note that fragment rather than parent molecules may be released by tumours. The ability of an assay to detect these fragments is variable and dependent on the epitopes against which the antibodies are generated. This is seen in patients with germ cell tumours which may secrete intact HCG with both  $\alpha$  and  $\beta$  subunits or indeed just the  $\beta$  subunit, necessitating the need to measure both the 'intact' and 'free- beta' HCG levels in patients with suspected germ cell tumours.

**Conclusion**

Early detection and treatment are significant predictors of outcome in most cancers. It is tempting to use a biomarker to diagnose malignancy as it is comparatively cheaper, easily accessible and minimally invasive. However, most tumour markers lack the sensitivity and specificity required of a diagnostic test. It is important to assess the risk of malignancy and be aware of potential confounders before requesting tumour markers. Assay interferences, although rare, are a possibility and thus all results must be interpreted in light of the patient's clinical condition and other diagnostic modalities; any result which may not be in keeping must be investigated through discussions with the laboratory.

*“Everything that can be counted does not necessarily count; everything that counts cannot necessarily be counted.”*

*Albert Einstein*

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**Poster Competition  
East & North Herts NHS Trust**

Lister Education Centre is proud to announce its first ever poster competition to be held in May 2012. The competition is open to all doctors in training at any grade within East & North Herts NHS Trust. Trainees will have an opportunity to display their work to peers and senior colleagues and win recognition. Fifteen poster entries will be selected and the participants will be invited to display their posters at the Lister Education Centre in May 2012.

Medical staff will be invited to view the displayed work. The entries will be judged by a panel of assessors and three posters will be selected for presentation at the Final Grand Round of the summer programme. The best poster will be selected by the audience through a vote at the end of the presentations. A certificate and prize of Amazon vouchers worth £50 will be awarded to the winner and the two runner ups will each receive £25 of Amazon vouchers along with certificates. Further details can be obtained from Dr S Khan, Editor HJM [shahidkhan@nhs.net](mailto:shahidkhan@nhs.net)

## Tooth Wear – A Diagnostic Indicator

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Tooth wear is becoming an increasingly common clinical problem. The latest Adult Dental Health Survey 2009<sup>1</sup> showed 52% of 16 to 24 year olds had some wear compared with 95% of 75 to 84 year olds. Similarly 4% of 16 to 24 year olds had moderate wear whereas 44 % of 75 to 84 year olds showed moderate wear. Given the fact that tooth wear is a natural process, the high prevalence of moderate wear in the older age groups is of less concern than the finding that a proportion of the younger age group is also affected with moderate to severe wear. The efficient, effective and reliable management of tooth wear is an ongoing, increasingly challenging and demanding process requiring specialist intervention. People expect to, and do, keep their teeth throughout life and the progressive nature of tooth wear has far reaching implications on the type of management indicated to ensure the long-term biological and financial costs are kept to a minimum.

Although tooth wear is a natural physiological part of ageing it may become pathological, where the rate of wear challenges the viability of teeth or is of concern to the patient through difficulty in eating, appearance, sharp, thin or fractured teeth and sensitivity. The aetiology, often complex, is usually divided into erosion, attrition, abrasion or a combination of these. Erosion is the irreversible loss of dental hard tissue due to a chemical process without the involvement of micro-organisms (non-carious damage)<sup>2</sup>, and occurs when the surface pH of enamel falls below 5.3.<sup>3</sup>

Attrition is the physical wear of one tooth against another.<sup>2</sup> Abrasion is physical wear caused by an external agent, classically the abrasive particles in toothpaste.<sup>2</sup> Current evidence suggests erosion is the most important cause of tooth wear and if it occurs in combination with abrasion or attrition the damage will be greater than if these processes occur independently.

Erosion is caused by extrinsic (dietary) and/or intrinsic (gastric) acids. The extrinsic acids include carbonated drinks, snacks, citric fruits/juices and vinegar. Gastric juices migrating into the mouth, as a result of GORD, bulimia, anorexia, rumination<sup>4</sup>, chronic alcoholism<sup>5</sup>, pregnancy and other conditions with dysfunctional oesophageal sphincters are the prime intrinsic acids. The characteristic clinical

features of intrinsic acid erosion in the early stages are loss of surface contour of the palatal enamel of the upper incisors, making them appearing smooth and shiny. With further enamel loss a halo effect

is produced around the edges of the teeth when viewed from the buccal. This develops into exposed dentine (Fig 1) on the:

- palatal surfaces of the upper teeth, primarily the incisors, but occasionally extending onto the upper posterior teeth.
- bucco-cervical and occlusal surfaces of the lower molar teeth undamaged lower incisors that are protected by the position of the tongue covering them during vomiting.



**Figure 1:** Erosion of enamel on incisors and bucco-cervically on posterior teeth in a male.

Once dentine is exposed, as it is less resistant to acid attack, the rate of erosion increases. Eventually, the damage can result in complete loss of palatal enamel and dentine that undermines the incisal edge of the teeth which slowly breaks away, producing a sharp jagged edge.

The presence of palatal erosion has been associated with acid originating from the stomach of patients with eating disorders.<sup>6</sup> In a study<sup>7</sup> of 36 patients presenting with significant palatal dental erosion, 64% had pathological levels of GORD using internationally recognised criteria. Of these 30% had no symptoms of GORD. The conclusion was that regurgitation of gastric juice caused by GORD is an important cause of palatal erosion and that not all patients are aware of GORD (silent refluxers). Extrinsic acids are found in many fruits and fruit-based drinks. They are organic acids such as citric, malic and oxalic. Of these citric acid is the most aggressive and known to chelate calcium. Fruits that are associated with erosion, such as oranges and lemons, have a high citric acid content, Table I.

Fruit Juice	Citric Acid Content
Apple	0
Blackcurrant	Trace
Grapefruit	1460
Lemon	6080
Orange	980
Pears	240

**Table I:** Citric acid content of some common fruits (mg per 100gms).<sup>8</sup>

Other sources of extrinsic acid include carbonated drinks, alcopops and designer drinks. These are becoming increasingly popular and their pH range lies in the region of 2.4 – 3.2<sup>9</sup>, which is below the critical pH for enamel dissolution. It is perceived that these alcoholic drinks appeal to a young age group. A survey<sup>10</sup> found that 1 in 5 teenagers aged 13 – 16 years old preferred designer drinks with 25% of this group drinking once a week and 28% drinking more frequently. In addition they found that 18 – 30 year old females preferred them to wine or beer. Orange juice has an erosive potential of 3.3 microns. Designer drinks have a range of 2.8 – 21.1 microns<sup>11</sup>. It is prudent to consider these drinks as a contributing aetiological factor in erosion amongst teenagers. Importantly saliva has a buffering capacity against erosive acids in the diet<sup>12</sup> but in some syndromes affecting salivary dysfunction, such as Sjögren’s, and in the presence of xerostomia there is a high level of erosion.<sup>13</sup>

Beers have an average pH range of 3.79 – 4.8<sup>14</sup> and due to their neutralisable acidity range it seems likely they will have a minimally erosive potential due to salivary buffering capacity. The pH of white wine has been reported as ranging from 3.0-3.6<sup>15</sup>. Professional wine tasting, up to 30 different wines a day, has been shown to be a risk factor for erosion.<sup>16</sup>

Given the causes of erosion Järvinen *et al*<sup>17</sup> ranked the various aetiological risk factors using an odds ratio analysis that indicated frequent citrus fruit intake created the greatest risk (Table II).

Factors	Odds Ratio
Citrus Fruit eaten >2x daily	37
History of vomiting	31
Low unstimulated salivary flow	5
Soft drinks consumed daily	4
Sport drink consumed daily	4

**Table II:** Risk factors for erosion. (after Järvinen *et al*)<sup>17</sup>

Interestingly ‘healthy’ alternatives to caffeine-based products include fruit teas which have a pH range of 3.2-3.8 compared to traditional black leaf tea of pH 5.7<sup>18</sup>. Not surprisingly black tea caused virtually no erosion and camomile – based tea, with a pH of 7.1, caused no erosion.

Teeth contact in normal function for very short periods of time. Contact for reasons other than eating can be considered as parafunctional and habitual. The cause of parafunctional activity remains unclear but it may be irregularities in the surface configuration of teeth, the occlusion or a form of stress relief used by the body usually at night. In the early stages matching wear facets area is noted on the occlusal surfaces of the molars and the incisal edges of the anterior teeth (Fig 2).



**Figure 2:** Reduced clinical crown height as a result of a parafunctional habit in a female. The teeth have worn, flattened and chipped incisal edges. Note the extensive development of the dento-alveolar complex with marked display of gingivae.

The surfaces of the wear facets are flat and flush with the opposing tooth in contact and slide over one another without any interferences or irregularities. As attrition progresses teeth get shorter, have a very even and regular appearance and contact against the opposing dentition. If the opposing flat surfaces do not contact evenly or there is a difference in the amount of wear in the opposite jaw the cause is probably multifactorial with erosion playing a major part (Fig 3).

Teeth maintain the lower third of the vertical face height from the nose to the chin. Where this wear progresses quickly the compensatory mechanism of dento-alveolar growth cannot keep pace with the reduction of the clinical height of the teeth. This leads to a reduction in the lower face height characterised by a typical ‘Mr Punch’ appearance. In those cases where tooth wear is gradual the compensatory mechanism, produced by continued growth of the alveolar bone and gingivae keeps

pace with the reduction of tooth height leading to a short clinical crown height<sup>19</sup> (Fig 2). This severely complicates the management of these teeth as there is no vertical space available to build restoration into.



**Figure 3:** Long standing tooth wear with an aetiology of erosion and attrition in a male.

The management of tooth wear requires accurate diagnosis and for this sensitive history taking is essential as patients are frequently reluctant to describe their symptoms and habits.<sup>20</sup> This should include questions about diet, frequency, volume and type of fruit intake, in particular citrus fruit, non-alcoholic (carbonated) and alcoholic drinks, fruit teas and other 'healthy' drinks or foods, symptoms of heart burn or gastric problems, eating habits, occupation and stress levels. General dental practitioners (GDPs) see their patients on a regular basis for maintenance, so they have an important role to play in detecting tooth wear early, often before any medical signs intervene. In an audit project Bartlett *et al*<sup>21</sup> concluded that referral by GDPs for patients with dental palatal erosion [via GPs] for 24hr ambulatory oesophageal pH measurement should be: where the symptoms of GORD are interfering with their quality of life and for patients who want to know the cause of their erosion.

The marked increase in consumption of fizzy drinks by children and teenagers can readily be identified by the direct clinical effects on teeth. When recognised early, damage to teeth can be limited through initial dietary research with subsequent counselling and advice. There is little evidence to support the concept that pathological levels of erosion or tooth wear are age dependant. There is, however, some evidence to suggest that normal levels of erosion or tooth wear are age dependant.<sup>22</sup> Pathological tooth wear is not necessarily a constant throughout life, often having a cyclic component of stop and start. Monitoring the rate of tooth wear using study models and intra-oral digital images is of great benefit. It delays more destructive interventional restorative

procedures creating a low cost biological approach with the preservation of tooth tissue, involving the use of fluoride mouthwash, counselling and awareness as the cornerstones of management. As tooth wear is increasingly diagnosed it creates challenges for its management. Recognising the signs and introducing early preventative measures, including medical intervention, is important. Once teeth are severely damaged their treatment becomes lengthy, potentially even more destructive of tooth tissue with a high biological and financial cost, requiring life-long maintenance.

### Learning Points

1. Sensitive and accurate history taking is essential to gain the patients' confidence ensuring they feel able to divulge any relevant information that will assist in diagnosis.
2. Increase the awareness of medical conditions and their effects on the dentition as a diagnostic tool.
3. Recognise the different aetiologies of tooth wear.
4. GDPs are in a good position to monitor tooth wear and make referrals to GPs for investigations and medical treatment.

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## Dupuytren's Contracture: Beyond Alcoholic Liver Disease

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Dupuytren's contracture, or Dupuytren's Disease is well known by medical students as a fixed flexion deformity of the hand (particularly the ring and little fingers), due to contracture of the palmar aponeurosis. We are taught to recognise it in an abdominal examination as a sign of liver cirrhosis, but the aetiology is far broader, and the pathophysiology of this condition is poorly understood. Dupuytren's contracture has a prevalence of around 4% in the general population, and increases with age. Debated aetiological factors include manual labour, genetics, alcohol, liver disease, diabetes, epilepsy, anticonvulsant drugs and HIV.

Dupuytren's contracture was described in 1832 by Baron Guillaume Dupuytren as occurring in "people who were obliged to make efforts with the palm of the hand", and his first case was his own coachman, who spent hours holding the reins of his horse.<sup>1</sup> In the 1950s patients with Dupuytren's contracture began claiming for compensation from their employers, but at the time no clear link was found between manual labour and Dupuytren's contracture. However, more recent studies have suggested that occupations exposing workers to high levels of vibration to the hand can increase the incidence of Dupuytren's contracture, and some questionnaire based studies of debatable reliability have even suggested the prevalence is higher in rock climbers.<sup>2</sup>

Probably the most established predisposing factors to Dupuytren's contracture are genetic. Dupuytren's contracture is rarely found in those of African or Asian origin, and is most commonly found in northern Europeans.<sup>3</sup> Its prevalence in Scotland over 300 years ago led Dupuytren's contracture to be called "the curse of the MacCrimmons", after a Scottish clan whose pipers were often unable to play in old age due to contractures of their fingers. At one point Dupuytren's contracture was thought to be an autosomal dominant condition with incomplete penetrance, but more recent studies have suggested that it is more likely to be polygenic.<sup>4</sup>

Alcohol and liver disease are frequently quoted causes of Dupuytren's contracture. A prospective study of 772 patients with Dupuytren's contracture found both alcohol intake and tobacco smoking were independently linked to an increased risk of Dupuytren's contracture.<sup>5</sup> However, another prospective study suggested this effect is not due to liver disease. In a population of 432 hospitalised

patients there was a high prevalence of Dupuytren's contracture in alcoholics, but not in those with non-alcoholic liver disease.<sup>6</sup> Prevalence in patients with alcoholic cirrhosis was 32.5% and with chronic alcoholism but without liver disease was 28%. In contrast, prevalence of Dupuytren's contracture in patients with non-alcoholic liver disease was 6%.

The prevalence of Dupuytren's contracture is higher in patients with diabetes (both types 1 and 2) than for the general population. A study where a hand surgeon assessed 150 adult diabetics and the same number of control subjects for Dupuytren's contracture found a prevalence of 43% in the diabetic group as compared to 18% in the control group.<sup>7</sup> Another group of 122 diabetics within the same study showed that Dupuytren's contracture was twice as common in patients who had suffered with diabetes for over 20 years as it was in those who had diabetes for up to 5 years. No difference was found in prevalence of Dupuytren's contracture between patients with good or poor diabetic control, and between insulin and non-insulin dependent diabetics. This suggests that it is not the poor glucose control that causes a link between diabetes and Dupuytren's contracture. One possibility is that genes predisposing to diabetes may also predispose a patient to Dupuytren's contracture. Alternatively, microvascular changes occurring in diabetes may cause local hypoxia, and hypoxia has been implicated in the pathophysiology of Dupuytren's contracture.

Dupuytren's contracture has been associated with epilepsy since a higher prevalence was noticed among epileptic patients in Denmark in the 1940s. A recent study found a Dupuytren's contracture prevalence of 38.1% in an epileptic centre as compared to 16% in the control population.<sup>8</sup> Some have suggested it is anticonvulsant drugs, rather than epilepsy per se, that causes Dupuytren's contracture. Facts purported to support the causative role of anticonvulsants include the lack of correlation between severity of epilepsy and Dupuytren's contracture, the increasing prevalence of Dupuytren's contracture alongside the duration of epilepsy, and the greater tendency for Dupuytren's contracture to be bilateral in epileptics. However these are purely theoretical arguments and in practise it would be very hard to tell whether it is the drugs or the condition that causes Dupuytren's contracture. Studies of patients on anticonvulsants for reasons other than epilepsy could shine some light on this matter.

There is limited evidence linking Dupuytren's contracture with HIV. A small study compared 50 patients with advanced HIV to 50 control subjects from a sexual health clinic. 18 of the patients with advanced HIV had Dupuytren's contracture, whereas none of the control subjects had Dupuytren's contracture.<sup>9</sup> The authors of this study propose that as free radicals are thought to be increased in HIV, and free radicals have been implicated in the pathophysiology of Dupuytren's contracture, this may be the mechanism of increased Dupuytren's contracture among the HIV population. This is an interesting proposition but not yet based on convincing evidence.

When examining a patient with Dupuytren's contracture it would be wise to bear in mind the wide number of different conditions associated with this sign. Baron Guillaume Dupuytren may have been right when he noticed a link with manual labour, but alcohol, smoking, diabetes and epilepsy may also play a role. The strongest evidence links genetic influences with Dupuytren's contracture, so it may be that the patient in front of you is simply from Scandinavia, rather than being an alcoholic.

### Key Learning Points

Factors associated with Dupuytren's contracture:

- 1 Genetic (Dupuytren's contracture occurs most commonly in those of Northern European ancestry).
- 2 Manual labour.
- 3 Alcoholic liver disease.
- 4 Diabetes.
- 5 Epilepsy.

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### Cardiorenal Syndrome and its Management Challenges

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Heart failure and renal failure are both conditions commonly seen in general practice and hospital settings. The prevalence of both is set to increase over the next decade. When these conditions occur simultaneously the potential result is to accelerate the disease process and to develop a poorer response to treatment.

At least a third of all heart failure patients have renal insufficiency<sup>1</sup> and approximately 70% of patients hospitalised due to heart failure are found to have at least stage 3A renal insufficiency (eGFR 45-59ml/min).<sup>2</sup> Congestive heart failure is present in approximately a quarter of chronic renal failure patients.<sup>3</sup> Significantly there is a correlation between the prevalence of heart failure and the severity of renal failure amongst these patients<sup>4</sup>. Co-morbid renal failure and heart failure has been shown to be a strong predictor of morbidity and mortality.<sup>3</sup> Cardiorenal syndrome, previously described as heart failure with rising creatinine, is now recognised as a triad of congestive heart failure, declining renal function and diuretic resistance.<sup>5</sup>

#### Pathophysiology

In heart failure there is decreased stroke volume and cardiac output, due to either a reduced ejection fraction (systolic heart failure) or ventricular under-filling (diastolic heart failure). This leads to stimulation of arterial baroreceptors which mediate the activation of vasoconstrictive and volume retaining mechanisms including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system activation and anti-diuretic hormone (ADH) release. This neurohormonal activation causes raised peripheral resistance and therefore hypertension which in turn leads to increased generation of reactive oxygen species (ROS), a type of free radical, throughout the body including the kidney. In normal circumstances these vasoconstrictive effects are counteracted by the release of multiple compounds including brain natriuretic peptide (BNP), prostaglandins, bradykinins and nitric oxide.<sup>6</sup> When ROS levels are great enough that there is insufficient nitric oxide to counteract their effects this state is known as 'oxidative stress'. Oxidative stress, in addition to chronic hypoxia and inflammation are the main factors contributing towards the decline in renal function observed in cardiorenal syndrome.<sup>7</sup>

#### Disease Markers and Prognosis Assessment

A strong link has been shown between renal function and prognosis in cardiorenal syndrome.<sup>3</sup> In terms of mortality this has been quantified to show that for every 0.5mg/dL increase in Cr there is a 15% increase in absolute risk for annual mortality and for every 10mL/min decrease in eGFR there is a 7% increased risk.<sup>5</sup> eGFR is the more reliable of the two measurements due to the tendency of serum creatinine to overestimate renal function in the elderly population.

In heart failure, brain natriuretic peptide (BNP) and N-Terminal pro-brain natriuretic peptide (NT-proBNP) can be used both to aid diagnosis and as a predictor of morbidity and mortality. Renal failure, in addition to structural heart damage, results in raised natriuretic peptide levels due to reduced clearance. NT-proBNP levels have been shown to increase more with decline in eGFR than BNP.<sup>8</sup> This has been hypothesised to be due to BNP having additional clearance mechanisms whilst NT-proBNP is believed to be cleared through glomerular filtration alone. NT-proBNP levels have been shown to be the strongest risk factor for death within 60 days.<sup>9</sup> Despite this, natriuretic peptide assays (like all investigations) still need to be interpreted according to clinical context, such as whether the patient is known to have any structural heart disease or renal impairment. Assessing NT-proBNP alongside creatinine clearance or eGFR could aid the clinician in distinguishing the cardiorenal syndrome from chronic cardiac or renal failure in isolation.

It is worth noting that there is an unusual trend, well documented in patients requiring regular renal replacement therapy due to end stage renal failure. Multiple sources suggest that raised body mass index, increased serum cholesterol and higher blood pressure in these patients result in favourable long term outcomes compared to their peers in terms of both morbidity and mortality.<sup>10,11</sup> One study suggests that this is the case in congestive heart failure.<sup>12</sup> This phenomenon has been described as 'reverse epidemiology' and is thought to be due to 'malnutrition-inflammation complex syndrome'.<sup>10</sup> Whilst this concept appears to contradict our most basic understanding of cardiovascular mortality risk, we should consider the fact that both end stage renal failure patients in addition to congestive heart failure patients are frequently in a catabolic state and often suffer from nausea leading to decreased nutritional intake. This leads to malnutrition, most significantly protein deficiency which in turn leads to immunodeficiency, increased oxidative stress,

poorer clearance of inflammatory response agents and a decreased response to erythropoietin therapy for associated anaemia. It remains open to debate if there are additional factors responsible for this trend and if there is an effective management to counteract its effects.

### RAAS Blockade and Vasodilators

The use of angiotensin converting enzyme (ACE) inhibitors in heart failure is well established however evidence is lacking when it comes to treating patients with cardiac and renal failure as they are normally excluded from clinical trials. For this reason clinical practice can significantly vary amongst clinicians due to concerns of ACE inhibitors reducing glomerular filtration rate despite the long term benefit of nephron protection. It must be remembered that ACE inhibitors protect the kidney structurally by reducing the pathological sympathetic activation and oxidative stress but can acutely decrease glomerular filtration rate through reduction of efferent arteriole pressure. This means that in many cases serum creatinine can significantly rise in patients after initiation or increased dose of ACE inhibitors and not just in those who have bilateral renal artery stenosis. Therefore the main issue facing clinicians is whether an increased creatinine after commencing an ACE inhibitor is transient, permanent but permissible given the long term benefit or permanent and severe enough to justify stopping ACE inhibitor therapy. One meta-analysis of twelve randomised controlled trials found that when commencing an ACE inhibitor in patients with known renal insufficiency, a 30% increase in creatinine that stabilised within two months was associated with improved long term renal function, in terms of reducing annual decline in eGFR.<sup>13</sup>

Therefore the general consensus is that ACE inhibitors can be used in cardiorenal syndrome provided certain qualifications are met. Firstly the patient must not be volume depleted, meaning ACE inhibitor initiation is frequently inappropriate in the acute setting. Secondly potassium must be within or below normal limits, as it is likely to increase with therapy. Finally patients should be started at low doses with initial close monitoring of serum creatinine. If serum creatinine increases dramatically (i.e. greater than 30%) then the therapy should be immediately reviewed and the possibility of bilateral renal artery stenosis considered.

Spironolactone is another drug that is well established in the heart failure population, unfortunately its role in the management of cardiorenal syndrome is limited due to the significant risk of hyperkalaemia. Normally this can be counteracted by careful titration of loop

diuretics but in this population the associated resistance to diuretics makes it harder to prevent a subsequent rise in potassium. Research into spironolactone use in the heart failure population indicates it is inappropriate if creatinine is greater than 220  $\mu\text{mol/L}$  or baseline potassium is greater than 5.0  $\text{mmol/L}$ .<sup>14</sup> At least one of these is likely to be the case in established cardiorenal syndrome limiting its use to the early stages only.

Vasodilator drugs such as intravenous nitroglycerin can be used for acute decompensated heart failure to reduce ventricular filling pressure and therefore ventricular workload and myocardial oxygen demand. In addition they reduce systemic vascular resistance which can lead to a drop in blood pressure. Careful titration is needed, especially in the presence of cardiorenal syndrome, in order to prevent a sudden drop in renal perfusion, leading to acute kidney injury. While valuable in the setting of acute volume overload it is yet to be established if there is significant benefit in terms of preserving renal function and mortality from long term use of vasodilators in cardiorenal syndrome.

### Use of Diuretics

Diuretics play a key role in the management of heart failure and while they are useful in managing cardiorenal syndrome, dose and administration need careful consideration. Inadequate diuretic dose at discharge is the most common cause of morbidity due to heart failure decompensation.<sup>15</sup> Loop diuretics are normally used in cardiorenal patients as thiazides have been shown to have poor efficacy when GFR is less than 30ml/min.<sup>16</sup> Heart failure results in hypoperfusion and oedema of the digestive system, therefore parenteral administration is the preferred method when patients are admitted to hospital.

The main limitation with diuretics in cardiorenal syndrome is that they often have a poor response with what would normally be an adequate dose, known as 'braking phenomenon'.<sup>17,18</sup> This occurs acutely due to a rebound increase in sodium absorption following a bolus injection and chronically as blockade of the sodium-potassium-chloride transporter leading to hypertrophy and increased sodium uptake of distal tubule cells.<sup>16</sup>

One meta-analysis concluded that diuretic effectiveness is greater if administered in multiple doses rather than via continuous infusion.<sup>19</sup> However, this was based on numerous underpowered trials and is yet to be definitively proven. Addition of a second diuretic in chronic therapy has been shown to counteract the enhanced distal tubule sodium reuptake in severe cases.<sup>20</sup> The drawback is that close monitoring is required due to increased risk of adverse effects.

One small study has investigated administering loop diuretics with small volumes of hypertonic saline<sup>21</sup>. The hypothesised advantage is it will cause additional fluid shift from the extracellular space into the circulation due to raised osmotic pressure and additionally overwhelm the rebound sodium retention mechanisms. The temporary increase in sodium delivery may also lead to RAAS suppression. The study found there to be a short term greater volume of diuresis and reductions in natriuretic peptide levels in those that were given hypertonic saline and furosemide versus furosemide alone. The main limitation of this study is that long term hard clinical outcomes, such as the decline in renal function and mortality were not assessed meaning there is insufficient evidence to recommend this in clinical practice.

### Ultrafiltration

For treatment of cardiorenal syndrome in the UK renal replacement therapy is rarely employed until renal function has declined into end stage renal failure and there is little other option. Theoretically the use of ultrafiltration could quickly and effectively overcome the diuretic resistance to reduce volume overload. In the acute setting this could improve dyspnoea and reduce length of hospital stay and has been hypothesised to improve renal function. Chronic use may result in decreased RAAS and sympathetic activation to preserve long term renal function by preventing structural damage due to oxidative stress and inflammation.

In the acute setting the largest randomised controlled trial found that in acute decompensated heart failure ultrafiltration is superior to IV diuretic therapy in terms of both net fluid loss after 48 hours and rehospitalisation rate within the following 90 days. There was however no significant difference in dyspnoea or serum creatinine<sup>22</sup>. Whilst this study was carried out on the general heart failure population the authors conclude that logically patients who are resistant to the effects of IV diuretics stand to gain most of all from the use of acute ultrafiltration. A more recent randomised controlled trial sought to assess if acute use of ultrafiltration could improve dynamic renal function by reducing volume overload leading to increased renal blood flow in comparison to IV diuretic therapy. The results showed no significant difference in urine output, glomerular filtration rate or renal plasma flow between the two treatments.<sup>23</sup> This would indicate that acute use of ultrafiltration can increase fluid loss and reduce short term morbidity compared to conventional therapy but does not appear to acutely improve renal function. In the chronic setting there is very little evidence regarding the use of ultrafiltration early on in the disease process, before the patient's renal function

has declined to become dependent on renal replacement therapy. Evidence comes mainly from case reports or small studies that were not fully controlled. One such study assessed 19 patients with congestive heart failure refractory to medical therapy who were given intermittent ultrafiltration over one year. The patient's New York Heart Association Index score and number of hospitalisations were compared to the year before ultrafiltration therapy and whilst receiving it. The study found that frequency of admission and NYHA index were both improved following one year of treatment but alarmingly 2 of the 19 patients died due to complications of ultrafiltration therapy.<sup>24</sup> The low number of patients and obvious flaws in design as well as the fatal complications does little to justify the chronic use of ultrafiltration for treating cardiorenal syndrome. Even if a large randomised controlled trial for the use of long term intermittent ultrafiltration versus conventional therapy in terms of long term decline in renal function, rate of hospital admissions and mortality was to be conducted the results would only be of academic interest. The NHS does not have resources to administer long term ultrafiltration to the vast number of patients this would involve even if there was definitive evidence of clinical benefit.

### Conclusion

As the prevalence of both heart failure and renal failure continue to rise cardiorenal syndrome will become an increasingly common problem in hospitalised and primary care. In recent years interest in this condition has grown significantly both in laboratory research and clinical trials. ACE inhibitors and diuretics form the main treatment options but they both have significant limitations. Ultrafiltration can effectively reduce fluid overload but long term benefit is unproven in addition to being too expensive and resource intensive to be practical on a large scale. Novel treatments for managing this complex group of patients will be an interesting area of future research.

### Key Points

- Cardiorenal syndrome is set to rise substantially in an ageing population
- Neurohormonal activation leading to oxidative stress is the main cause of deterioration in renal function
- NT-proBNP offers the most accurate assessment of disease severity
- ACE inhibitors can be used with caution
- Conventional diuretic therapy is inadequate in advanced disease

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## The Outpatient Management of Heart Failure

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Chronic Heart Failure (CHF) affects at least one in every 100 people in the UK, increasing to about 7% in men and women over 75 years. The number of patients with heart failure will increase substantially over the next twenty years, due to the combined effects of the ageing population and improved survival in patients who will develop cardiovascular disease.

Despite advances in the treatment of heart failure, survival rates remain worse than for many cancers, with annual mortality ranging from 10 - 50%. Also, patients with heart failure often have a poor quality of life, with symptoms limiting their activities and with over a third experiencing severe and prolonged depressive illness.

There is good evidence that appropriate assessment and diagnosis of the cause of heart failure, followed by optimised treatment and ongoing support can improve quality of life, reduce morbidity (for example hospital admissions) and reduce mortality (by over 50% with optimal treatment). Disappointingly many patients do not receive such optimised treatment and are denied improvement in quality and quantity of life.

Heart failure is not a single diagnosis, but a clinical syndrome, characterised by evidence of some structural or functional cardiac abnormality (for example using echocardiography, ECG and natriuretic peptides), together with symptoms and signs such as:

- Breathlessness (dyspnoea) on exertion, orthopnoea and paroxysmal nocturnal dyspnoea (PND).
- Exercise intolerance.
- Fatigue.
- Tendency to fluid retention causing peripheral oedema (but not in all cases).
- Sometimes cachexia rather than oedema (resembling malignant disease with an unknown primary).
- General malaise and depression.

Symptom severity is traditionally described using the New York Heart Association (NYHA) scheme, which categorises patients as:

- NYHA I: No symptoms.
- NYHA II: Symptoms on mild exercise.
- NYHA III: Symptoms on moderate exercise.
- NYHA IV: Symptoms even at rest.

However, symptoms are a poor indicator of prognosis. A person may have no symptoms and no clinical features of heart failure and yet have very poor cardiac function with a very poor prognosis, unless detected and treated. There is no such thing as “mild heart failure”, only mild symptoms perhaps.

Many pathologies can lead to a similar clinical presentation of heart failure, and many other conditions can mimic heart failure. In order to treat heart failure appropriately, you must first try and determine the underlying cause, and assess if any other conditions co-exist that confuse the presentation.

The commonest causes of CHF are myocardial dysfunction, valvular disease, arrhythmia or any combination of these. Left Ventricular Systolic Dysfunction (LVSD) is the commonest cause, present in the majority of patients with heart failure younger than 65, but in older patients clinical heart failure becomes common even with preserved systolic function - either because of valve disease, or with what used to be called “diastolic dysfunction”, but is now more correctly described as “Heart Failure with Preserved Systolic Function” (HF-PEF, pronounced “huff-puff”).

### Initial Assessment

When a patient presents in an outpatient (non-emergency) setting with a history, symptoms and/or signs that suggest heart failure, there are four important questions to address:

1. **Is the presentation really due to heart failure**, or is there another explanation for the patient’s condition?
2. If heart failure can be “confirmed”, **what is the cause?** (remembering that “heart failure” is not by itself a sufficient diagnosis).
3. **What treatments can be offered** with evidence of benefit for such a cause?
4. **What is the Prognosis?**  
Remembering that symptoms are a poor predictor of prognosis. Be aware that there are no symptoms or signs sensitive and specific enough to enable you to make an accurate “diagnosis” of heart failure, but clinical

**Table 1:** Causes of Heart Failure.

<ul style="list-style-type: none"> <li>• <b>LV Myocardial Dysfunction</b> (LV Failure = “LVF”)             <ul style="list-style-type: none"> <li>• <b>Systolic:</b> Myocardial Infarction / Ischaemia, Dilated Cardiomyopathy, Myocarditis, Alcohol, Drugs.</li> <li>• <b>HF-PEF</b> (“Diastolic Dysfunction”): Myocardial Ischaemia, LV Hypertrophy (LVH), Hypertrophic Cardiomyopathy, Increasing Age (usually &gt;75), Infiltrative Diseases (Amyloid, Sarcoid).</li> </ul> </li> <li>• <b>Valve disease</b> <ul style="list-style-type: none"> <li>• Pressure load: e.g. Aortic Stenosis (AS).</li> <li>• Volume load: e.g. Mitral or Aortic Regurgitation (MR, AR).</li> <li>• Poor flow: e.g. Mitral Stenosis (MS).</li> </ul> </li> <li>• <b>Arrhythmias</b> <ul style="list-style-type: none"> <li>• Atrial Fibrillation (AF), or other uncontrolled tachycardia.</li> <li>• Severe bradycardia, e.g. Complete Heart Block (CHB).</li> </ul> </li> <li>• <b>Pericardial disease</b>, usually causing constrictive problems to right and left ventricular function.</li> <li>• <b>Adult congenital heart disease</b>, for example late presentation of ASD, or previously corrected complex congenital lesion.</li> <li>• <b>Right ventricular dysfunction</b> (usually systolic), due to:             <ul style="list-style-type: none"> <li>• Acute pulmonary embolism.</li> <li>• <b>Pulmonary hypertension</b> which can be either:                 <ul style="list-style-type: none"> <li>Primary</li> <li>Secondary to chronic obstructive pulmonary disease (COPD) causing “cor pulmonale”, chronic thromboembolic disease, LV dysfunction, mitral regurgitation or in congenital heart disease.</li> </ul> </li> </ul> </li> <li>• <b>Drugs:</b> NSAIDs or steroids can cause fluid retention. Herceptin and other cytotoxics may impair LV function and most anti-arrhythmic drugs have negative inotropic effect.</li> <li>• <b>Extracardiac causes</b> that can affect cardiac function: anaemia, thyroid disease, glycogen storage diseases, vitamin deficiency, etc.</li> </ul>
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assessment provides useful clues as to the possible underlying cause, for example a history of previous documented heart attack, or the finding of uncontrolled atrial fibrillation, or hearing a prominent murmur. A “diagnosis” of heart failure based only on clinical features such as exertional breathlessness and ankle swelling is likely to be correct in only 50% of patients and is even less in women.

The most useful investigations in the assessment of CHF are:

**Blood Tests:** including electrolytes, renal function, full blood count, and liver and thyroid function.

**Natriuretic Peptides:** BNP or NT-proBNP.

**12 lead ECG:** with accurate interpretation.

**Transthoracic Echocardiography:** including 2D and doppler assessments.

It is also helpful to assess respiratory function, for example with spirometry.

- **Breathlessness**
  - ◆ Angina equivalent (transient ischaemic LV dysfunction, may not cause chest pain or discomfort).
  - ◆ Obesity / lack of stamina.
  - ◆ Anaemia.
  - ◆ Chest disease: lung disease (for example, COPD, asthma), diaphragm or chest wall problem.
  - ◆ Pulmonary thromboembolic disease.
  - ◆ Arrhythmia.
  - ◆ Tachyarrhythmia (for example, new onset atrial fibrillation).
  - ◆ Bradycardia and chronotropic incompetence (inability of the heart rate to increase adequately with exercise).
  
- **Oedema**
  - ◆ Sedentary, dependent oedema.
  - ◆ Venous insufficiency in lower limbs/varicose veins.
  - ◆ Excess salt/sodium intake.
  - ◆ Drug induced ankle swelling (for example, dihydropyridine calcium channel blockers, alpha blockers).
  - ◆ Drug induced fluid retention (for example, NSAIDs, steroids, sodium containing antacids).
  - ◆ Hypoalbuminaemia.
  - ◆ Intrinsic renal or hepatic disease.
  
- **Fatigue**
  - ◆ Depression with or without anxiety.
  - ◆ Anaemia or thyroid disease.
  - ◆ Malignant disease.
  - ◆ Sleep apnoea.

**Table 2:** Conditions that can mimic heart failure.

Natriuretic peptides are released by the ventricles (left much more than right) when they are stretched, as part of normal fluid volume homeostasis. The hormonal effect on the kidneys causes sodium loss (natriuresis) and thus fluid loss, and they also cause vasodilatation. If there is something causing “strain” on the ventricles, natriuretic peptides will likely be elevated. Conversely, if the natriuretic peptide level is “normal” then it is very unlikely that there is any “heart failure”. Thus the measurement of natriuretic peptides is a very efficient way of excluding CHF (from whatever cause). If a patient presents with features suggestive of heart failure, but the natriuretic peptide level is normal, heart failure is unlikely. Natriuretic peptide levels are reduced in obesity, and with effective treatment of heart failure, but can be increased moderately in the absence of chronic left ventricular failure, for example in myocardial ischaemia, renal failure, sepsis, after a tachyarrhythmia, or if there is right heart strain as with pulmonary embolism, pneumonia, COPD or “cor-pulmonale”.

Whereas normal natriuretic peptide levels virtually exclude “heart failure”, elevated levels do not explain the underlying cause, but provide an

assessment of prognosis: the higher the level, the worse the prognosis, and the greater the urgency for specialist assessment and optimised care.

The NICE Clinical Guideline for Chronic Heart Failure (2010), provides a detailed outline to the approach to the initial assessment, and thus an understanding of the cause of heart failure, and thus the appropriate evidence-based treatments that should be offered (see Figure 1).

The guidelines highlight the need for rapid specialist assessment of patients with suspected heart failure: within 2 weeks if they have had a previous myocardial infarction, or have markedly elevated levels of natriuretic peptides, otherwise within 6 weeks. There is no longer any place for a patient with suspected heart failure to be managed initially only in the community or primary care, except for patients who have normal levels of natriuretic peptide (and ideally also a normal ECG) in whom “heart failure” is unlikely, and an alternative cause for their presentation is more likely.

Many patients will be found to have LVSD, and for such patients there is well established evidence-based treatment that dramatically improves long term prognosis and quality of life.

If the patient presents with typical heart failure with elevated natriuretic peptide level but there is no obvious structural abnormality or arrhythmia, and other causes of apparent heart failure (such as anaemia or thyroid disease) have been excluded, then it is likely (especially if the patient is older) that they have “Heart Failure with Preserved Systolic Function” (HF-PEF). This is usually due to left ventricular “diastolic dysfunction”, for which there is little evidence-base for treatment, so referral to a specialist is recommended.

### Treatment

If the initial assessment confirms heart failure, and ideally provides clues as to the underlying cause, focussed treatment can be offered.

Treatment may be specific to the cause, for example control of arrhythmia or surgical repair for specific structural lesions. Treatment for HF-PEF is less well defined than for LVSD, and so requires specialist care, but usually relies on basic principles: improve lifestyle, provide education and support, maintain some exercise, control hypertension, minimise the possibility of myocardial ischaemia, control any arrhythmia, monitor carefully and use individually optimised drug therapy.

### Lifestyle & Education

Give the patient information about reducing salt intake, stopping smoking (it's never too late!), reducing alcohol consumption (if relevant) and ideally refer to the local heart failure cardiac rehabilitation team for a supervised exercise program.

Explain to patients that in heart failure, with reduced blood flow and blood pressure, the body responds as if it were dehydrated by releasing hormones that stimulate salt and fluid retention as well as (over)stimulating the heart. Advise patients to reduce salt intake, and to weigh themselves daily to get early warning of any fluid retention, and explain that the effective drugs work to try and prevent the body's inappropriate reactions, by preventing fluid retention (ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists) and by protecting the heart ( $\beta$  Blockers), whereas diuretics only help to get rid of excess fluid, and that in general one tries to use as little diuretic as possible.

Advise that if weight increases abruptly (because of

fluid retention) the dose of diuretic should be increased for a day or two to try and return to “dry” weight, but if the patient has diarrhoea or vomiting then they should avoid taking for a day or two any ACE inhibitor, angiotensin receptor blocker or aldosterone antagonist, to avoid dehydration, severe hypotension and renal failure. Sudden deterioration of heart failure is unlikely with brief withdrawal of these drugs in such circumstances.

At any time if there is some deterioration, early contact with the local specialist “heart failure team”, such as with community specialist heart failure nurses, can help avoid progressive decline, and can help reduce hospital admissions, or can help involve the local palliative care team when appropriate.

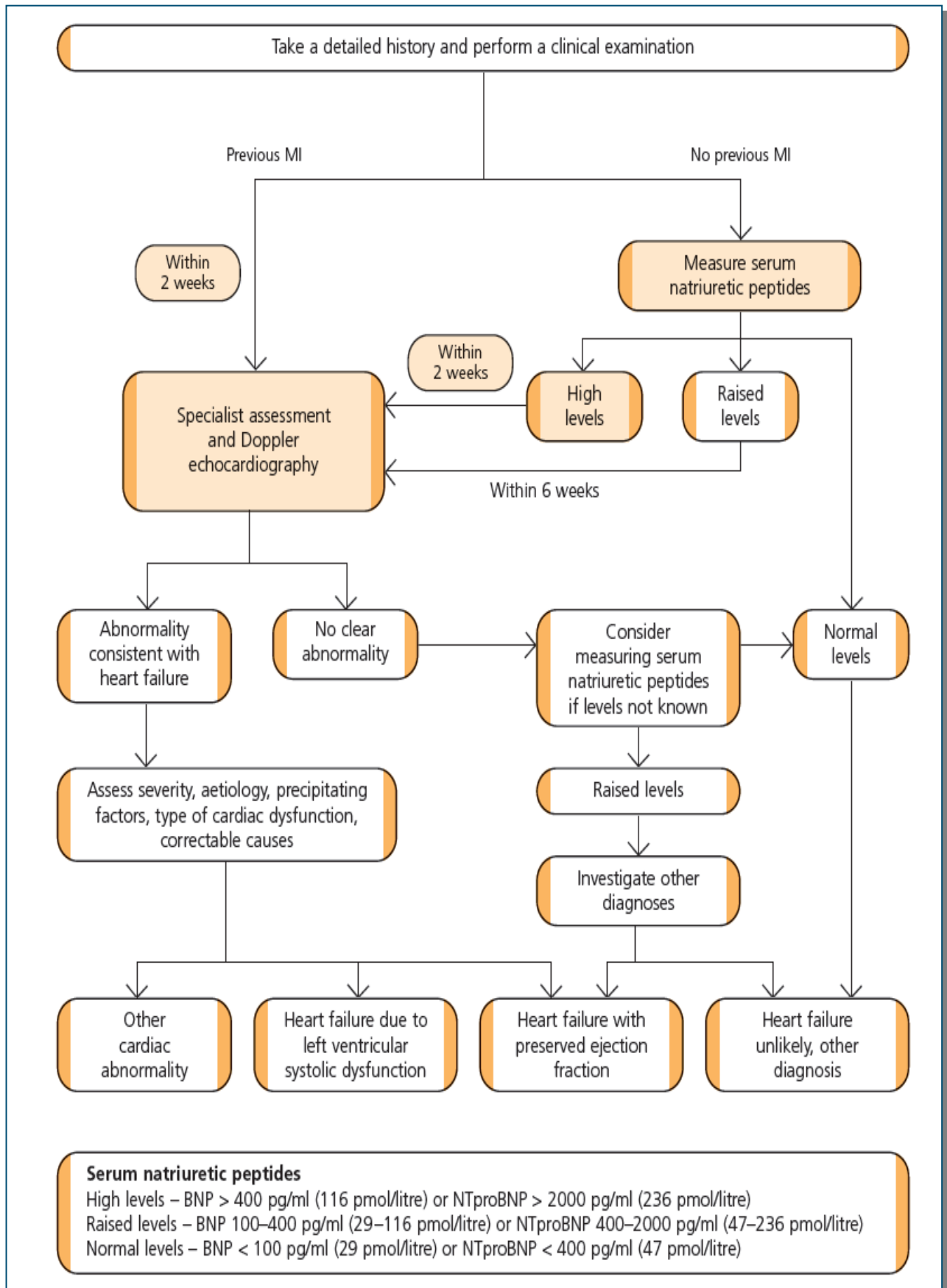
### Drug Therapy

The NICE Clinical Guideline for Chronic Heart Failure (2010), provides an outline to the evidence-based treatments that should be offered.

In general, patients with LVSD should receive a  $\beta$  blocker and an ACE inhibitor as joint 1<sup>st</sup> line treatments, and often an aldosterone antagonist as well, because these neuroendocrine blockers inhibit the harmful hormonal “vicious cycle” induced by the reduced cardiac output and reduced blood pressure, and because it is with such neuroendocrine treatments that one can improve prognosis quite dramatically. Diuretics need only be used just enough to minimise oedema. Hydralazine combined with Isosorbide Mononitrate may be useful in Afro-Caribbean patients with CHF (who tend to benefit less from ACE Inhibitors).

In patients with LVSD, the original 2003 NICE guidelines recommended starting an ACE inhibitor first, and subsequently adding a  $\beta$  blocker. But many patients ended up never receiving a  $\beta$  Blocker, and there is compelling evidence to suggest that in CHF  $\beta$  blockers are at least if not more beneficial than ACE Inhibitors.

The updated 2010 NICE guidelines now recommend offering both  $\beta$  blockers (licensed for heart failure) and ACE inhibitors to all patients with heart failure due to LVSD, and using clinical judgement when deciding which drug to start first. A patient with angina or tendency to arrhythmias is more likely to benefit from a  $\beta$  blocker first, whereas a patient with oedema and fluid retention is more likely to improve initially with an ACE inhibitor, aldosterone antagonist and diuretic (but then should have a  $\beta$  blocker added later).



**Figure 1:** Initial assessment of suspected heart failure (from NICE Clinical Guideline 108 2010).

$\beta$  blockers have been shown in many trials to improve survival by up to 30% in patients with heart failure, so they should be used far more freely, or there should be a well documented reason to deny a patient such effective treatment!

Start a  $\beta$  blocker (licensed for CHF) when the patient is stable, even if asymptomatic, and even in the presence of peripheral vascular disease, erectile dysfunction, diabetes mellitus, interstitial pulmonary disease or chronic obstructive pulmonary disease (COPD) without reversibility because the evidence is that even with these co-morbidities prognosis is improved, and not adversely affected. Do not introduce a  $\beta$  blocker when the patient's condition is deteriorating, or if they have 2° or 3° heart block, hypotension (systolic blood pressure < 100 mmHg) or a confirmed diagnosis of asthma. Occasional use of a salbutamol inhaler because the patient was a bit wheezy in the past during a chest infection – but with no respiratory function tests or formal diagnosis of airways constriction – is not enough of a reason to deny a patient  $\beta$  Blocker therapy!

Three  $\beta$  blockers are beneficial in CHF and licensed for this use in the UK: bisoprolol, carvedilol, and nebivolol. You should consider switching patients with LVSD who are already taking another beta blocker to one shown to be of benefit in CHF (not all beta blockers are the same, for example the COMET trial showed that carvedilol reduced mortality by 17% more than metoprolol).

Many trials have shown that ACE inhibitors reduce morbidity and mortality in patients with LVSD. Consider prescribing ACE inhibitors for all patients with LVSD, even if asymptomatic. The clinical benefit of angiotensin receptor blockers may not be as great as that of ACE inhibitors, so use them only in patients who cannot tolerate ACE inhibitors (only candesartan and valsartan are licensed for heart failure). The combination of ACE inhibitor and angiotensin receptor blocker is no longer recommended because of the risk of hypotension and renal dysfunction.

Start the  $\beta$  blocker and ACE inhibitor at a low dose, and gradually titrate the dose up in steps of 2-4 weeks, with careful monitoring of clinical features, blood pressure, pulse rate and renal function / electrolytes after each change of dose (“start low, go slow”). You should be trying to reach the target adult dose, but if the blood pressure is low it is better to stop

increasing the ACE inhibitor to allow some (more) introduction of  $\beta$  blocker, or if the pulse is slow to stop increasing the  $\beta$  blocker to allow (more) introduction of ACE inhibitor. It is better to be on some of both  $\beta$  blocker and ACE inhibitor than all of one but none of the other.

Consider aldosterone antagonists (spironolactone, eplerenone) for patients who are still symptomatic despite taking an ACE inhibitor and  $\beta$  blocker at the maximum tolerated dose, and especially if they still have oedema, or seem to require higher doses of loop diuretic (e.g. furosemide 80mg daily or more). Aldosterone antagonists reduce the tendency to fluid retention (so you may be able to reduce the loop diuretic dose), reduce the rate of hospital admissions, and they reduce mortality by 20% or more even in patients with few symptoms (NYHA I-II), so earlier introduction of an aldosterone antagonist is to be favoured. Hyperkalaemia can develop and renal function can deteriorate, so regular monitoring is important: within 2 weeks of starting, and at least 6 monthly thereafter. Do not start if the potassium level is >5.5mmol/l, if creatinine is >200mmol/l or eGFR <30ml/min, and discontinue treatment if potassium increases >6mmol/l, or creatinine increases >50%, but consider trying again later (perhaps with a smaller dose e.g. 12.5mg on alternate days), especially if you can reduce the diuretic dose first., trying to offer this treatment which can be so effective. Eplerenone can be substituted for spironolactone if your male patient develops gynaecomastia or sore nipples on spironolactone.

Use loop diuretics in patients with heart failure only to relieve fluid retention and dyspnoea (furosemide initially 20–40 mg once daily or bumetanide 1-2mg once daily, in morning). There is little evidence that diuretics improved survival, but they are needed to relieve oedema in most patients and can be withdrawn as oedema responds to treatment, especially once ACE inhibitors and aldosterone antagonists have started to be effective.

If oedema is not reducing on furosemide 80mg od, or bumetanide 2mg od combined with an aldosterone antagonist, try adding a thiazide diuretic (such as bendroflumethiazide 2.5mg, or metolazone 2.5-5mg daily) for a few days, as such combination therapy can be very

effective. Otherwise the patient will need intravenous diuretic treatment, or even haemofiltration, to clear the oedema.

Consider digoxin only as a second or third-line agent in CHF, as there is little evidence of benefit, and well known adverse effects. In patients with atrial fibrillation who also have heart failure, a  $\beta$  blocker is the preferred option to control the ventricular rate.

Consider offering anticoagulation with warfarin in patients in atrial fibrillation in heart failure, because their risks of thromboembolic stroke are greatly increased and this risk can be more than halved by anticoagulation.

Offer aspirin only to patients with existing atheromatous cardiovascular disease, for secondary prevention.

Despite the fact that much heart failure is due to coronary heart disease, there is no evidence that statin use is beneficial once CHF is established.

In patients with CHF, avoid using NSAIDs, rate limiting calcium channel blockers diltiazem and verapamil, short-acting dihydropyridine calcium channel blockers (eg nifedipine), alpha blockers (e.g. doxazosin), as such drugs can exacerbate heart failure and fluid retention.

### Device Therapy

Patients with LVSD who remain symptomatic despite optimised lifestyle and drug therapy, and who have ECG left bundle branch block (LBBB) in sinus rhythm, may benefit from device therapy with cardiac resynchronisation therapy (biventricular pacing, CRT-P). In LBBB, the lateral wall of the LV contracts late, and such dyssynchronous contraction reduces cardiac output. LV contraction can be resynchronised with biventricular pacing, which improves symptoms and prognosis, over and above the beneficial effects of optimised medical treatment. In the CARE-HF trial, CRT-P reduced mortality by 37% in patients who were already on optimised medical therapy!

Of patients with severely symptomatic CHF (NYHA III-IV), 56% will die of worsening heart failure, but 33% will die suddenly when otherwise stable. In patients with milder symptoms (NYHA II) 64% will die suddenly. This high proportion of patients dying suddenly (almost always because of sudden ventricular

arrhythmias, VT and VF) can be reduced by implantable cardioverter defibrillator (ICD) devices. In heart failure, many such patients can be fitted with a biventricular pacing ICD that combines CRT and ICD therapies (CRT-D).

In the COMPANION trial, patients with CHF due to LVSD on optimised medical therapy had a 1 year mortality of 19%, but those that were randomised to just CRT-P biventricular pacing (no ICD) had 15% mortality (24% reduction compared to medical therapy alone) and those with a device that provided biventricular pacing and ICD functions (CRT-D) had only 12% 1 year mortality (36% reduction, NNT for 1 year = 14).

Patients with CHF and LVSD (LV EF<35%) who have survived sudden cardiac death (SCD) have documented VT, or those who are at high risk of SCD (previous MI, LVSD with LVEF<30-35%, and ECG LBBB with QRS duration  $\geq 120$ ms) should be considered for implantation of an ICD device (usually CRT-D).

### Chronic Disease Management, Monitoring, Rehabilitation and End of Life Issues

Patients with confirmed CHF, and their family and carers, need a lot of support and education trying to help them become more “expert” in the management of this chronic condition, to help them cope and come to terms with the likely effects on quality and quantity of life. specialist heart failure nurses, and heart failure rehabilitation programmes are very helpful in providing such education and support. All CHF patients should be offered a supervised group exercise-based rehabilitation programme

Start early the process of discussing long-term chronic disease management, including end-of-life issues. It is harder to predict prognosis in heart failure than in cancer, so it is better for the patient to have had contact and preliminary discussions with the local palliative care team sooner rather than too late. Palliative care support to the CHF patient and their family and carers can provide extremely important benefits – it should not be ignored.

### Summary and Good Practice Points

- a) Chronic heart failure is common in the elderly, but is difficult to assess clinically. Make early use of BNP and echocardiography for more accurate diagnosis of the syndrome and cause.

- b) Refer patients for specialist initial assessment, but if CHF is confirmed and is due to LVSD, management can be delivered very effectively in Primary Care if treatment is optimised.
- c) Lifestyle adjustments are important: advise your patient to stop eating salty food or adding salt, and to weigh themselves daily so as to judge if their dose of diuretic needs adjusting.
- d) When prescribing diuretics, ACE inhibitors or angiotensin antagonists, remember to advise your patient that if they have diarrhoea or vomiting, or if they are not drinking sufficient fluid, that they should stop taking these medications for one to two days until they recover.
- e) In severe or intractable fluid retention, the combination of a loop and a thiazide diuretic can be very helpful.
- f) Patients may need far lower doses of loop diuretics once their ACE inhibitor (with or without aldosterone antagonist) therapy is optimized.
- g) Spironolactone may cause gynaecomastia in men. If this is a problem, change to eplerenone, which does not have this effect.
- h) Do not be afraid to start  $\beta$  blockers in stable patients: the benefit greatly outweighs the (small) risk.
- i) COPD is not a contraindication to beta blocker use unless the patient has documented (spirometry) evidence of bronchoconstriction and definite benefit from a beta2 agonist.
- j) A patient with LVSD and ECG LBBB who is on optimal medical therapy may benefit by an additional 30% reduction in mortality from biventricular pacing for Cardiac Resynchronisation Therapy (CRT-P)
- k) A patient who has survived sudden cardiac death, or who has documented ventricular arrhythmias with CHF, LVSD and LBBB should be considered for an ICD (often combined with CRT).

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## Clinical Quiz

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### A Constant Headache

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A 34 year-old female patient presented with a history of intermittent headache, which was predominantly frontal, non-pulsatile, and worsened when the patient was standing. She reported taking analgesics with little relief. She is normally fit and well with no past medical problems.

She reported no focal neurological signs and her physical examination and CT head were normal. On further questioning she revealed she had recently given birth to her two month old daughter under spinal anaesthesia and noticed that her symptoms seemed to have developed since then.

### Questions

- 1) What is the diagnosis?
- 2) What is the pathophysiology of this condition?
- 3) How can this condition be treated and prevented?

### Answers

- 1) **Post Dural Puncture Headache (PDPH).**
- 2) **It is described as a bilateral headache that develops within seven days after dural puncture with the majority disappearing after 14 days,** however cases lasting longer than 6 months have been reported. It is typically a frontal or occipital headache with a positional element whereby it is exacerbated in a vertical position and alleviated on lying flat.<sup>1</sup> Other clinical signs include tinnitus, hearing loss, autophonia, dizziness, photophobia, double vision and isolated cranial nerve palsies. The headache occurs post lumbar puncture, spinal anaesthesia and accidental dural puncture post epidural anaesthesia. A simple bedside test can be used to aid diagnosis. Whilst the headache is present the patient lies supine and a constant pressure is applied on the abdomen and the back, the headache typically disappears after 30 seconds and returns upon releasing the pressure.<sup>2</sup> PDPH occurs more often in young adults, especially in the 18-30 age group and particularly in young women with a low BMI.<sup>3</sup>
- 3) **The precise mechanisms of PDPH are unclear.**  
It is thought that the loss of CSF leads to a reduced cushioning effect around the brain and its sensitive meningeal vascular covering. Upon vertical positioning the gravitational traction on these structures produces the classic positional headache. It is also thought that the decrease in CSF may cause an activation in adenosine receptors causing cerebral vasodilatation and stretching of pain sensitive cerebral structures.<sup>4</sup>
- 4) **Conservative management.**  
Abdominal binders that raise intra-abdominal pressure are thought to transmit pressure to the epidural space and may be used to alleviate PDPH.

Data on pharmacological agents has been limited due to lack of large randomised controlled trials. Desmopressin, ACTH and sumatriptan have been used but with variable effects. Caffeine, a cerebral vasoconstrictor, has been demonstrated to be effective however the effects have been temporary.

reported success rate of 70% -98%.<sup>5</sup> 20-30mls of venous blood is obtained from the patient and injected into the epidural space by an anaesthetist. It is thought that the blood will be distributed up and down the segments of the spine and coagulated into a clot, which will block the leakage of CSF at the site of the dural puncture. Other techniques are available such as epidural saline and dextran injections or insertion of intrathecal catheters which have limited evidence. The last resort would be for surgical intervention with an attempt to close the dural defect, which carries with it obvious surgical risks.<sup>6</sup>

### Prevention

- Measures can be adopted to prevent the development of PDPH. These steps have been demonstrated in studies to reduce PDPH.
- Small gauge spinal needle < 22G.
- Direction of the needle bevel inserted parallel to the dural fibres which run longitudinally down the spine.
- Atraumatic needles which separate the dural fibres as opposed to cutting through them.
- Replacement of the stylet prior to withdrawing the needle.
- Reducing number of puncture attempts.
- Good hydration.
- Bed rest has been shown to have no benefit in preventing PDPH

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Invasive techniques: Epidural blood patching has become more of a popular technique, with a

### A Challenging Microbiological Diagnosis

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#### Abstract

A nutritionally variant streptococcus identified as *Granulicatella adiacens* was eventually isolated from four of four blood cultures collected from a patient with prolonged fever. The microbiological diagnosis was delayed because of the failure of this organism to grow on routine solid media. Subsequently, recognition of the likelihood of a nutritionally dependent organism in a second blood culture facilitated the clinical diagnosis of endocarditis. The clinical microbiologist has significant role in the diagnosis and management of infective endocarditis.

#### Case Report

A blood culture was received in the microbiology laboratory as part of the investigation of fever for 10 days. The child had travelled to a tropical area 6 months earlier. The laboratory uses an automated blood culture system BD Bactec FX (Becton, Dickinson and Company). Within 24 hours the blood culture signalled positive and a Gram stain revealed Gram-positive cocci in chains. Clinical notes in the laboratory information system indicate that light growth was observed on sensitivity plates but not on chocolate or blood agar at 24 and 48 hours of incubation. A report of no growth from the blood culture was issued. No urine sample was submitted. A full blood count the day before admission revealed hypochromic microcytic anaemia, mild thrombocytopenia and a false-positive immunochromatographic test for malaria. A chest X-ray report indicated no signs of consolidation. Ten days later a second blood culture was submitted. Within 24 hours this bottle had signalled positive and a similar Gram stain result observed. The clinical microbiologist (not previously involved with the case) realised the high probability of infective endocarditis with a nutritionally variant streptococcus and telephoned the clinicians. By this time the clinicians were also suspecting the possibility of endocarditis as the patient had a congenital heart defect. Indeed this clinical information may have helped raise the clinical microbiologist's suspicion of endocarditis earlier had it been provided on the initial request. The microbiologist advised commencing the patient on benzyl-penicillin and gentamicin after collecting two further blood cultures at different times.

Once the possibility of a nutritionally variant streptococcus was recognised, the blood culture

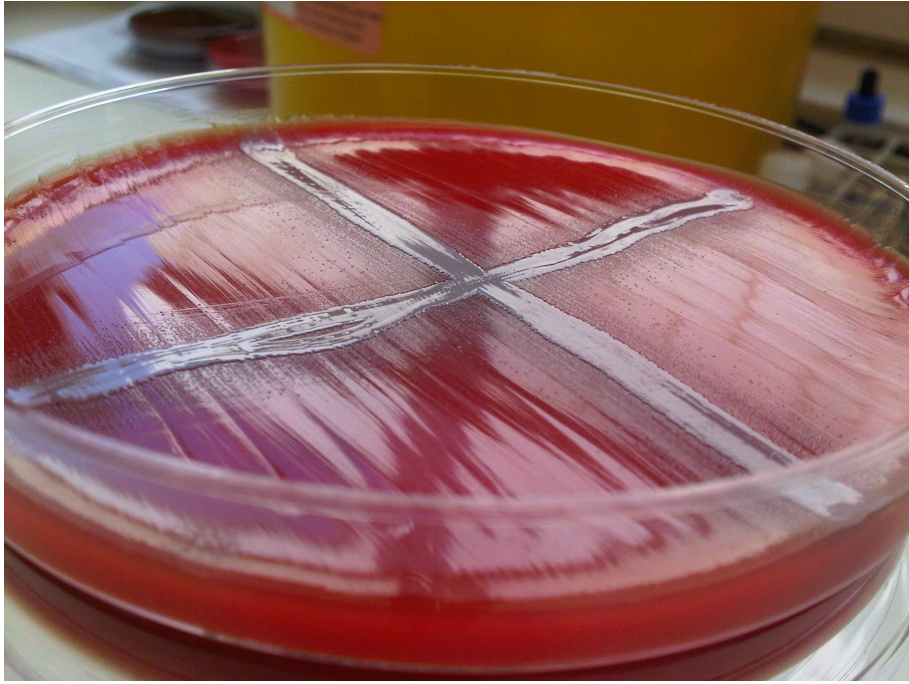
was subcultured onto a more enriched medium (Fastidious Anaerobic Agar, Oxoid) and the isolate was successfully isolated. The organism was shown to satellite around a *Staphylococcus aureus* streak (Figure 1). This is characteristic of nutritionally dependent streptococci. The organism was identified locally (API Strep, bioMérieux) as *Granulicatella adiacens*. This was confirmed by the reference laboratory (Respiratory and Systemic Infection Laboratory, Health Protection Agency, Colindale). The MIC to penicillin was  $\leq 0.06$  mg/L (sensitive). The organism was also isolated from the two additional blood cultures.

#### Discussion

Positive blood cultures are a major criterion in the Duke criteria for the diagnosis of infective endocarditis<sup>1</sup>. Current recommendations are for 3 sets of blood cultures to be taken from separate venepuncture sites over 24 hours<sup>2</sup>. Nutritionally variant streptococci form part of the normal oral flora and cause about 5% of infective endocarditis<sup>1</sup>. The nutritionally variant streptococci were initially considered to be mutants of oral viridans streptococci but are now considered to be separate species: *Granulicatella adiacens*, *G. elegans* and *Abiotrophia defectiva*<sup>3</sup>. Isolation of nutritionally variant streptococci has implications for management and prognosis<sup>1,2</sup>. The complexity of microbiological diagnosis is not always appreciated by clinicians and it is recommended that they provide as many clinical details as possible to microbiologists in order to optimise the processing of the specimens submitted.

#### Learning Points

- 1 The isolation of nutritionally variant streptococci may provide a challenge to microbiology laboratories.
- 2 Clinicians should provide as many clinical details as possible to microbiologists, either on the request or by telephone, if they wish to optimise the processing of submitted specimens.
- 3 The clinical microbiologist has significant role in the diagnosis and management of infective endocarditis.



**Figure 1:** Growth of nutritionally variant streptococcus around growth of *Staphylococcus aureus* (satellitism).

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### Immunosuppression Resistant Polymyositis due to Occult Oesophageal Carcinoma

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#### Abstract

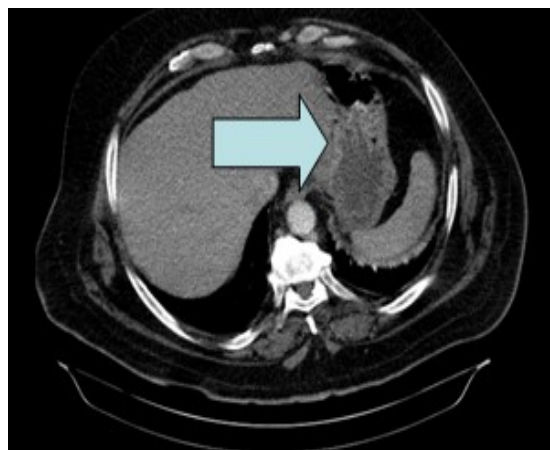
Polymyositis and dermatomyositis are inflammatory myopathies, which have a recognised association with cancers. Paraneoplastic polymyositis is a rare cause of proximal muscle weakness in association with different cancers especially with oesophageal cancer. We describe a case of proximal polymyositis with mild muscle inflammation in a patient with oesophageal adenocarcinoma. After developing acute proximal muscle weakness, the patient experienced good recovery in muscle weakness with chemo and radiotherapy of primary oesophageal carcinoma.

#### Case Report

A 59 year old male presented to A&E with inability to weight bear for 3 months. He had a past medical history of hypertension but no autoimmune disease. He was unable to weight bear on crutches. He had no power in the proximal muscles or the lower limbs and suffered with morbid obesity. His initial clinical examination revealed proximal muscle weakness MRC grade 0/5 mainly in the lower limbs. There was less marked proximal muscle weakness in his upper limbs.

On admission, serum creatinine kinase (CK) was 14560 but he was not on steroids or statin therapy. Liver function tests were deranged (Table 1) but ultrasound scan of the liver was normal. Chest x-ray showed no abnormality. A CT scan of the abdomen and pelvis revealed no evidence of neoplasia. The electromyography (EMG) indices were consistent with polymyositis.

The patient was treated with a course of prednisolone 100mg for six weeks and then azathioprine 150mg for two weeks with little resolution in the symptoms. Prednisolone was tapered to 60mg and then 40mg over a 12 week period. CK post treatment remained at 8000-10000. A muscle biopsy revealed abnormal muscle fibres with infiltration with inflammatory cells consistent with steroid treated polymyositis. Microscopic examination of the muscle fibres revealed vacuolation of degenerative origin with macrophage and T cell infiltration.



**Figure 1:** CT Thorax showing circumferential thickening at the distal gastroesophageal junction (see arrow).

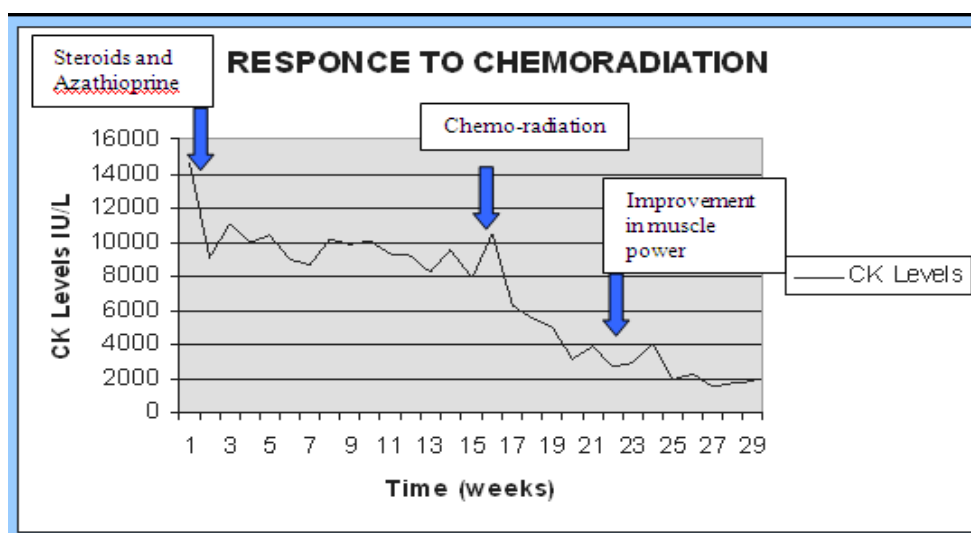
The patient had two episodes of melaena and dropped his haemoglobin by two grams on prophylactic anticoagulation with enoxaparin 40 mg. An upper gastrointestinal gastroscopy showed distal ulceration in oesophagus at the gastro-oesophageal junction. The histological examination of the ulcer revealed adenocarcinoma of the distal oesophagus.

Retrospective review of the CT scan of abdomen and chest revealed circumferential thickening within the stomach extending to gastro-oesophageal junction with enlarged gastro-hepatic lymph nodes (Figure 1).

Further management continued with 4 courses of chemotherapy (5FU 1500mg and cisplatin 40mg) with radiotherapy (six courses of 40 Gy in 28 fractions) over five weeks. There was gradual improvement in proximal muscle power from MRC grade 0/5 to 3/5 and serum CK levels (Figure 2). The patient was able to transfer himself between the bed and chair independently and was continued on azathioprine.

**Table 1:** Blood Results on admission

		(Normal Range)			(Normal Range)
<b>Hb</b>	15.3g/dl	13-17g/dl	<b>Na</b>	136mmol/l	133-145mmol/l
<b>MCV</b>	83fl	78-101	<b>K</b>	3.8mmol/l	3.6-5.2mmol/l
<b>WCC</b>	$19.5 \times 10^9/l$	$4-11 \times 10^9/l$	<b>Urea</b>	5mmol/l	3.5-10mmol/l
<b>CK</b>	14560iu/l	24-171iu/l	<b>Cr</b>	30umol/l	59-104umol/l
<b>Cholesterol</b>	5.9mmol/l	<5 as per Guidelines	<b>CRP</b>	74mg/l	0-5mg/l
<b>Triglyceride</b>	2.14mg/dl	0.3-1.8mg/dl	<b>Cortisol</b>	403nmol/l	200nmol/l
<b>Bilirubin</b>	11umol/l	0-17umol/l	<b>CA 199</b>	10 U/ml	0-35U/ml
<b>ALP</b>	79iu/l	40iu/l	<b>CEA</b>	<1.0ug/l	0-4ug/l
<b>ALT</b>	265iu/l	40iu/l	<b>PSA</b>	0.2ug/l	0-4 ug/l
<b>Albumin</b>	30g/l	35-42g/l	<b>Calcium</b>	2.26mmol/l	2.2-2.6 mmol/l
<b>Glucose</b>	5.1mmol/l	3.5-8.0mmol/l			



**Figure 2:** Response of CK and muscle power to chemo-radiation.

### Discussion and Literature Review

In contrast to inflammatory myopathies, paraneoplastic polymyositis is a rare clinical entity.<sup>1,2</sup> It starts as acute or subacute weakness over a few weeks, with symmetrical proximal muscle weakness. The frequency of polymyositis with gastrointestinal tumours, small cell lung cancer and breast cancer is well established but the relative risk with oesophageal carcinoma was quoted at only less than 1% in one study.<sup>2</sup> We report a case of paraneoplastic myopathy with a mild inflammatory component associated with adenocarcinoma of oesophagus and resolution of

weakness with chemo and radiotherapy of the primary malignancy.

The association of polymyositis and cancer was first highlighted in 1916 but was disputed.<sup>3</sup> Clinical symptoms not directly related to cancers are described as paraneoplastic syndrome and can be acute or subacute in presentation. Inflammatory myopathy is a classical syndrome associated with various cancers. The association has been described in 15 % of cases, mainly with GI tumours, small cell cancers and breast cancers.<sup>2,4</sup> The understanding of the mechanism remains unclear

and treatment of the underlying cancer is the mainstay of management.<sup>5</sup>

In a recent population based study there was a two fold increase in the risk of malignancy in polymyositis.<sup>2</sup> This study showed that with polymyositis, an increase was found for 1-5 years after the diagnosis of myositis and may be due to increased surveillance. In another Swedish population based study cancers were diagnosed at the same time or after polymyositis in 9% of patients.<sup>6</sup> Polymyositis was also associated with higher risk of non-Hodgkin's lymphoma, lung and bladder cancers.<sup>3</sup>

The underlying mechanism of association remains unclear. Common auto-antigens are expressed in both tumour cells and undifferentiated myoblasts. It leads to generation of T and B cells against the antigens and anti tumour activity. In few patients, the muscle damage is due to other causes including viral infection or trauma.

The definitive diagnosis requires a muscle biopsy. In a few instances the diagnosis can be made based on clinical grounds. EMG confirms the myopathic process with presence of prominent spontaneous muscle fibre potentials in patients with active myositis.<sup>7</sup> The electron microscopy normally shows inclusions in cytoplasm of vacuolated muscle fibres and mononuclear cell infiltrate in non necrotic muscle fibres. The histological findings range from sparse segmental necrotic lesions to massive necrosis.

This case stresses the importance of histopathological diagnosis in such clinical scenario.<sup>5,7</sup> EMG normally shows short duration and low amplitude, polyphasic motor unit potentials with spontaneous fibrillation potentials. The decreased amplitude of the motor unit potentials in chronic polymyositis may be the result of the smaller size of regenerating muscle fibres.<sup>7</sup>

The association of polymyositis with immune disorders like Hashimoto's thyroiditis stresses that the aetiology is due to underlying autoimmune disease.<sup>8</sup> It is difficult to understand whether both paraneoplastic and endocrine-associated myopathy are different ends of the same spectrum.<sup>8</sup>

The goal of therapy is to achieve recovery of muscle weakness by treatment with oral steroids or immunosuppressive agents.<sup>7</sup> In our case the recovery of muscle weakness was in response to treatment of the primary cancer but showed no response to steroids or immunosuppressive therapy.

There are various treatment modalities which have been suggested in the literature. Intravenous immunoglobulins have been shown to lead to a

significant improvement in few case reports in spite of tumour progression.<sup>4,6</sup> Cetuximab is another alternative used with chemotherapy in patients with metastatic colon cancer despite of lack of improvement in underlying cancer.<sup>9,10</sup> In one case study complete resection of a primary oesophageal carcinoma led to complete remission of associated polymyositis.<sup>12</sup>

To conclude, the outcomes in response to different treatment modalities for paraneoplastic polymyositis are varied, which can present a challenge in day to day treatment and management decisions. The use of EMG as an adjunct to clinical suspicion and further confirmation by muscle biopsy can be valuable in establishing the clear diagnosis in some clinical cases.

### Learning Points

In patients with polymyositis showing poor response to traditional immunosuppressive treatment with steroids and azathioprine, a search for internal malignancy is advisable.

Muscle biopsy and EMG may confirm the diagnosis of paraneoplastic myositis.

The role of continuing immune suppression to sustain the improvement in muscle power with tumour control by chemotherapy and radiotherapy remains unclear.

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