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WJMER

World Journal of Medical Education and Research

An Official Publication of the Education and Research Division of Doctors Academy

In this edition, these topics and more....

The Role of Cell-Based Imaging in Drug Discovery

Antigen Microarrays for Rapid Screening of Rheumatoid Arthritis and Other Autoimmune Diseases

Management of Major Trauma: A Malaysian Perspective

Abstracts from the International Academic & Research Conference 2012

Assessment and Management of Head and Spinal Cord Injuries

Osteoradionecrosis (ORN) of the jaw

Role of Cloud Computing in Global Healthcare Provision

Introduction

The World Journal of Medical Education and Research (WJMER) is the online publication of the Doctors Academy Group of Educational Establishments. Published on a quarterly basis, it's aim is to promote academia and research amongst all members of the multi-disciplinary healthcare team including doctors, dentists, scientists, and students of these specialties from all parts of the world. The principal objective of this journal is to encourage the aforementioned from developing countries in particular to publish their work. The journal intends to promote the healthy transfer of knowledge, opinions and expertise between those who have the benefit of cutting edge technology and those who need to innovate within their resource constraints. It is our hope that this will help to develop medical knowledge and to provide optimal clinical care in different settings all over the world. We envisage an incessant stream of information will flow along the channels that WJMER will create and that a surfeit of ideas will be gleaned from this process. We look forward to sharing these experiences with our readers in our subsequent editions. We are honoured to welcome you to WJMER.

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WELCOME

Dear Colleague,

'To practice medicine without books is like going to sea without charts but to practice medicine without patients is not to go to sea at all…'

So said the 20th century Canadian physician Sir William Osler (and the person to whom the ultimate accolade has been bestowed upon, 'The Father of modern medicine'). For those who have not yet embarked upon some maritime endeavour (and our experiences have hitherto been vicarious) it is the seafarers of excitement and trepidation that will accompany you on such adventures.

Compiling the second issue of the World Journal of Medical Education and Research (WJMER) has, in many ways, been an arduous journey. After having braved the elements and endured the tempestuous storms on our voyage we finally arrived at our destination and in doing so we, the editorial team, have derived immense satisfaction that we would like to share with our readers, those students of knowledge who seek to augment their medical acumen by perusing our pages. We invite you, then, to accompany us on this odyssey for professional growth and self-development and to allow our articles to be the beacon of light to aid you on your quest.

This issue contains a broad array of articles for a diverse readership. We realise that medics will encounter tributaries on their journey throughout medical school and their medical careers; thus it is difficult to navigate and know which direction to take without sound guidance and wise advice.

At Doctors Academy, we foster the reconciliation between research, academia and clinical medicine and this issue of WJMER is no exception. We hope that our high calibre research articles from Ms Wing and Dr Seewoodhary will whet the appetite of even the most voracious medics who feast on the fruits that sprout on the tree of academia. Our, 'An Introduction to...' series of articles hopes to provide you with the charts to trawl through even the murkiest of waters and help you make an informed decision about what career trajectory is most suited for you.

In keeping with the ethos of WJMER in promoting the global transfer of knowledge, this edition has two highly informative and instructive articles on trauma management from Kedah, Malaysia, that aim to encourage the reader to reflect on, among other matters, first principles and the universality of medical knowledge. Likewise, the irrefutable synergy between healthcare and cutting-edge scientific advances in engineering is indubitably illustrated in the article 'Role of Cloud Computing in Healthcare Provision' by the team from NI University, India.

This issue also contains the abstracts of the research papers that were showcased in the Doctors Academy's flagship event, 'The Future Excellence International Academic and Research Conference, 2012'. The heterogeneity of the abstracts, we feel, is illustrative of the depth and breadth of the scope of WJMER.

Having provided you with the map we feel confident to allow you to set sail into the vast ocean of academic and clinical medicine. You can be rest assured, courageous sailor, that for those who delve deep enough the treasure of augmenting your medical acumen will always be discovered and revelled upon…

With very best wishes,

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Research Article
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The Role of Cell-Based Imaging in Drug Discovery

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Keywords:
Cell Based Imaging; Drug Discovery; High Throughput Screening; Fluorescence; Assays

Cell imaging has an important function in drug discovery and this review will critically consider these roles. The process of drug development will be outlined followed by a discussion on how different types of cell-based imaging assays have contributed to this.

Drug discovery is the process by which drugs are discovered and starts with High Throughput Screening (HTS), which is a scientific method that uses robotics, data processing and control software, liquid handling devices, and sensitive detectors to rapidly perform millions of pharmacological tests on compound libraries to identify ligands that modulate targeted pathways of disease processes. These ligands are termed'hits'. The hit -to-lead phase is the follow-up of HTS and includes: hit confirmation; hit expansion; and the lead optimisation phase. Following on from this, pre-clinical studies occur prior to entry into clinical trials.

Cellular imaging refers to the visual representation, characterisation, and quantification of cellular processes. Microscopy has contributed to the drug discovery pipeline by visualising the unfolding of pathological mechanisms and identifying targets for drug development. Novel innovations in microscopy have enhanced experimental throughput by improving spatial resolution and tissue penetration and have overcome physical access issues. This has been achieved by: the development of super-resolution microscopes capable of resolving structures to below the diffraction limit of 200nm; incorporating multi-photon techniques into intravital and fibre-optic microscopy, which allow image collection at greater tissue depths; and the automation of microscopy and image analysis for HTS[1].

The use of fluorescence is central to the role of cell based imaging in drug discovery. Fluorescent probes label and track 'targets' central to pathological processes; targets mainly include single genes or proteins. Targets can be tagged with fluorescent proteins such as Green Fluorescent Protein (GFP), which auto-fluoresces without substrates or co-factors and allows for real-time analysis of molecular events in living cells. GFP has revolutionised orphan receptor research; endogenous ligands have been identified by imaging GFP-tagged therapeutic proteins[2]. GFP-tagged proteins have been used to determine the site and time course of receptor expression and to relate receptor dynamics with therapeutic outcomes[3]. For example, automated imaging of fluorescent protein reporters has facilitated the interrogation of the Gonadotrophin Releasing Hormone Receptor (GnRHR) signalling to the Raf/MEK/ERK and Ca^{2+} /calmodulin/ calcineurin/NFAT cascades. This has contributed to the development of cetrorelix, a GnRHR antagonist used to treat hormone sensitive cancers of the prostate and breast[4].

Direct and indirect immunofluorescence, which involves the conjugation of fluorescently labelled proteins to primary and secondary antibodies, has contributed to the selection, characterisation and target validation process in drug discovery. To illustrate this principle direct and indirect immunofluorescence has been used to characterise neurotransmitter release in multimeric voltage-gated K+ channels (Kv1); this has pharmacological implications for drug discovery in disorders such as Alzheimer's disease, which are characterised by impaired neurotransmitter release from central Kv1 ion channels[5].

Fluorescence Resonant Energy Transfer (FRET) microscopy is a HTS cell imaging technique based on the physicochemical property of an excited fluorophore rapidly losing energy to a nearby molecule that is capable of absorbing it. Therefore, FRET is a powerful tool to detect and locate protein interaction sites within live cells and can be used to measure targeted events, such as a pharmacological intervention, which produces changes in the molecular proximity of two proteins[6]. Other similar high-throughput cell-imaging assays include: bimolecular fluorescence complementation; enzyme fragment complementation; and the yeast two-hybrid assay, which can detect protein-protein or protein-DNA interactions.

Flow cytometry has contributed to the drug discovery pipeline. For example, flow cytometry has been used for ex vivo analysis of in vivo efficacy of chemotherapeutic agents such as enzastaurin, a protein kinase C inhibitor, on intracellular phosphoprotein signalling in monocytes obtained from cancer patients. These results confirmed the efficacy of enzastaurin by revealing reduced PKC activity following drug administration[7].

Cell-based reporter assays using luciferase have contributed to HTS and drug development by enabling the assessment of target transcriptional activity. For example miRNA's, which regulate gene expression, have been linked to cancer and viral infections, identifying miRNA'sas potential targets for drug discovery. HTS using luciferase reporter assays have facilitated cell-based imaging of miRNA's[8]. However, cell based reporter assays are not ideal for drug discovery as they have a high false positive rate. Furthermore, luciferase reporter assays are unable to confirm whether the positive result is due to the test compound rather than the induction of alternative signalling pathways by the test compound or hydrolysed products of the test compound.

Cell imaging using radio-ligand binding assays, which are low-throughput methods, have facilitated the identification of compounds capable of binding to and either activating or inhibiting target GPCR's.They can also quantify second messenger responses. Further benefits include generating data to: measure binding affinity by saturation or competition analysis; determine dose-response relationships; and determine the potency and efficacy of novel compounds. Other examples of low throughput cell based imaging techniques that have been used in drug discovery include: conventional and confocal microscopy; and western blotting to detect targets that are phosphorylated.

Cell based imaging techniques have played a key role in assessing the safety of drugs as part of the drug development process. This can be illustrated by use of the In vitro micronucleus assay, which detects micronuclei (damaged pieces of chromosomes), which serve as markers of drug-induced genotoxicity[9]. Pharmaceutical regulatory bodies require the application of tests that screen for genotoxicity prior to drug approval.

Despite the multitude of both high throughput and low throughput cell-based imaging assays currently available the future of cellular imaging in drug discovery may reside with non-invasive imaging. For example, Raman spectroscopy, which is a scattering technique that uses vibrational information specific to chemical bonds and molecular symmetry, will inevitably expose novel approaches to non-invasively identify pharmacological targets whilst being equally or more accurate, predictive and cost-effective relative to current methods.

In summary cell-based imaging assays have proven instrumental in drug discovery. Fine-tuning existing assays coupled with the development of non-invasive imaging techniques will enhance the signal to noise ratio of cell-based imaging assays down to genomic, transcriptomic and proteomic levels, with the aim of unravelling disease processes and identifying new therapeutic targets. This will turn the hope of advancing drug discovery into a more realistic and exciting expectation.

References:

1. Starkuviene V, Pepperkok R. The potential of high-content high-throughput microscopy in drug discovery. Br J Pharmacol. 152 (2007) pp: 62-61.
2. Daly CJ, McGrath JC. Fluorescent ligands, antibodies, and proteins for the study of receptors. Pharmacol. Ther. 100 (2003) pp: 101-18.
3. Arun KH, Kaul CL *et al*. Green fluorescent proteins in receptor research: an emerging tool for drug discovery. J Pharmacol Toxicol Methods. 51 (2005) pp: 1-23.
4. Reissmann T, Schally AV *et al*., 2000. The LHRH antagonist cetrorelix: a review. Hum Reprod Update6 (2000) pp: 322-31.
5. Skaper SD. Ion channels on microglia: therapeutic targets for neuroprotection. CNS Neurol Disord Drug Targets10 (2011) pp: 44-56.
6. Viladarga JD. Studying ligand efficacy at G protein-coupled receptors using FRET. Methods Mol Biol.756 (2011) pp: 133-48.
7. Green LJ, Marder P, *et al*. Development and validation of a drug activity biomarker that shows target inhibition in cancer patients receiving enzastaurin, a novel protein kinase C-beta inhibitor. Clin Cancer Res. 12 (2006) pp: 3408–3415.
8. Connelly CM, Thomas M *et al*. High-Throughput Luciferase Reporter Assay for Small-Molecule Inhibitors of MicroRNA Function. J Biomol Screen (2012) doi: 10.1177/1087057112439606
9. Lang P, Yeow K *et al*. Cellular imaging in drug discovery. Nature Reviews Drug Discovery 5 (2006) pp: 343-356.

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Antigen Microarrays for Rapid Screening of Rheumatoid Arthritis and Other Autoimmune Diseases

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INTRODUCTION

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic and extremely disabling disease, primarily characterised by extensive synovial inflammatory attack, leading to progressive autoimmune destruction of cartilage, ligaments and occasionally bone[1-4]. Approximately 580,000 patients in England and Wales suffer from this multi-factorial disease[2], costing the UK an estimated £3.8-4.75 billion per annum[4,5]. As the complexity of the disease aetiology is still relatively unidentified, the disease remains incurable[6].

Diagnosis

In 2009, NICE guidelines advocated the importance of early RA diagnosis, as Disease Modifying Anti-Rheumatic Drugs (DMARDs) significantly enhance prognosis if started early in disease progression[4]. This led to the 2010 American College of Rheumatology diagnostic criteria[7], as previous 1987 criteria depended heavily upon clinical presentation, which is equivocal in early stages[8,9]. It also relied upon detection of Rheumatoid Factor (RF)[9,10] that, despite being highly sensitive, is poorly specific. (Approximately 60% of Sjögren's Syndrome patients and 5% of healthy populations are sero-positive[3,11].) Hence, novel laboratory diagnostic techniques evolved with a greater sensitivity, specificity and ability to detect RA before irreversible joint destruction occurs [3,12].

A prime example is testing for anti-citrullinated protein antibodies (ACPA) against a synthetic peptide termed cyclic citrullinated peptide (CCP). These are well recognised serological markers of RA presenting years before symptom onset[13], and are virtually absent in healthy individuals and other rheumatic diseases[14]: this is because inflammatory processes in RA release Peptidylarginine Deiminase (PAD) enzyme into the synovium. PAD converts arginine subunits of membrane proteins into citrulline and researchers believe this post-translational modification alters protein antigenicity, triggering autoimmune processes[8].

Research is currently investigating the spectrum of citrullinated proteins involved in pathogenesis and their relationship with certain ACPA isotypes and classes/ subclasses [11,15-18].

Recent ACPA ELISAs have the ability to be, as a minimum, equal to RF sensitivity (82%) with an even greater specificity (98%)[11]. Consequently, ACPA assays have emerged as a superior diagnostic test to RF and have been incorporated into the 2010 American College of Rheumatology criteria[7,19]. However, current ELISA techniques limit the possibility of screening worldwide arthritis populations for all ACPA isotypes and specificities, due to time-scales and costing. For this reason, there is emerging potential to develop an improved technique with this capability.

Protein Microarrays

Advances in technology have brought protein microarrays to the forefront as a validated method of autoantibody detection and have so far shown very promising results[16,20,21]. They can simultaneously detect multiple autoantibodies and ACPA isotypes in a single assay, whilst maintaining similar sensitivities and specificities to current ELISA methods[22]. By aiding diagnosis and management, monitoring response to therapeutics and identifying disease subgroups or novel autoantigens[21], microarray potential in the world of immunology is far superior to current methods.

Research Proposal

The project aim is to investigate a new method of screening for autoantibodies in the serum of autoimmune patients, including RA, to aid patient categorisation.

Protein microarrays will particularly assess the significance of known autoantigens, second generation cyclic citrullinated peptides (CCP2), citrullinated proteins and their non-citrullinated counterparts. Antigens will be robotically printed onto microscope slides alongside

control proteins. The assays will screen donated patient sera for autoantibodies and, in terms of RA, the project will hope to observe ACPA in patient sera. Only a tiny volume of patient serum (less than 5µl, compared to 5ml required with ELISA21) will be required to simultaneously screen for autoimmunity against a wide range of autoantigens.

Objectives

1) To analyse protein microassay potential of diagnosing RA in early stages.
2) To determine whether protein microarrays can provide useful information in other autoimmune conditions.
3) To establish the possibility of creating biomarker profiles that relate to disease severity, course and prognosis.
4)To discover if protein microarrays have the ability to classify patients into disease subgroups.

EXPERIMENTAL PROCEDURES

Chemicals and Reagents

All chemicals and reagents used in the following experiments were purchased from SIGMA ALDRICH CHEMISTRY®, USA and stored at room temperature, unless otherwise stated. Experiments were also carried out at room temperature, unless otherwise stated.

Antigens

CCP2 was printed in both PBS and in Dimethyl Sulfoxide (DMSO) solvent to aid correct peptide formation, along with a range of citrullinated proteins and their non-citrullinated counterparts. Citrullination was performed prior to this study.

Various other antigens covering a wide range of autoimmune diseases were also printed alongside putative Chronic Obstructive Pulmonary Disease (COPD) biomarkers - as both COPD and RA are linked with smoking, it has been questioned whether COPD biomarkers act as autoantigens in RA[11](**Figure 1**).

Stock antigen samples were diluted using a 5 times stock solution of PBS-Trehalose-Tween20 buffer (0.5mls PBS, 0.5mls Trehalose and 2µl Tween20) to give 10 µl of a of 0.1µg/µl concentration. Samples with unknown stock concentrations were assumed to be at a concentration of 1mg/ml, and samples with very weak stock concentrations were not diluted. Calculations were produced to ensure the buffer used in every sample was at a 1 times concentration.

Printing Proteins

Each sample was transferred into a 384 well microtitre plate and printed onto PVDF coated slides by means of a Genomic Solutions Microgrid II 610 Arrayer with use of a silicon PETC (partially etched through channel) pin (PARALLEL SYNTHESIS TECHNOLOGIES, USA). Three triplicate spots of autoantigens were printed in each grid to monitor reproducibility. Two rows of a 2-fold serial dilution of human IgG (with the same diluent and buffer as above) were also printed per grid to serve as a positive control.

In each case, proteins were robotically printed in a 12x12 grid with each spot approximately 150 microns in diameter. Sixteen identical grids (roughly 6x6mm each) were printed onto each slide in an 8x2 array (**Figure 1**).

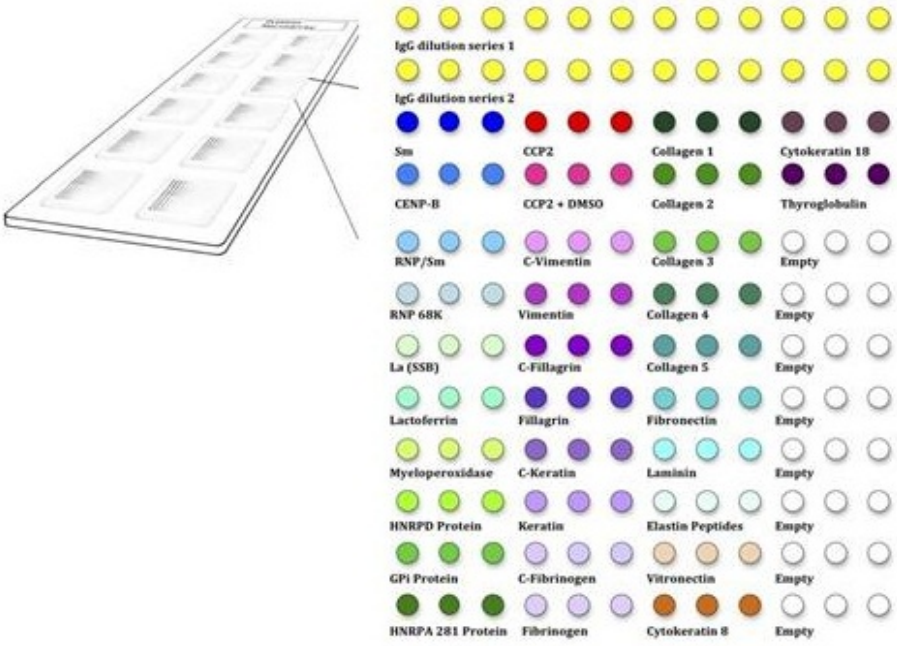

Figure 1: Autoantigens were printed in 12 X 12 squares, in the adjascent format, onto PVDF-coated slides using a microarrayer

Probing Slides

1) Slides were inserted into a Grace-BioLabs 16-well plastic slide gasket
2) One hundred micro litre (100µl) of 0.2% I-block (0.05 grams of I-block pellets dissolved in 25mls of Phosphate Buffered Saline-Tween 20[PBS-Tween]; stored in a fridge) was added to each well [NB. A 1 litre stock solution of PBS-Tween was previously prepared using 10 PBS tablets dissolved in 1 litre of distilled water and 500µl of 100% Tween20].
3) Slides were covered with cling-film and left to shake for 1 hour at room temperature
4) Each well was washed with PBS-Tween 3 times, each for 5 minutes
5) One hundred micro litre (100µl) of patient serum (1:100 with Antibody Diluent) was added to each well
6) Slides were covered with cling-film and left to shake for 1 hour
7) Each well was washed with PBS-Tween 3 times, each for 5 minutes
8) One hundred micro litre (100µl) of biotinylated anti-human IgG antibody (1:1000 in Antibody Diluent) was added to each well
9) Slides were covered with cling-film and left to shake overnight in a coldroom at 4^{o}C
10) Each well was washed with PBS-Tween 3 times, each for 5 minutes
11) One hundred micro litre (100µl) of Streptavidin-IR780 (1:5000 in PBS-Tween) was added to each well
12) Slides were covered with silver foil and left to shake for 30 minutes
13) Each well was washed with PBS-Tween 3 times, each for 5 minutes
14) Slides were briefly washed with distilled water, immediately dried with dry nitrogen gas and scanned using a a Licor Odyssey Infrared Scanner (School of Biomedical Sciences) to obtain digital images for analysis
15) Primary data acquisition (spot identification, feature and background measurements) was performed using Molecular Devices Genepix Pro V6.25 software within the Post-Genomic Technologies Facility, A floor, West Block, QMC

Patient Serum

Thirty patient sera samples were probed onto two PVDF coated slides. The samples encompassed a wide range of autoimmune diseases, including the same patient over time, whilst receiving treatment and during a flare of symptoms. Three RA, 11 SLE, three Palindromic Arthritis (PA), two Scleroderma, two Myositis, four Wegener's Granulomatosis and five Sjögren's Syndrome samples were tested (**Figure 2**). Wells 15 and 16 on one of the slides were probed with I-block instead of primary antibody to serve as control wells.

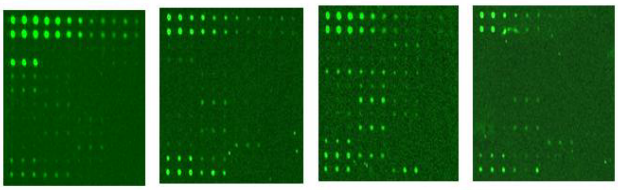

***Figure 2*: Florescent images obtained from Sera Test. Reading left to right, images obtained were from 0946 Scleroderma, 0954 SLE, 1071 Palindromic Arthritis and 0934 RA sera samples. Refer to **Figure 2** for a layout of autoantigens.**

Analysis

Graphs were created using Prism 5.04 (GraphPad Prism Inc)[23]. Comparison of sample profiles was undertaken using MeV 4.6 (Institute for Genome Research)[24]. Due to the small number of samples available, statistical analytical methods were limited. Hierarchical Clustering Algorithms using Pearson's Correlation were successfully created to determine the propensity of samples from similar disease diagnoses to cluster together.

RESULTS

IgG Dilution Series

Signals were detected consistently and as expected with the IgG dilution series, validating the techniques and methods used.

Sera Test

Of the three RA samples tested (**Figure 3**), results obtained suggested negligible autoantibody titres throughout. CCP2 peptides produced weak signals, despite two samples known to be CCP2 positive. Subsequent testing later indicated that the CCP2 peptide

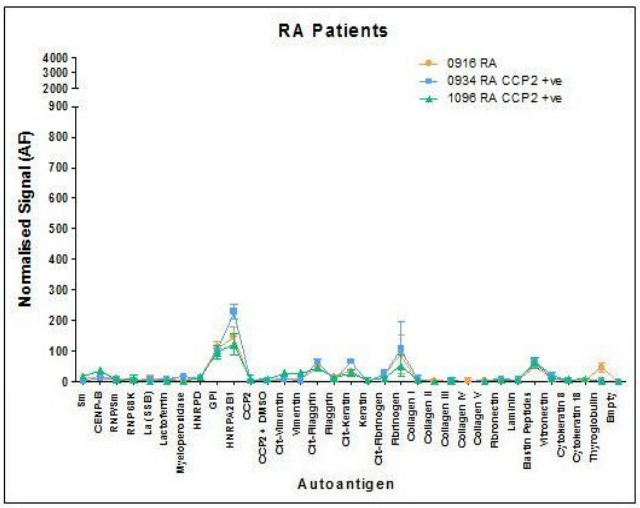

Figure 3

did not bind successfully onto the PVDF slides, limiting analysis potential. Small signals were obtained with citrullinated Filaggrin and Keratin, yet not with citrullinated Fibrinogen or Vimentin. In relation to the putative COPD biomarkers, low signals were obtained.

PA patients appeared to have similar autoantibodies to RA, but to different citrullinated proteins (Vimentin, Keratin and Fibrinogen) and with higher autoantibody titres (**Figure 4**). As PA is associated with ACPA[25], comparing Graphs A and B may suggest that PA is serologically more reactive than RA, yet similar in terms of autoantibody targets.

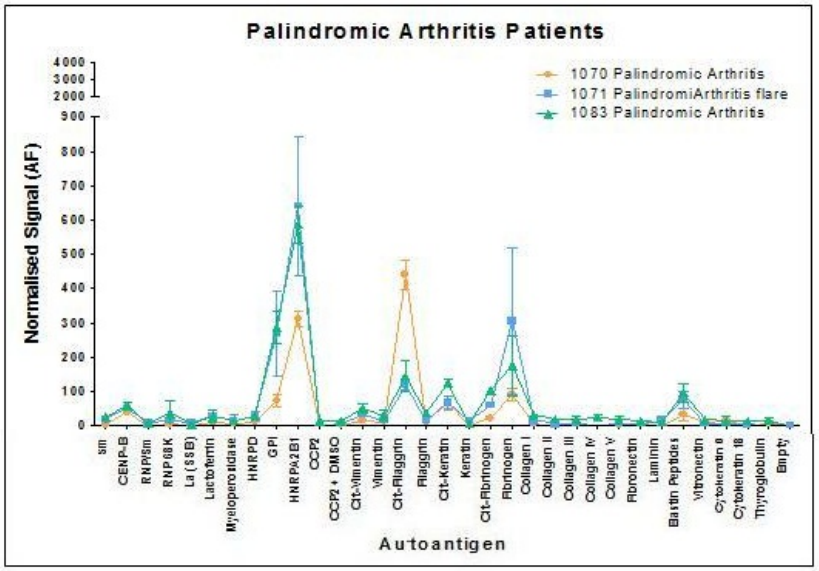

Figure 4

Autoantibody responses were largely similar between the two Scleroderma patients (**Figure 5**).

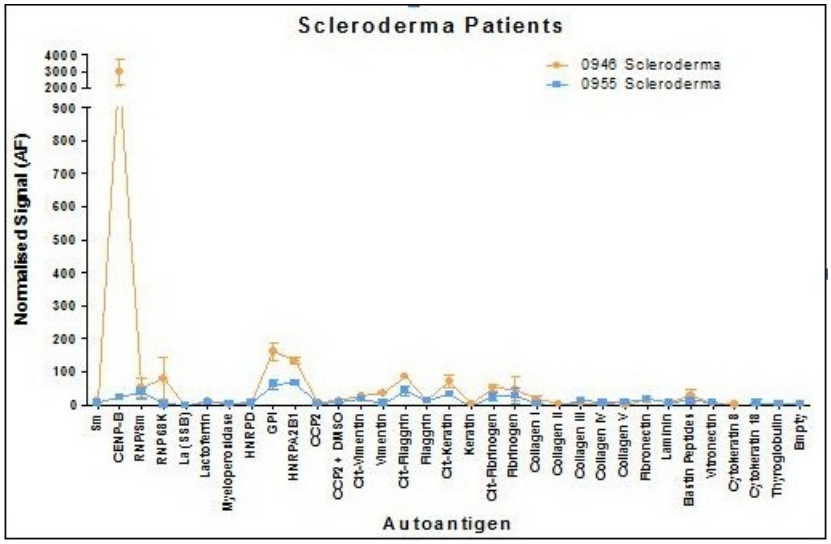

Figure 5

SLE responses (**Figure 6 and 7**) are much more varied between individual patients than all other diseases tested. As expected, RNP/Sm, RNP 68K and La(SSB) gave several high signal values [26].Samples 0903 and 0954 were taken from the same patient over time and results demonstrate a 2-fold increase in autoantibodies to Cytokeratin 8. In total, three patients with alleged inactive forms were tested: sample 1067 had relatively low signal values across the range of autoantigens, whereas the remaining two samples (0903 and 0918) had comparatively high signal values. When comparing sample 0903 with an active sample taken from the same patient (0954), it is clear that inactive signal intensities are far smaller than in the active sample. This highlights the relationship between autoantibody titre and clinical presentation in SLE.

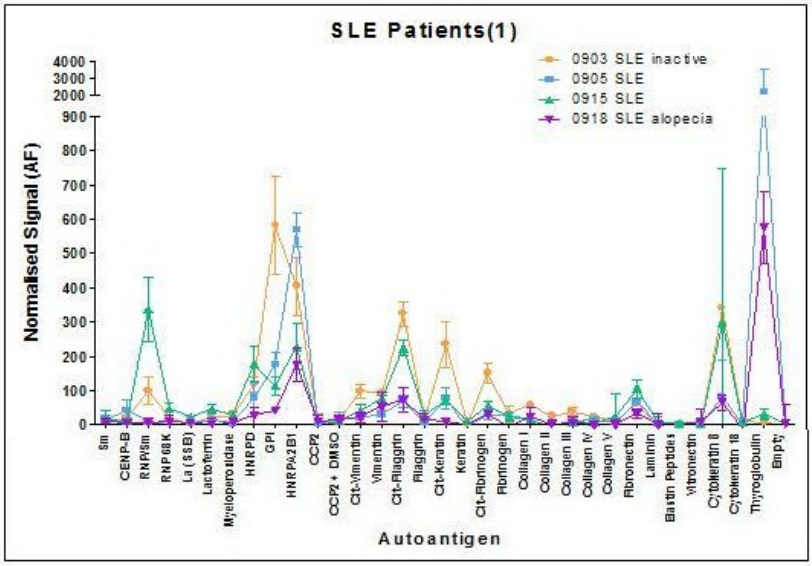

Figure 6

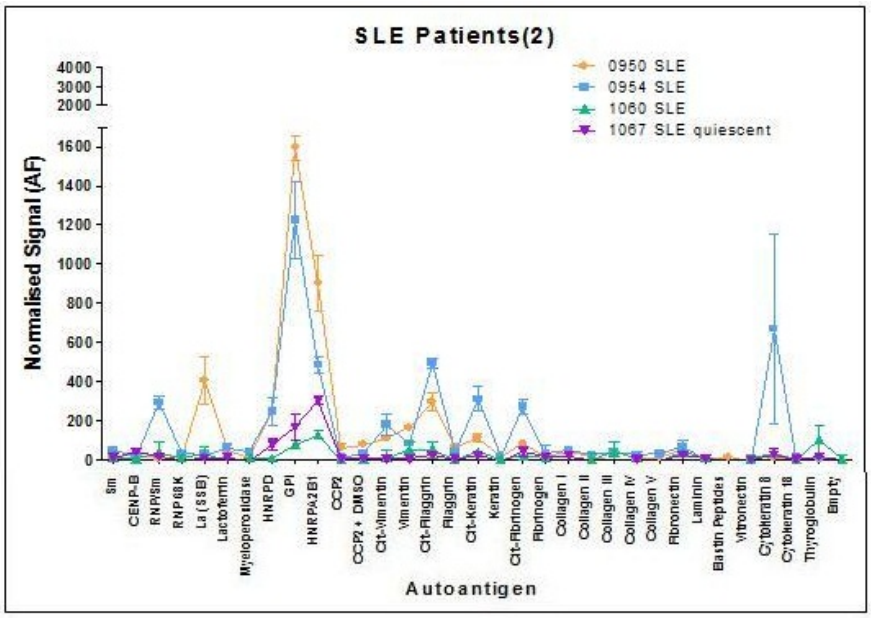

Figure 7

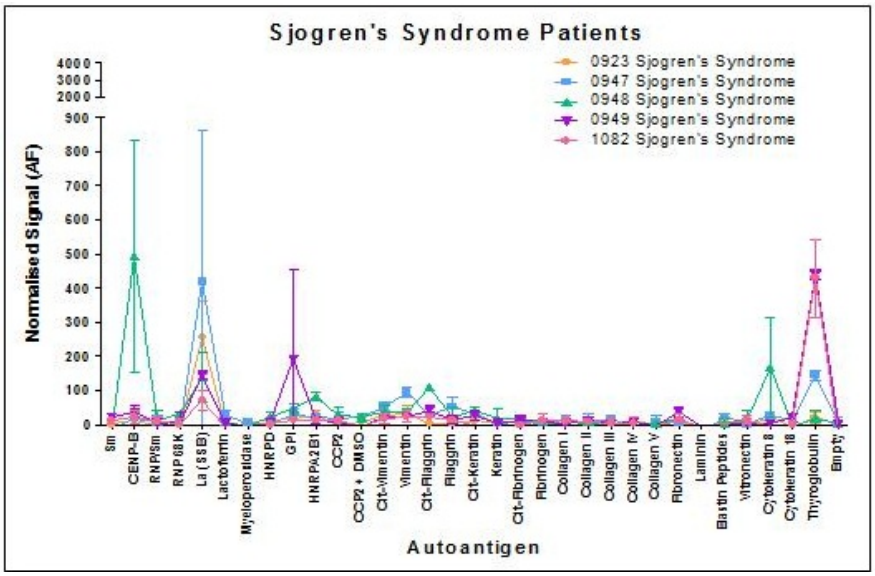

Figure 8

Sjögren's Syndrome data (**Figure 8)** also illustrates variation between individual patients. As evidence suggests[26], autoantibodies were present against both CENP-B and La(SSB), yet signals were absent against RNP/Sm or RNP/68K.

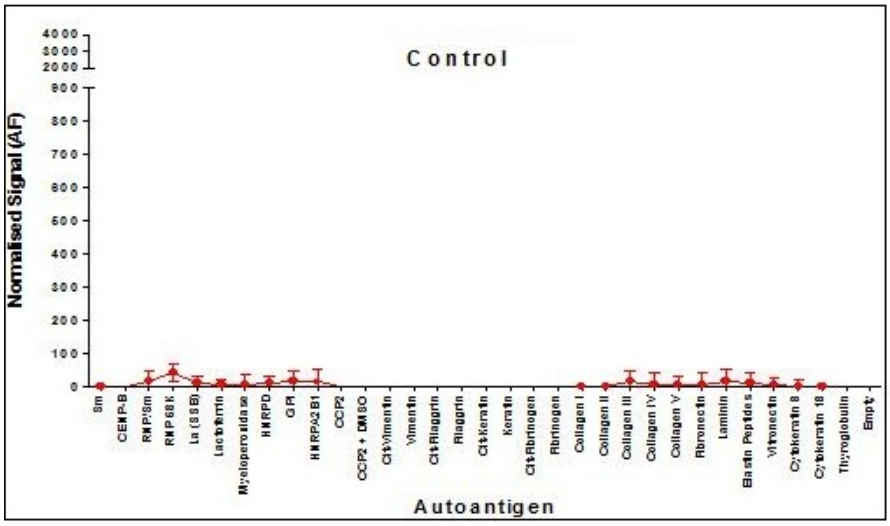

Figure 9

Figure 9 demonstrates the very small signals generated in the absence of primary antibody. Consequently, any signals above 1 standard deviation of the mean control values have been considered as positive signals.

Analyses comparing differences between several autoimmune diagnoses reveals the true potential of microarrays for diagnosis, classification and recognition of specific biomarker profiles that relate to evolution of new diseases and subsets. **Figure 10** is a cluster representation of the patterns recognised between samples. The majority of RA and PA samples cluster together, highlighting strong similarities between the autoantibody profiles of these two conditions. In terms of the autoantigens, there is a strong cluster of antibodies towards Fibrinogen and Elastin Peptides in both RA and PA samples, indicating a possible role for these antigens in the two disease pathogeneses. In addition, there appears to be two distinct clusters of SLE samples that have distinguishably different autoantibody profiles, and all of the Sjögren's Syndrome samples clustered together.

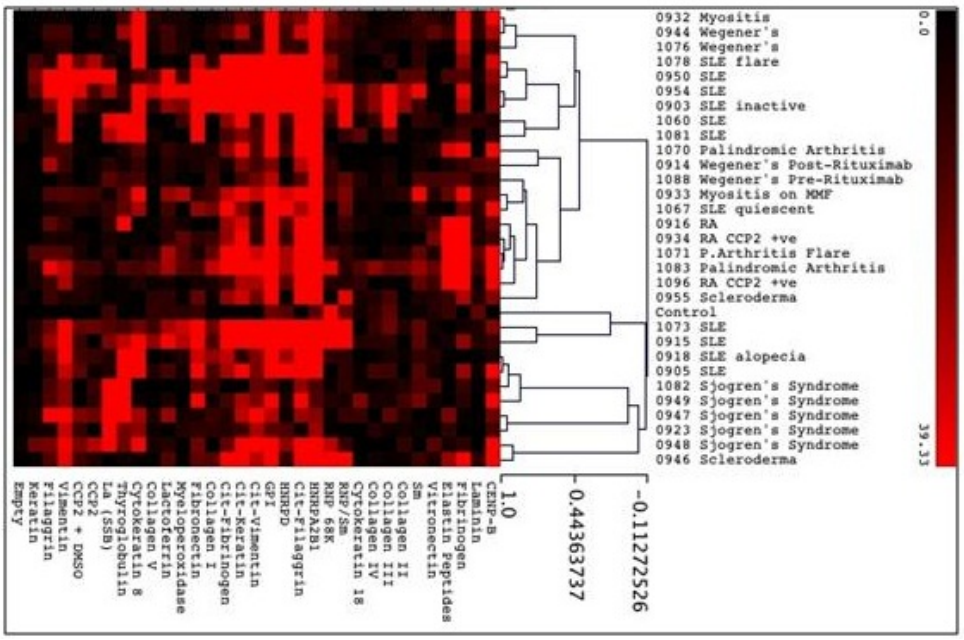

Figure 10

DISCUSSION

Analysis of Sera Tests

Hierarchical Clustering Analysis allows comparisons to be made between related autoimmune diseases (*i.e.*, PA and RA). Further work may aid in understanding similarities between disease aetiologies or what makes them pathologically distinguishable. Incorporating many autoantigens into an assay alongside full utilisation of patient clinical data can lead to novel associations and may identify new disease subgroups (for example, two possible SLE subgroups).

Microarrays also have a potential role in monitoring treatments. Comparative analysis of patients over treatment periods were made and current research indicates there is often a relationship between autoantibody titre and clinical presentation. By monitoring titres before and during treatment, scientists can potentially discover new drug mechanisms and there is a possibility to tailor treatments to an individual's own needs if current regimens are ineffective.

Although evidence associates both RA and COPD with smoking, it would be highly unrealistic to associate RA with COPD in terms of autoantibody targeting from this study; further testing with more samples is needed.

Limitations

Patient samples available to carry out this study were limited. Future research should involve screening with a more even spread of samples on a wider scale. Another limitation was to only use an IgG secondary antibody. Microarrays allow simultaneous detection of multiple antibody isotypes by incorporating multicolour fluorescent detection with anti-isotype specific secondary antibodies[21]. Incorporating this would help identify associations between isotype and pathogenesis, a concept currently under investigation in RA[15,18].

Future Work

- To permit testing for even more autoantibodies, additional antigens can be added to the microarray: many spots remained empty and the design can compress to 20x20 grids. Hueber *et al*. describe an interesting concept, however, that despite best efforts, the number of autoantigens on an array will never be representative of the vast number of expressed proteins in a synovial joint[16].
- Recall antigens that the majority of individuals have immunity towards (*i.e.*, Epstein - Barr virus), can be added to act as positive controls, as is currently undertaken in Paediatric ELISAs.
- It has been argued through three hypotheses ('Citrulline Specific', 'Peptide Specific' and 'Antigen Specific'[11]) that CCPs are not representative of the citrullinated epitopes that exist in vivo. There is, therefore, a growing importance to discover and include the exact citrullinated epitopes acting as ACPA targets to develop more effective and sensitive assays[19].

- Sera samples from healthy individuals would allow a full comparison between disease and non-disease states and give scientists clues as to the role of tolerance towards certain antigens in autoimmune conditions.
- Results should be compared to current ELISA techniques. This would indicate whether identical results can be achieved within a reduced time and costing scale.

Conclusion

Microarrays compress multiple assays into a small space equivalent to a single well of an ELISA, allowing simultaneous testing for autoantibodies to multiple autoantigens in a very confined area. The procedure demonstrates a proof of purpose, with a promising potential to allow accurate diagnosis of RA and other autoimmune conditions. With improvement, there seems to be the capability of diagnosing RA in early stages, complying with NICE guidelines [4,7]. Biomarker profiles can be generated that may relate to symptom severity, treatment response or disease classification and progression[21]. The new method is less time-consuming and less costly, yet maximises patient data collection to unprecedented levels. The minimal volume of blood required also has great significance in terms of seriously ill patients and children. There is a potential to develop the technique further using microfluidics devices, which could take the test into GP clinics. Microarrays could also aid in diagnosis of 'mystery' autoimmune conditions, through elimination of possible candidate diseases or the creation of novel biomarker profiles. It is evidently clear, therefore, that protein microarrays have pivotal future roles in many aspects of immunology.

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References:

1. Arthritis Research UK. http://www.arthritisresearchuk.org/arthritis_information/arthritis_types__symptoms/rheumatoid_arthritis.aspx. Accessed 09/01/11.
2. NHS - Rheumatoid Arthritis. http://www.nhs.uk/conditions/Rheumatoid-arthritis/Pages/Introduction.aspx. Accessed 09/01/11.
3. Westwood OM, Nelson PN, Hay FC. Rheumatoid factors: what's new? *Rheumatology (Oxford).* Apr 2006;45(4):379-385.
4. NICE Guidelines: Rheumatoid Arthritis. 2009; http://www.nice.org.uk/nicemedia/pdf/CG79FullGuideline.pdf. Accessed 10/01/11.
5. NRAS - National Rheumatoid Arthritis Society. http://www.nras.org.uk/about_rheumatoid_arthritis/default.aspx. Accessed 09/01/11.
6. Orozco G, Barton A. Update on the genetic risk factors for rheumatoid arthritis. *Expert Rev Clin Immunol.* Jan 2010;6(1):61-75.
7. Aletaha D, Neogi T, Silman AJ, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* Sep 2010;62(9):2569-2581.
8. Van Venrooij WJ, Pruijn GJ. Citrullination: a small change for a protein with great consequences for rheumatoid arthritis. *Arthritis Res.* 2000;2(4):249-251.
9. Singh U, Vishwanath A, Verma PK, *et al*. Is rheumatoid factor still a superior test for the diagnosis of rheumatoid arthritis? *Rheumatology International.* Jun 2010;30(8):1115-1119.
10. Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* Mar 1988;31(3):315-324.
11. Wegner N, Lundberg K, Kinloch A, *et al*. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. *Immunol Rev.* Jan 2010;233(1):34-54.
12. Carlone JP. Implications of the 2010 rheumatoid arthritis classification criteria. *Br J Community Nurs.* Nov 2010;15(11):537-538.
13. Rantapää-Dahlqvist S, de Jong BA, Berglin E, *et al*. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum.* Oct 2003;48(10):2741-2749.
14. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. *Ann Rheum Dis.* Jul 2006;65(7):845-851.
15. Ioan-Facsinay A, Willemze A, Robinson DB, *et al*. Marked differences in fine specificity and isotype usage of the anti-citrullinated protein antibody in health and disease. *Arthritis Rheum.* Oct 2008;58(10):3000-3008.
16. Hueber W, Kidd BA, Tomooka BH, *et al*. Antigen microarray profiling of autoantibodies in rheumatoid arthritis. *Arthritis Rheum.* Sep 2005;52(9):2645-2655.
17. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest.* Jan 1998;101(1):273-281.
18. Robinson WH, DiGennaro C, Hueber W, *et al*. Autoantigen microarrays for multiplex characterization of autoantibody responses. *Nat Med.* Mar 2002;8(3):295-301.
19. Szodoray P, Szabó Z, Kapitány A, *et al*. Anti-citrullinated protein/peptide autoantibodies in association with genetic and environmental factors as indicators of disease outcome in rheumatoid arthritis. *Autoimmun Rev.* Jan 2010;9(3):140-143.
20. Urbanowska T, Mangialaio S, Hartmann C, Legay F. Development of protein microarray technology to monitor biomarkers of rheumatoid arthritis disease. *Cell Biol Toxicol.* Jun 2003;19(3):189-202.
21. Balboni I, Chan SM, Kattah M, Tenenbaum JD, Butte AJ, Utz PJ. Multiplexed protein array platforms for analysis of autoimmune diseases. *Annu Rev Immunol.* 2006;24:391-418.
22. Joos TO, Schrenk M, Höpfl P, *et al*. A microarray enzyme-linked immunosorbent assay for autoimmune diagnostics. *Electrophoresis.* Jul 2000;21(13):2641-2650.
23. *GraphPad Prism Version 5.04 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com* [computer program].
24. Saeed AI, Sharov V, White J, *et al*. TM4: a free, open-source system for microarray data management and analysis. *Biotechniques.* 2003 Feb;34(2):374-378.
25. Salvador G, Gomez A, Vinas O, *et al*. Prevalence and clinical significance of anti-cyclic citrullinated peptide and antikeratin antibodies in palindromic rheumatism. An abortive form of rheumatoid arthritis? *Rheumatology (Oxford).* Aug 2003;42 (8):972-975.
26. Arotec Diagnostics Limited - Product Information. http://arodia.com/abode/getCategoryProducts.do/_siteId__15/method__getCategoryProducts/_categoryId__1541/resultSetStart__0/resultSetCount__10/orderByAttribute__caption. Accessed 11/01/11.

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Role of Cloud Computing in the Provision of Healthcare

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Medical advances, healthcare provision, cloud computing, resource-poor population, health monitoring.

Abstract

Rapid strides in information technology coupled with enhancing interest in hybrid computing environments have resulted in the development of 'cloud computing'. This is an application that can be accessed anytime and anywhere in the world based on the 'pay-per-use' model. The healthcare industry is in a period of accelerating change that requires continued innovation. Cloud computing has got a significant potential in the healthcare system and provision of healthcare in the future. This technological advancement has led to the design of a real-time health monitoring and analysis system that is scalable and economical for people who require frequent monitoring of their health. Peoples' health data is collected and disseminated to a cloud-based information repository that facilitates analysis of the data using software services hosted in the cloud. This article reviews the existing work carried out in the healthcare system using cloud computing. It analyzes the measures, drawbacks and challenges (including security) of cloud computing in the healthcare system.

Introduction

Cloud computing provides high quality and low-cost information services based on the pay-per-use model. It reduces the investment on hardware, software and professional skills[1]. It helps user applications to access various computing resources to any specified location. This technology also allows consumers and businesses to use application without installation and access their personal files at any computer with Internet access.

In the early part of the 20th century, medical care was delivered at home, through visiting family physicians who packed the necessary medical technology into a doctor's bag. Later, advanced medical technology and specialist providers had to be centralized in hospitals to make their utilization effective. In the current century, the lack of sufficient hospitals in rural and resource-poor areas, the exponential complexity of lifestyle (mainly urban) and the increasing of chronic diseases make healthcare a serious issue[2]. Driven by quality and cost metrics, the healthcare systems have to change radically in the near future from current healthcare professional-centric systems to one of distributed network and mobile healthcare systems. In this movement, the leading part is attributed to the cloud computing technologies. Cloud healthcare, in contrast, tries to change the healthcare delivery model: from doctor-centric to patient-centric, from acute reactive to continuous preventive, and from sampling to monitoring. This approach however is to complement and not replace traditional medicine.

Rural residents have higher poverty rates, a larger percentage of elderly tend to be in poorer health, have fewer doctors and hospitals, and face more difficulty getting to health services[3]. Hence, one challenge of a cloud healthcare system is the provision of better healthcare services to people using limited financial and human resources. Many medical errors occur due to lack of correct and complete information necessary at the location at a particular time, resulting in incorrect diagnosis and drug interaction problems[3]. The required medical information can be made available at any place at any time using sophisticated devices and widely deployed wireless networks.

The design and construction of a cloud computing system for healthcare in rural areas appears very effective. It comes as a solution to help patients adjust lifestyle to their health requirements. Apart from that, through patients' behavioral recognition we can detect symptoms of diseases and predict their progression over time.

Existing system

Figure 1 depicts how the process works based on manual notes[4]. The interactions are described below:

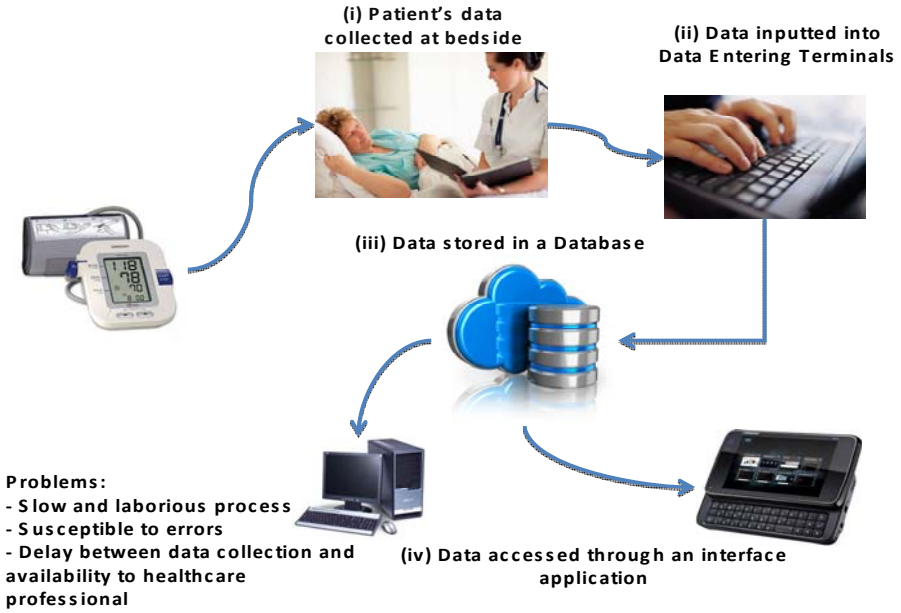

Figure 1: Illustration of existing system that is commonly used in current healthcare

(i) A staff member collects patient's data at bedside, writing it down to a paper spreadsheet;
(ii) The notes are typed in data entering terminals;
(iii) The data is transmitted to a database server that organizes, indexes, and make it accessible through a database interface; and
(iv) At this point, medical staff can access this information through an interface application. It is clear that there is latency between data gathering and information accessibility. This is undesirable and prevents real-time monitoring of vital patients' data, restricting the clinician's monitoring capabilities. Moreover, this process is error prone, as there is a possibility of incorrect input.

Cloud computing in health care

The system of manual notes is replaced by the cloud. **Figure 2** depicts the proposed system structure.

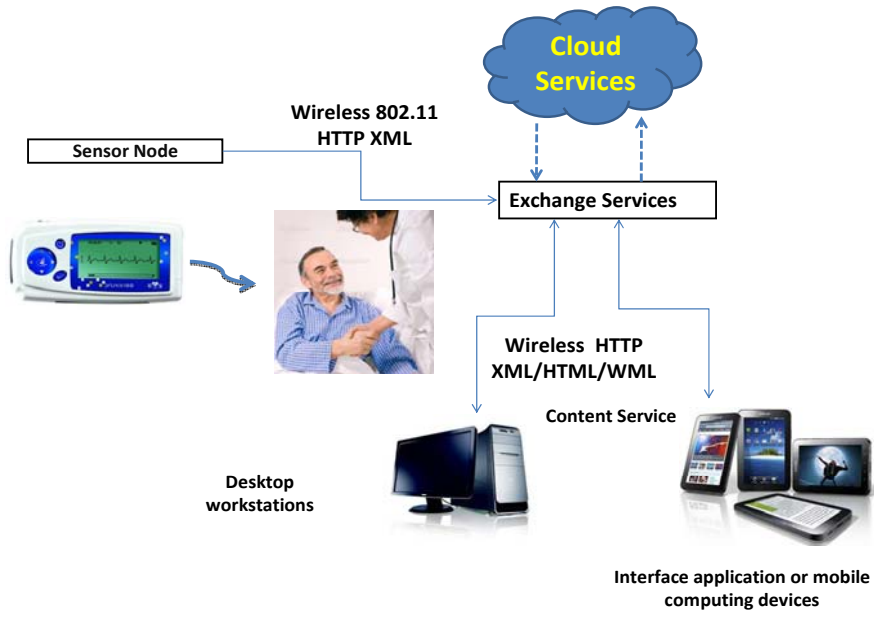

Figure 2: Illustration of cloud computing technology in healthcare

Patient's Data Collection in Health Care Using Cloud Computing

A solution to automate the patient data collection process by using sensors attached to existing medical equipments that are inter-connected to exchange service has been previously explored[4]. This is based on the concepts of utility computing and wireless sensor networks. The information becomes available in the cloud from which it can be processed by expert systems and/or distributed to medical staff. The proof-of-concept design applies commodity computing integrated to legacy medical devices, ensuring cost effectiveness and simple integration. This paper used the cloud based services such as 'Infrastructure' as a Service, 'Platform' as a Service, 'Software' as a service and it was found to be cost-effective. The disadvantages however are the security and management with interaction of third party infrastructure service are not considered.

Cloud Computing Security in Patient Health Care Monitoring

Secure open cloud architecture (OpenCloudCare) for remote patient health monitoring was proposed by Mouleeswaran and colleagues[5]. It defines the front-end and back-end architecture that would integrate healthcare devices into the enterprise cloud. The major components required for securing the cloud infrastructure are also identified. Here the security in electronic health record (EHR) is implemented by using cloud security infrastructure. EHR stores all the data related to human activities. The human activity depicts all the actions and non actions performed by the human. Mouleeswaran and colleagues[5] discusses security in patient health record while the individual security components are not considered.

Hosting ECG Data Analysis Service in Autonomic Cloud Environment

The design aspects of an autonomic cloud environment that collects people's health data and disseminate them to a cloud-based information repository and facilitate analysis on the data using software services hosted in the cloud were discussed by Suraj Pandey and colleagues[6]. To evaluate the software design, a prototype system was developed that uses an experimental test bed on a specific use case, namely, the collection of electrocardiogram (ECG) data obtained at real-time from volunteers to perform basic ECG beat analysis. In this work a heuristic-based method minimizes the cost of using cloud resources while maintaining user quality-of-service satisfaction. This could be done by cloud resource availability, and user allocations based on user priority and varying cloud resource costs. The problem which is not addressed is data security while using distributed cloud storage.

Intelligent Manipulation of Human Activities using Cloud computing

Intelligent manipulation of activities using Context-aware Activity Manipulation Engine (CAME) and the Human Activity Recognition Engine (HARE) has been the focus of discussion in the study by Asad Khattak and colleagues[7]. The human activity is recognized using video-based, wearable sensor-based and location-based activity recognition engines for context analysis. The objective of CAME is to receive real-time low level activity information from Activity Recognition engines and infer higher level activities, make situation analysis, and after intelligent processing of activities with their corresponding information take appropriate decisions. To achieve this objective, two phase filtering technique for intelligent processing of information is used and appropriate decisions based on description logic rules. The experimental results for intelligent processing of activity information showed relatively good accuracy. The security concern is not addressed in this work.

Cloud Computing Framework for New Medical Interface Technologies

Maya Dimitrova *et al.*[8] proposed to formulate a new development framework for cloud computing called User Interface as a Service (UIaaS), which is used to act as an interface between cloud and user. New multimodal interface technologies for medical instrumentation compatible with web platforms have been recently developed. The framework that explicitly aims at supporting seamless and ubiquitous health monitoring based on cloud services for healthcare are presented. The aim of this framework is the implementation of new interface technologies providing the doctors and patients with useful tools to explore conditions and perform monitoring across diagnoses – in an indirect, safe, secure and harmless way - operating as new UIaaS. The device will be integrated in a sophisticated and intelligent backend environment enabling productive end-to-end usage as a step towards modern and ubiquitous healthcare in a cloud computing framework. The security problem is not addressed in this work.

Table 1 compares the related work carried out in health care using cloud computing along with their performance metrics and major drawback.

Related Work	Metrics	Drawback
Patient's Data Collection in Health Care Using Cloud Computing[4]	Time, Cost	Security
Cloud Computing Security in Patient Health Care Monitoring[5]	Time, Cost, Privacy	Security
Hosting ECG Data Analysis Service in Autonomic Cloud Environment[6]	Scalability, Cost	Security in storage
Intelligent Manipulation of Human Activities using Cloud computing[7]	Cost, Accuracy	Security
Cloud Computing Framework for New Medical Interface Technologies[8]	Cost, Time	Security

Table 1: Comparison of Related Work in Cloud Computing

Conclusion and future work

Cloud computing revolutionizes all scientific fields, including healthcare. Health monitoring system monitors human health and shares this information with doctors, healthcare providers, care-takers, clinics, and pharmacies obtained from the cloud to provide low-cost and high-quality service to users. Although security can be provided in healthcare monitoring systems using the encryption method, it continues to remain as a major issue that needs to be addressed and should be the subject of future work.

References:

1. J. Geelan, Twenty one experts define cloud computing virtualization. Electronic Magazine, 2008, http://virtualization.syscon.com.
2. U.Varshney, Pervasive Healthcare and Wireless Health Monitoring, 2007.http://portal.acm.org/citation.
3. R.Suresh, C.R.Rene Robin, An Efficient VOIP Enabled Health Monitoring System using Cloud Computing, International Conference on Emerging Technology Trends, 2011, p.1-9.
4. Carlos Oberdan Rolim, Fernando Luiz Koch, A Cloud Computing Solution for Patient's Data Collection in Health Care Institutions, Second International Conference on eHealth, Telemedicine and Social Medicine, 2010.
5. S.K. Mouleeswaran, Ashok Rangaswamy, Dr. H. Abdul Rauf, Harnessing and Securing Cloud in Patient Health Monitoring, International Conference on Computer Communication and Informatics, Jan 2012, p.10-12.
6. Suraj Pandey, William Voorsluys, Sheng Niua, Ahsan Khandoker, Rajkumar Buyya, An autonomic cloud environment for hosting ECG data analysis services, Future Generation Computer Systems 28, 2012, p.147–154, www.elsevier.com/locate/fgcs.
7. Asad Masood Khattak, Zeeshan Pervez, Intelligent Manipulation of Human Activities using Cloud computing for u-Life Care, 10th Annual International Symposium on Applications and the Internet, 2010.
8. Mayadimitrova, SiyaLozanova, Cloud Computing Framework for New Medical Interface Technologies, 2011, www.sprers.eu.

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Stem Cell Treatments for Huntington's Disease

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Stem Cells; Huntington's disease; Transgenic Animal Models; RNAi; Transplantation

This review will critically consider the evidence that supports the use of stem cells in the management of Huntington's Disease (HD) including that provided by animal models.

HD is a chronic progressive neurodegenerative condition associated with motor, cognitive, and psychiatric symptoms. It has a prevalence of 4-8 per 100,000 and is caused by an autosomal dominant mutation in the Huntingtin gene(HTT) located at 4p16.3, which codes for the protein Huntingtin. Part of the HTT gene contains a repeated trinuleotide sequence of the bases CAG, which encodes a polyglutamine chain; the diagnosis of HD is confirmed by the detection of an expansion of >36 CAG repeats coupled with a positive family history and characteristic clinical features. Patient's become symptomatic between~ 35 - 44 years and the average survival time is 15 to 18 years thereafter[1].

Unfortunately current licensed treatments for HD are limited to symptom control and palliation. Stem cells offer a new dimension that provides insights into: understanding the genomics and proteomics of HD potentially identifying drug targets; providing a cellular HD model to validate gene therapies such as those based on RNAi; and providing a source of human striatal cells for transplantation. Such principles have been applied to animal models of HD. These will be discussed in turn.

Both human embryonic stem- (ES) and induced pluripotent stem- (iPS) cells from affected donors have been used as cellular models to understand the molecular mechanisms of HD[2]. Mutant HD ES cell lines with CAG expansions in the adult-onset range of ~40-51 repeatsand iPS cell lines, which include some with CAG triplet repeat lengths associated with juvenile onset HD, are available from laboratories. Studies[3] using these cell lines have reliably reported the replication of known molecular pathological mechanisms although the relevance of these findings is limited for two reasons. Firstly "age equivalence", that is discrepancies in the chronobiology of the in vitro ES- and iPS cells, which are immature in relation to "developmental age" compared to thein vivo situation in HD patients whereby the disease process is developmentally more mature having a late clinical age of onset. This maybe important as RNA processing may be controlled differently in the embryo relative to adults and gene expression could be dependent upon developmental age. Secondly, human HD ES- and iPS cell lines provide a disease specific cellular model that is inherently biased towards cell autonomous mechanisms. Therefore, validating transcriptomic results from HD ES- and iPS- cells in vitro by comparison against transcriptomic results of the in vivo model in the HD patient is not clear-cut.

HD-specific iPS cell neural derivatives have been used for assaying new drugs that disrupt cell-autonomous mechanisms of HD. These cells can be used to validate gene therapy and provide an ideal alternative to the 'gold standard' that is HD brain tissue, which is difficult to obtain and limited to post-mortem samples. RNAi using shRNA and small synthetic oligonucleotide RNA molecules targeted against mutant HTT mRNA silences the HTT gene by inhibiting its translation[4]. In a mouse HD model this resulted in improved motor symptoms and longevity[5]. HD-specific iPS cell neural derivatives are now being used to escalate validating gene therapy evenfurther via "allele specific RNAi", which involves using synthetic oligonucleotides to suppress translation of mutant HTT leaving normal levels unaltered. The results of these trials are awaited[6]. This may be limited by varying levels of basal HTT gene expression in different neural cell types.

ES-, adult- and iPS- cells can all be used as a source of striatal cells for transplantation in HD. These will be discussed in turn.

Recent evidence from a rodent model showed that human ES-cell derived striatal grafts produced neural precursors capable of differentiating into DARPP-32 expressing (a dopamine receptor marker) GABAergic neurons[7]. These extensively integrated into host neuronal circuits contributing to dopaminergic and glutamatergic neurotransmission within the midbrain and cortex respectively with a resultant functional rescue of motor deficits. The ES-cell derived striatal grafts showed no evidence of tumorigenesis at 16 weeks post-transplantation.

Adult stem cells have been used as a source of striatal cells for transplantation in HD. In a rat model of HD, adipose-derived stem cells from human subcutaneous tissue transplanted into the striatal border were found to improve behavioural symptoms and slowed striatal degeneration[8]. Further evidence has shown that intra-striatal transplantation of homotypic foetal tissue improved functional symptoms in HD patients[9]. However, adult stem cells have a limited role in cell transplantation for HD due to a lack of donor tissue. Furthermore, there are logistical difficulties associated with the acquisition and preparation of foetal stem cells and thus very few patients have benefited from foetal stem cell transplantation. The results of large on-going clinical trials looking at the role of foetal stem cells in HD are awaited.

Transplanted iPS cells derived from a patient with juvenile onset HD carrying 72 CAG repeats regenerated GABAergic striatal neurons and when transplanted into a rat model of HD significantly improved behavioural symptoms[10]. Limitations included: the iPS cells had a lower neuronal differentiating capability compared to ES cells; and the hope of iPS cells providing a cure for HD was hindered by the post-transplantation observation that iPS cells are prone to proteasome inhibition with subsequent development of HD pathognomonic features. The aforementioned evidence embodies the importance of transgenic animal models in developing stem cell treatments for HD with the aim that stem cell derivatives can, in the first instance, repair the brain of HD transgenic animal models and then ultimately that of human HD patients. The criteria of what constitutes a reasonable transgenic animal model of HD should include: age and time-dependence, that is demonstrating a gradual and progressive decline in striatal neurons; an ability to measure the motor, cognitive and behavioural impairment associated with HD; and demonstrable pathognomonic hallmarks of HD such as polyglutamine neuronal inclusions and striatal degeneration. These principles are exemplified by the R6/2 transgenic mouse model of HD, which is created by transfecting exon 1 of the human HD gene containing expanded CAG triplet repeats into the murine germ line[11]. These transgenic mice replicate many features of human HD. Tests such as the fixed speed rotarod test can measure functional impairment due to motor deficits and similar tests exist for quantifying cognitive and psychiatric symptoms. Post-mortem studies on the brain of R6/2 transgenic mice have identified polyglutamine neuronal inclusions that existed before symptom onset. These neuronal inclusions occurred prior to any selective neuronal cell death being identified[12].

A study looked at the effects of transplanting the C17.2 neural stem cell line into the lateral ventricle of R6/2 transgenic mice[13]. Trehalose was co-administered to inhibit polyglutamine aggregate formation. The effects of this combined treatment on the R6/2 transgenic mouse model included: reduced polyglutamine aggregate inclusions; reduced striatal volume and ubiquitin-positive aggregation; and increased life expectancy. Motor function improved as measured by behavioural evaluation.

In addition to transplantation therapy, R6/2 transgenic mice have been used as a model for screening other therapies for HD. These novel therapies include: antagonism of histone methylation and deacetylation, caspase inhibition, inhibition of excitotoxicity, inhibiting oligomerization and misfolding of protein aggregates, environmental fortification, improving metabolic symptoms including hyperglycaemia, transglutaminase inhibition, antioxidant medications, genetic manipulations, and restoring neurogenesis. Results from phase I and II clinical trials on these new drug discovery targets have been disappointing with no clinical interventions tested in murine models significantly delaying HD progression[14].

The results of studies using transgenic HD animal models are limited in their application. R6/2 transgenic mouse models express, as a third allele, fragments of or full length HTT protein. As the cause of striatal degeneration in HD involves both ‘‘a toxic gain of function’’ of the mutant HTT and ‘‘a loss of function’’ of the normal HTT, transgenic mouse models such as R6/2 fail to ‘model’ the pathology and clinical phenotypes that result from the loss of human wild-type HTT and the expression of full-length mutant HTT. Furthermore, xenotransplantation experiments involving transgenic mouse HD models are capricious, which makes extrapolating the significance of results to human HD patients difficult. Differences in size of the human striatum relative to the rodent striatum considerably changes the extent of proliferation of neuronal stem cell derivatives needed and the spatial

ability of graft-derived neurites to integrate into host neuronal circuits and contribute to dopaminergic and glutamatergic neurotransmission within the midbrain and cortex respectively. Finally as the age of onset of HD in humans is ~35-44 years, the short two-year lifespan of a mouse limits its usefulness as a transgenic HD model.

In summary, stem cells have offered a hope, which has now turned to an expectation that developing curative therapies for HD are within the realms of possibility. However, until a credible and tested human stem cell neural model of HD is created then the discrepancies between promising data from experimental animal models and clinical studies will continue to be a barrier that hinders the search for a cure.

References:

1. Pringsheim T, Wiltshire K *et al*., The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Movement disorders: official journal of the Movement Disorder Society27 (2012): pp 1083-91.
2. Park IH, Arora N *et al*., Disease-specific induced pluripotent stem cells. Cell134 (2008): pp 877-886.
3. Camnasio S, Carri AD *et al*., The first reported generation of several induced pluripotent stem cell lines from homozygous and heterozygous Huntington's disease patients demonstrates mutation related enhanced lysosomal activity. Neurobiol. Dis.46 (2012): pp 41–51.
4. Matsui M, Corey DR. Allele-selective inhibition of trinucleotide repeat genes. Drug Discov. Today17 (2012): pp 443-450.
5. Harper SQ, Staber PD *et al*., RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. Proc. Natl. Acad. Sci.102 (2005): pp 5820–5825.
6. Stiles DK, Zhang Z *et al*., Widespread suppression of Huntingtin with convection-enhanced delivery of siRNA. Exp. Neurol.233 (2012): pp 463–471.
7. Aubry L, Bugi A *et al*., Striatal progenitors derived from human ES cells mature into DARPP32 neurons in vitro and in quinolinic acid-lesioned rats. Proc. Natl. Acad. Sci.105 (2008): pp 16707–16712.
8. Wooseok LM, Soon-Tae L *et al*., Transplantation of patient-derived adipose stem cells in YAC128 Huntington's disease transgenic mice. PLoS Curr2 (2010): doi 10.1371/currents.RRN1183.
9. Bachoud-Levi AC, Gaura V *et al*., Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. Lancet Neurol.5 (2006): pp 303–309.
10. Zhang N, An MC *et al*., Characterisation of human Huntington's disease cell model from induced pluripotent stem cells. PLoS Curr2 (2010): doi 10.1371/currents.RRN1193.
11. Tang B, Seredenina T *et al*., Gene expression profiling of R6/2 transgenic mice with different CAG repeat lengths reveals genes associated with disease onset and progression in Huntington's disease. Neurobiol. Dis.42 (2011): pp 459-67.
12. Cowin RM, Roscic A *et al*., Neuronal aggregates are associated with phenotypic onset in the R6/2 Huntington's disease transgenic mouse. Behav. Brain Res.229 (2012): pp 308-19.
13. Yang CR, Yu RK. Intracerebral transplantation of neural stem cells combined with Trehalose ingestion alleviates pathology in a mouse model of Huntington's disease. J Neurosci Res.87 (2009): pp 26-33.
14. Gil GM, Rego AC. The R6 lines of transgenic mice: a model for screening new therapies for Huntington's disease. Brain Res. Rev.59 (2009): pp 410-31.

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Management of Major Trauma: A Malaysian Perspective

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Introduction

Trauma and accidental injuries remain a leading cause of morbidity and mortality worldwide. With every death, two people suffer permanent disability. In the developing world, the impact is further pronounced in view of the increasing population and the associated use of motor vehicles. The society's livelihood depends on a full functioning body as manual labour contributes greatly to the workforce in developing countries hence families faced with disability would suffer tremendously as they are often dependent on a single bread-winner. Thus, establishment of functioning trauma care systems is crucial.

In developed countries, the increased awareness of seatbelts over the recent years has resulted in a reduced number of long bone traumas[1]. In Malaysia road traffic accidents account for almost 80% of major trauma cases and it is the leading cause for admission to government hospitals. These trauma cases largely involve the younger population (between 15-24 years of age), 66% of which are associated with motorcyclists. This is becoming more pronounced as over speeding of motor bikes and lane splitting, more common amongst the younger age group, is on the rise. Poor awareness on importance of helmet use and motorcycle safety is also a contributing factor.

Trauma patients suffering from multiple injuries impose tremendous demands at all levels within hospitals particularly on those doctors, nurses and clinical officers caring for the patient within the first few hours of hospital admission. The first hour of admission, known as the "golden hour" for multiple trauma patients are critical in reducing permanent irreversible damage. Therefore in view of this, guidelines for major trauma care have been developed.

This article which will be accompanied by case studies summarizes important topics related to major trauma focusing on its management. The topics include:

a. Management of patient according to the ATLS principles
b. Management of pelvic fractures
c. Management of acute abdominal trauma
d. Management of limb threatening injuries
e. Management of amputations to limbs or digits.

A. Advanced Trauma Life Support (ATLS) for major trauma

Primary Survey

Airway (with cervical spine protection)

Patients with airway compromise may need acute airway management to avoid a preventable cause of hypoxia. Always maintain cervical spine immobilization by applying devices as described below in section (d).

(a) Assess airway

- ❑ Stabilize the patient's head by placing a hand on either side of the patient's head prior to communicating with them to protect the C-spine
- ❑ Talk to the patient to establish patency, evaluate for voice change and stridor
- ❑ Perform a general inspection looking for pooling of secretions, cyanosis, facial injuries or expanding haematomas
- ❑ Is the patient conscious or unconscious?
- ❑ Consider use of a naso or oropharyngeal airway during bag-valve mask ventilations (BVM)
- ❑ Rapid Sequence intubation if needed for airway stabilization or protection *i.e.,* for Glasgow Coma Scale (GCS) of 9 or less
- ❑ Consider surgical airway if difficulty intubating in patients unable to maintain their own airway.

(b) Improve airway

Most common form of airway obstruction is a prolapsed tongue, thus manoeuvres below may help to clear the airway:

- Head Tilt/Chin Lift (*Only use this method once C-spine injury has been excluded*)

Place one of your hands on the patient's forehead and apply gentle, firm, backward pressure using the palm of your hand. Place the fingers of the other hand under the bony part of the chin. Lift the chin forward and support the jaw, helping to tilt the head back (**Figure 1**). This manoeuvre will lift the patient's tongue away from the back of the throat and provide an adequate airway. If the head tilt / chin lift is not possible, or is contraindicated (possible cervical spine injury), then the jaw thrust manoeuvre can be performed.

Figure 1: The head tilt/chin lift manoeuvre

- Jaw thrust

Grasp angles of the patient's lower jaw and lift with both hands, one on each side (**Figure 2**). This will displace the mandible forward and prevent the tongue obstructing the hypopharynx. Care must be taken to prevent extension of the neck whilst performing this manoeuvre.

Figure 2: Jaw thrust

(c) Remove foreign bodies

The oral cavity is inspected. Any visible debris is removed manually and secretion is cleared via suction.

(d) Cervical spine immobilization

Devices such as cervical collar and head immobilizer (consisting of head blocks and straps) should be placed on patient prior to patient movement (**Figure 3**). If no collar can be made to fit patient, towel or blanket rolls may be used to support neutral head alignment. The head must be supported at all times prior to exclusion of C-spine injuries, hence prior to use of collar and immobilisers or if they are removed at any point (*e.g.*, when log-rolling to perform a full examination), neutral alignment must be maintained manually with a hand placed on either side of the patient's head. Use rigid spinal boards during patient transfer to prevent unstable fractures causing further neurological deficits.

Figure 3: Cervical collar and head immobilizer in place

Top Tips

Box 1

Suspect cervical spine injury if there is:

- ✓N – neurological deficit
- ✓S – spinal tenderness
- ✓A – altered mental status
- ✓I – intoxication of drug/alcohol
- ✓D – distracting injury

Top Tips

Box 2

Seven life threatening thoracic conditions:

- ✓A – airway obstruction
- ✓T – tension penumothorax
- ✓O – open pneumothorax
- ✓M- massive haemothorax
- ✓F – flail chest
- ✓C – cardiac tamponade
- ✓H – severe haemorrhage

Breathing

Place your ear near the victim's nose and mouth with your eyes looking towards their chest. Inspect for difficulty in breathing, asymmetrical chest movements, or see-saw appearance. In infants, intercostal recession may be present. Listen for breath sounds (normal, laboured or shallow) or abnormal sounds *i.e.,* complete silence (complete obstruction), cough or wheeze (bronchoconstriction). Feel for breathing, the absence of which may indicate inadequate air moving through the nose or mouth.

The respiratory rate is often the most sensitive indicator of sick patients. Monitor the respiratory rate (normally between 12 to 25) by calculating the breaths per minute (BPM) rate by counting the chest movements 15 seconds, then multiplying by four. Treat hypoventilation and identify seven life threatening thoracic conditions (see **Box 2**).

Give the patient high flow oxygen 15L via a non-breathable mask, even in patients with COPD. In acute situations, hypoxia will kill more quickly than hypercarbia. Once stabilized and the patient shows signs of CO_2 retention, then oxygen levels can be tailored to the individual.

Oxygen treatment can be monitored by blood gas measurements or non-invasively by pulse oximetry. Blood gas analysis provides accurate information on the pH, PaO_2, and $PaCO_2$. Oximetry provides continuous monitoring of the state of oxygenation.

Circulation

The aim of cardiovascular management is to ensure adequate circulation of blood volume by controlling haemorrhage and replacing lost fluid. Pallor, tachycardia, hypotension, cold, clammy peripheries and a decreased level of consciousness are signs of decreased perfusion. The capillary refill time and pulse rate can be assessed in any setting and is useful in gauging patient's overall perfusion. Any external bleeding should be controlled by applying direct pressure - not tourniquets. Occult blood loss may be from the chest, abdomen, pelvis or from the long bones.

Intravenous access (two large bore lines) should be immediately established followed by fluid resuscitation. Bloods should be sent for cross match. Bladder catheterisation (provided there are no signs of urethral damage) should also be performed to assess urine output.

Continuous bedside monitoring including cardiac monitoring and blood pressure measurements are essential to gauge patient response to ongoing treatment.

The ATLS classification of haemorrhagic shock is illustrated in **Appendix 1**[2]**.**

Disability (Neurological Evaluation)

A quick assessment of the patient's neurological status can be done using the AVPU scale shown in **Table 1** below:

Component	Description
A - Alert	a fully awake patient
V - Voice	patient responds when verbally addressed
P - Pain	patient responds to painful stimuli
U - Unresponsive	patient does not give any eye, voice or motor response to voice or painful stimuli.

Table 1: AVPU scale

A gross motor/sensory examination is performed to determine if the cranial nerve system is intact. This is not a full neurologic examination. For example, the patient is asked to wiggle his toes to assess motor response to a verbal command. A full neurologic exam is done later in the secondary survey.

Pupils are assessed for size, symmetry and reactivity. Uncal herniation will present as a "blown pupil." A dilated pupil is seen due to unopposed sympathetic activity.

A more objective way of recording a patient's state of consciousness is by using the GCS (**Table 2**). The best possible score is 15 and the worst score is 3.

Eye Opening Response	Verbal Response	Motor Response
4 - spontaneous	5 – oriented	6 - obeys command
3 - to verbal command	4 – confused	5 - localizes to pain
2 –to pain	3 –inappropriate	4 - withdraws from pain
1 - none	2 –incomprehensible speech	3 - Abnormal (spastic) flexion, decorticate posture
	1 - none	2 - Extensor (rigid) response, decerebrate posture
		1 - none

Table 2: GCS scale

Exposure and Environmental control

Patient should be completely undressed to provide adequate exposure. At the same time, warm blankets should be used to prevent hypothermia.

Finally, log roll the patient using spinal immobilization technique to palpate the spine for step-offs or tenderness (**Figure 4**). To perform the ''log roll'', at least 5 people are required - three are to manoeuvre the body, one to position the head and lastly one to examine. Steps on performing the log roll are as follow[2]:

Figure 4: The log roll

- ❑ Apply and maintain cervical stabilization. Assess distal function in all extremities
- ❑ Apply a cervical collar
- ❑ Rescuers at an appropriate level to the patient *i.e.,* if the patient is on the floor, then three people should kneel on one side of the patient and place hands on the far side of the patient. One person should be at the head and this person should communicate clearly with the rest of the team when to roll the patient.
- ❑ On command, rescuers roll the patient toward themselves, quickly examine the back, slide the backboard under the patient and roll the patient on to the board
- ❑ Position the patient in the middle of the board
- ❑ Secure the upper torso first
- ❑ Secure the chest, pelvis and upper legs
- ❑ Begin to secure the patient's head by using a commercial immobilization device or rolled towels
- ❑ Place tape across the patient's forehead
- ❑ Check all straps and readjust as needed. Reassess distal function in all extremities.

Primary survey adjuncts

Below are investigations that can be done during the primary survey:

- ❑ Standard Trauma X-rays: lateral cervical, AP chest and pelvis
- ❑ Focused Assessment Sonography in Trauma (FAST)
  The four views include sub-xiphoid cardiac, spleno-renal, hepato-renal and bladder views. Any free fluid detected during the FAST exam may represent peritoneal penetration

- Basic laboratory tests should be ordered simulateneously
- Further x-rays are best grouped and ordered after the secondary survey.

Secondary Survey

Once the primary survey is completed, head to toe evaluation of a trauma patient begins which includes a complete history, full physical examination and reassessment of all vital signs. Each region of the body is fully examined and additional X-rays as indicated by clinical suspicion are obtained.

Box 3

Top Tips

The hidden eight injuries include:

- ✓P – pulmonary contusion
- ✓A – aortic disruption
- ✓T – tracheobronchiole disruption
- ✓M – myocardial contusion
- ✓E – esophageal disruption
- ✓T – traumatic diaphragmatic hernia
- ✓S – spontaneous haemothorax
- ✓H – haemothorax

If at any time during the secondary survey the patient deteriorates, another primary survey is carried out as a potential life threat may be present.

Summary of approach to the trauma patient as practised at the Emergency Department, Sultan Abdul Halim Hospital, Sungai Petani, Kedah, Malaysia is illustrated in **Appendix 2.**

B. Management of pelvic fractures

The pelvis comprises of two innominate bones and the sacrum.Trauma to the pelvis results in fractures, which may be stable or unstable in nature. The former is common especially amongst the elderly after a simple fall. Unstable fractures, however results from significant kinetic forces such as a fall from height or a motor vehicle accident which often include an increased risk of associated injuries, morbidity and mortality.

Details of treatment strategies are illustrated in the algorithm[3] below (**Figure 5**).

Pre-hospital management of patients including appropriate immobilization, airway protection and initial circulatory support with expedient transport is vital.

Case Study

A 24-year-old gentleman was brought to the Red Zone at the Emergency Department after a motor vehicle accident. Upon arrival, his GCS was 15 however he was clinically pale. His BP was 70/40mmHg and pulse was 125/min. On examination, there was scrotal haematoma with bruising over the suprapubic region.

- *What sort of injury should be suspected?*
- *What are the initial investigations to be performed?*
- *How should this patient be managed?*

Box 4

Top Tip

Pelvic ring disruption may shear blood vessels such as the pelvic venous plexus or internal iliac arterial system leading to severe haemorrhage *i.e.,* up to 2-3L of blood loss which may be hidden

Upon arrival at ED, pelvic stabilization to help tamponade bleeding in patients with pelvic fractures who are haemodynamically unstable is crucial. Initial treatments include using a pneumatic anti-shock garment (PASG), wrapping a sheet around the pelvis or placing a pelvic binder[4]. A chest radiograph and a FAST should be done promptly to exclude other sources of haemorrhage. If the patient continues to be unstable, arterial angiography and embolization should be considered.

If possible, pelvic fractures should be classified according to the Tile and Young and Burgess Systems. These classifications describe fractures based on integrity of the posterior sacroiliac complex (Tile) or based on mechanism of injury (Young).

If the pelvic fracture type is unstable (Tile B or C; Young and Burgess APC II, APC III, LC II, LC III, VS), the patient will require operative fixation and can be treated with more definitive stabilization, such as an external fixator or a pelvic C-clamp.

The principles of pelvic fracture fixation[5] are:

- With complete instability of the posterior ring (*i.e.,* the posterior SI ligaments are disrupted), anterior fixation alone is inadequate

- With complete instability of the posterior ring and vertical instability, any posterior fixation should be supplemented with some form of anterior stabilization.
- With partial instability of the pelvic ring (*i.e.,* the posterior SI ligaments are intact), anterior fixation alone is adequate and full weight-bearing may be permitted.

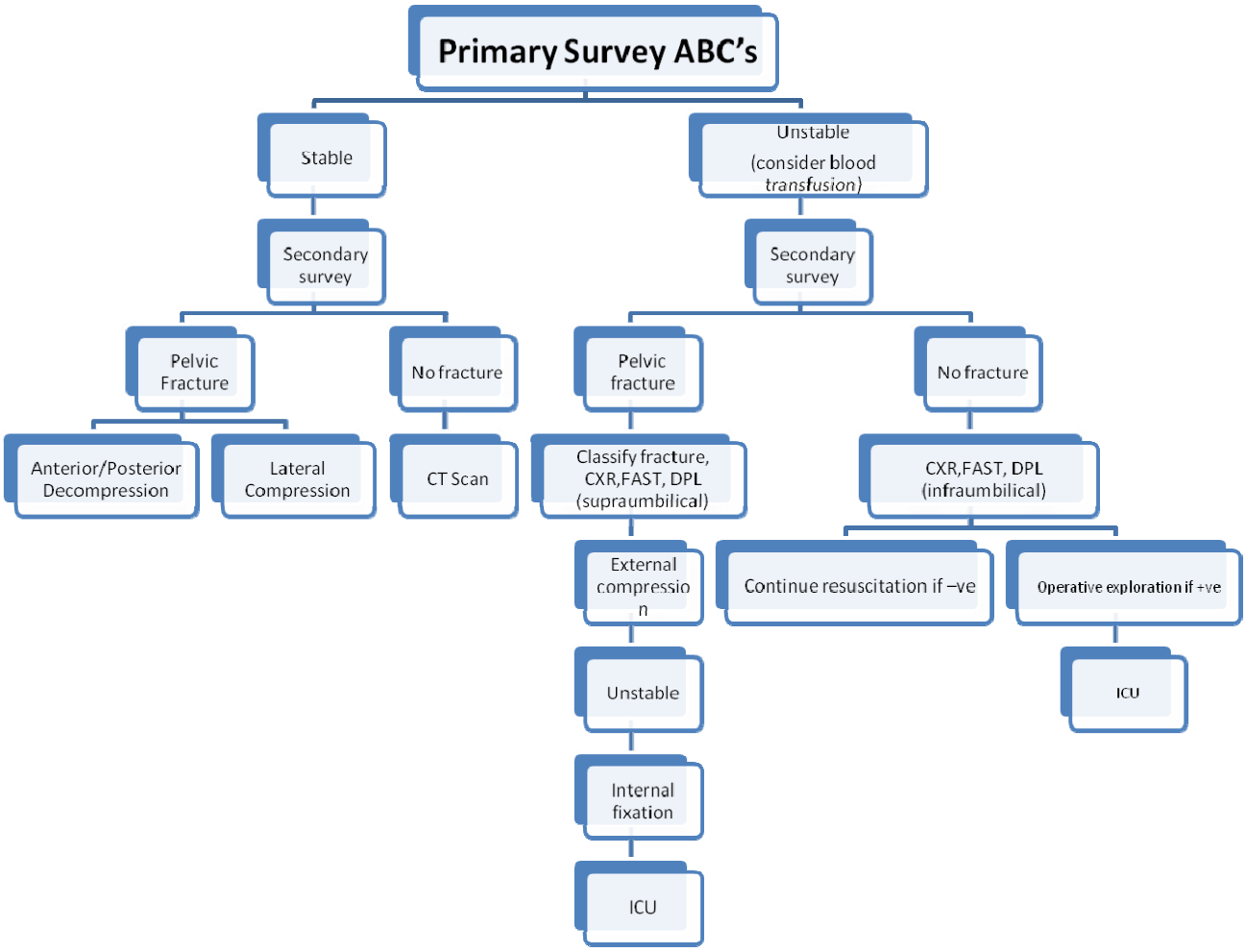

Figure 5: Pelvic fracture management algorithm

C. Management of Acute Abdominal Trauma

Case Study

A 33-year-old lady was brought in by ambulance and was attended promptly by the surgical resident on call. This patient was knocked down by a motorcycle from behind while walking along the roadside. Her vital signs were stable and her GCS was full. Upon examination, there was bruising over the upper abdomen and along her left flank. Also noted, blood stained urine in the catheter bag.

- *What sort of injury should be suspected?*
- *What are the initial investigations to be performed?*
- *How should this patient be managed?*

Abdominal trauma can be broadly divided into penetrating *i.e.,* stab wounds, gunshot wounds or blunt injuries *i.e.,* motor vehicle accidents, falls, assaults and occupational accidents. From an anatomical perspective, abdominal trauma can be categorized into intra-peritoneal, retro-peritoneal and pelvic injuries.

Signs and symptoms include abdominal pain, tenderness, rigidity, distension, haematoma and diminished or absent bowel sounds. Early indications of abdominal trauma include nausea, vomiting, and fever. Haematuria is another salient sign. Seatbelt injuries if significant enough to cause external bruising may have related internal injuries which will also need to be excluded.

Investigations may include ultrasonography, computed tomography, exploratory laparotomy and peritoneal lavage. Treatment may be conservative but if the patient is unstable, he or she will require surgery.

Box 5

Top Tip

Look for Cullen's sign of periumbilical bruising or Grey-Turner's sign of flank bruising, both associated with retroperitoneal haemorrhage

Hepatic injuries

CT is the recommended diagnostic modality for evaluation of hepatic trauma.

A. Penetrating trauma

- Initial haemostasis
  Rapid mobilization of the injured lobe is done by bimanual compression and perihepatic packing
- Definitive haemostasis
  Deeper wounds are usually managed by hepatotomy and with selective ligation of bleeding vessels
- Damage control
  Perihepatic packing with ICU admission and resuscitation followed by return to the operating room in 24-48 hours

B. Blunt trauma

- Haemodynamically unstable
  Require operative exploration and control of haemorrhage
- Haemodynamically stable
  Patient is treated conservatively whereby ongoing assessment is done to monitor blood loss

Splenic Injuries

A. Penetrating trauma

- Penetrating splenic injuries are diagnosed at laparotomy. Initial haemostasis is possible through manual compression. Bleeding from small capsular lacerations can be controlled with direct pressure or topical haemostatic agents. In stable patients, splenorrhaphy can be employed[6]. Devitalized tissue should be debrided.

B. Blunt trauma

- CT remains the diagnostic modality of choice in diagnosing blunt splenic injuries. In stable patients, close observation with continuous monitoring of vital signs and bed rest is indicated. However, if patient becomes unstable, splenectomy is performed.

Bowel injuries

CT abdomen is the investigation of choice in evaluating abdominal trauma.

A. Small bowel

- Given its large volume and anatomy, the small bowel is prone to penetrating and blunt trauma (**Figure 6**). Besides imaging, diagnosis can also be made during laparotomy. Treatment consists of primary repair or segmental resection with anastomosis[7]. Mesenteric defects should be closed.

Figure 6: Penetrating bowel injury post motor vehicle accident

B. Large bowel

- Colonic injuries typically occur secondary to penetrating trauma and are diagnosed at laparotomy. Single agent prophylactic antibiotics are indicated during surgery due to risk of faecal contamination. Primary repair should be considered in all colonic injuries *i.e.,* end to end anastomosis with diverting colostomy.

Kidney injuries

Ultrasound and intravenous pyelogram (IVP) have commonly been used in the past in investigating kidney injuries. Currently, the gold standard in diagnosing kidney injuries is with CT urography.

If the patient is stable and injury to other organ systems has been ruled out, non-surgical treatment is opted. The patient will need bed rest and continuous monitoring to ensure haematuria resolves.

For clinically unstable patients, surgical exploration and kidney repair is indicated. Evidence of kidney dysfunction should prompt arteriography of renal artery. If the injury is discovered within six hours, revascularization is performed. Nephrectomy is indicated if laparotomy is performed for associated injuries[8].

There are also other less invasive techniques to treat kidney injuries such as angiographic embolization.

D. Management of limb threatening injuries

Case Study

A 45-year-old construction worker had a fall from a 10-feet height platform. Fortunately he landed on a sand pit however he hit his right leg on an edge of a metal frame. Subsequently, he was unable to ambulate and his right calf was grossly swollen. Patient claims there was no head trauma and he remained conscious throughout the event. On further examination, there was a ragged wound noted over the medial aspect of his right calf measuring 5x2 cm as well as a bony protrusion seen at the proximal tibia with minimal blood oozing from the wound.

- *What type of fracture has this patient sustained?*
- *How should this patient be managed?*
- *What is the best method of fixation for this injury?*

Vascular injury

Penetrating wound and blunt force trauma such as fractures and dislocations may cause arterial and other vascular injuries. This may lead to significant haemorrhage through the open wound and soft tissue.

Assessment

Injured extremities should be assessed for external bleeding, loss of previously palpable pulses and change in pulse quality. A cold, pale and pulseless extremity indicates an interruption of the arterial supply. A rapidly expanding hematoma also suggests a significant vascular injury.Doppler Ultrasound is a useful tool to check for pulses.

Management

Before surgery, the application of tourniquet is lifesaving. It is not advisable to apply vascular clamps in bleeding open wounds unless a superficial vessel is clearly identified. During surgery, arterial repair and sometimes arteriography is done[9].

Crush Injury

Crush injury of the limbs can lead to crush syndrome or traumatic rhabdomyolysis (**Figure 7**). A combination of muscle ischaemia and cell death releases myoglobin which can cause acute renal failure. As a result, elevated creatine kinase levels in these patients may precipitate disseminated intravascular coagulation (DIVC)[10].

Figure 7: Crush injury caused by sugarcane grinder machine

Assessment

Dark amber urine that may test positive for haemoglobin is a useful indicator for rhabdomyolysis in this clinical scenario. Rhabdomyolysis can lead to hypovolemia, metabolic acidosis, hyperkalemia, hypocalcemia, renal failure and disseminated intravascular coagulopathy.

Management

Fluid resuscitation along with administration of sodium bicarbonate and electrolytes is done to prevent renal failure. Myoglobin induced renal failure can be prevented by intravascular fluid expansion and osmotic diuresis to maintain high tubular volume and urine flow. It is recommended to maintain urinary output at 100ml/ hour until the myoglobinuria is cleared. If the limb cannot be salvaged and/or the patient is developing sepsis or severe systemic effects from the trauma, then amputation of the affected limb can be considered.

Compound/open fractures of the lower limb

Open fractures represent a communication between the external environment and the bone. This break in barrier makes fracture sites prone to infection thus subsequently affects healing and may cause loss of function.

The classification of open fracture as described by Gustillo-Anderson is illustrated in **Appendix 3**.

Assessment

Look at size of the wound, extent of soft tissue injury or any signs of neurovascular compromise.

Management

Wound irrigation is done with Normal Saline whereby amount of saline needed depends on severity of the fracture *i.e.,* wounds measuring > 10cm requires at least 9 litres of normal saline irrigation. Additionally, broad spectrum IV antibiotics should be started.

Wound debridement is compulsory if contamination is noted to be severe. Definitive fixation of the bone is ideally done within 24 hours.

The best method of fixation in open fractures is external fixation or Ilizarov[11].

Figures 8-11 illustrate the preoperative and postoperative sequence of management of an open tibia/ fibula fracture.

Figure 8: Grade IIIB open distal tibia/fibula fracture. The wound size measures > 10cm and soft tissue is severely damaged. However, there is no vascular involvement

Figure 9: An AP view of a distal comminuted tibia/ fibula fracture with butterfly fragment

Figure 10: Post-operative application of biplanar external fixation at the fracture site

Figure 11: Lateral view of biplanar external fixation under radiological imaging

Top Tips

Box 6

Acute compartment syndrome usually develops after a severe injury and the clinical manifestations can be described as the 6Ps:

- ✓Pain
- ✓Pressure
- ✓Paraesthesia
- ✓Paralysis
- ✓Pallor
- ✓Pulselessness

E. Management of amputation to limbs or digits

Case Study

A 5-year-old boy was injured after a firecracker he lit went off unexpectedly. He was rushed to the nearest hospital as his left hand was blown apart. At the Emergency Department, his father managed to bring in the detached part (left hand) in a plastic bag filled with ice within 1 hour post trauma.

- ❑ *Is the detached left hand salvageable?*
- ❑ *What are the contraindications for replantation in amputated limbs?*
- ❑ *How should this patient be managed?*

An amputation is a surgical or traumatic separation of a particular body part from its origin (**Figure 8**).

Amputations involving the upper limb or children are usually prioritized when selecting candidates for replantation. Clean cut injuries with minimal contamination are associated with higher rates of successful replantation.

Contraindications for replantation of amputated limbs include coexisting serious injuries or disease that preclude a prolonged operative time, multiple levels of amputation, severely crush or degloving injury, dirty mangled wound, prolonged ischaemia time and mentally unstable patients or self-inflicted wound[6].

Handling of amputated limb part

The goal is to preserve the limb for reattachment. Therefore, delays in transportation should be avoided. The amputated part should be covered with saline moistened gauze and sealed in a clear plastic bag on a mixture of ice and water. The part should never be placed directly on ice or immersed in saline[12].

Figure 12: Amputated right hand after a 'parang' assault

Amputation repair techniques

The aim is to preserve residual limb length balanced with soft tissue as well as reconstruction to ensure good healing, non-tender and functioning residual limb. The proximal stump is cleaned and a compressive dressing is applied. Tourniquets are not used. The sequence of repair involves identification of affected structures, debriding edges for reattachment, stabilizing bone by using plates, screws or external fixation. The amputated bony edges must be well smoothened. After providing bone stability, the arteries are repaired, followed by repair of the tendon and then veins and nerves. As for the skin, a tension free flap may be attempted or alternatively, a skin graft can be done.

Top Tip

Box 7

The acceptable window period for replantation (ischaemia time) is 6 hours for proximal limb amputations and 12 hours for fingers.[6]

Rehabilitation

Limb amputation should not be viewed as a failure but as a way of enabling the patient to function at a higher level. The importance of approaching amputation with a positive, constructive frame of mind cannot be overemphasized. On-going, long term rehabilitation aids patients particularly those facing difficulties with prosthetic fitting, the residual limb, performing specific activities and psychosocial adjustment.

Conclusion

Pre-hospital treatment along with prior preparation of the resuscitation room is the key to successful trauma management. Establishment of a trauma team whereby there is efficient coordination between emergency room physicians and trauma surgeons is vital to ensure a satisfactory final outcome. The advanced trauma life support algorithm provides a good basis in identifying life threatening conditions rapidly as well as stabilizing patients to buy time for definitive assessment. Assessment of the trauma patient must involve a full assessment of the actual and potential injuries with the appreciation that resuscitation is often on-going and the patient's condition can change dramatically at any point of time. Prompt recognition and identification of patients requiring immediate surgery is often life-saving and provides a chance for patients to make a better recovery.

Appendices

Appendix 1: ATLS classification of haemorrhagic shock

	Heart Rate	Blood Pressure	CNS status	Urine output	Blood Loss	Treatment
Class I	<100	Normal	Slightly anxious	>30ml/hr	<15%	Normal Saline
Class II	>100	Normal	Mildly anxious	20-30	15 - 30%	Normal Saline
Class III	>120	Decreased	Confused	5-15	30 - 40%	NS + Blood
Class IV	>140	Decreased	Lethargic	nil	>40%	NS + Blood

Appendix 2: Approach to the Trauma Patient practised at Sultan Abdul Halim Hospital, Sungai Petani, Kedah, Malaysia

PRIMARY SURVEY

		Assess and Identify	Immediate Management
A	AIRWAY + Cervical Immobilization	**A** Airway obstruction	Blood/secretion ❑ suction/remove debris Floppy tongue ❑ oropharyngeal airway Maxillo-facial injury ❑ attempt reduction, intubation, cricothyrotomy Mechanical blockade ❑ finger sweep and removal of foreign object Partially obstructed airway ❑ jaw thrust/chin lift
B	BREATHING	**T** Tension pneumothorax Clinical diagnosis, not radiological ❑ Tracheal deviation ❑ Respiratory distress ❑ Absence of breath sounds – unilateral ❑ Distended neck vein Cyanosis – late sign	Needle thoracocentesis Chest tube insertion
		O Open pneumothorax ''Open sucking chest wound''	*Do not remove object * Cover defect with 'sterile occlusive dressing'' Chest tube insertion Definitive surgical closure
C	CIRCULATION	**M** Massive haemothorax 1500mls immediately evacuated or 200mls/hour for 3 hours or 300mls/hour for 2 hours Paediatric – 30mls/kg/hour	Rapid volume restoration Chest tube for chest compression Thoracotomy
		F Flail chest When three or more adjacent ribs are fractured at two points	Adequate ventilation and oxygen Volume restoration Analgesia Chest tube if required
		C Cardiac tamponade Beck's triad ❑ Muffled heart sounds ❑ Distended neck veins ❑ Elevated JVP Narrowed pulse pressure Kussmaul's sign FAST – pericardial effusion	Pericardiocentesis Open thoracotomy
		H Severe Haemorrhage Eg: Total amputation	Control bleeding Fluid replacement Blood transfusion Intraosseouscannulation
D	DISABILITY	Assess conscious level (AVPU), GCS and pupil size	For definitive airway if GCS<8

*Survey Adjuncts: Xrays - lateral cervical, chest and pelvic as well as FAST

SECONDARY SURVEY

Assess	Identify	Management
Further History + examination	Identify ''hidden eight injuries'' PATMET + SH	
AMPLE history Head to Toe Examination A – Allergy M – Medication P – Past medical illness L – Last meal E – Event	P – pulmonary contusion A – aortic disruption T – tracheobronchiole disruption M – myocardial contusion E – esophageal disruption T – traumatic diaphragmatic hernia S – spontaneous haemaothorax H – haemaothorax	Advanced intervention Adjuncts and tests

Appendix 3: **Gustillo-Anderson classification of open fractures**

Grade 1	❑ Wound < 1 cm ❑ clean ❑ simple bone fracture with minimal comminution
Grade 2	❑ Wound> 1 cm ❑ no extensive soft tissue damage ❑ minimal crushing ❑ moderate comminution and contamination
Grade 3	❑ Extensive skin damage with muscle and neurovascular involvement ❑ High-speed crush injury ❑ Segmental or highly comminuted fracture ❑ Segmental diaphyseal loss ❑ Wound from high velocity weapon ❑ Extensive contamination of the wound bed ❑ Any size open injury with farm contamination
3A	❑ Extensive laceration of soft tissues with bone fragments covered ❑ usually high-speed traumas with severe comminution or segmental fractures
3B	❑ Extensive lesion of soft tissues with periosteal stripping and contamination ❑ severe comminution due to high-speed traumas ❑ usually requires replacement of exposed bone with a local or free flap as a cover
3C	❑ Exposed fracture with arterial damage that requires repair

References:

1. Wrathall, G. The Management of Major Trauma. Updates in Anaesthesia.1996; Issue 6, p. 1-9.
2. American College of Surgeons. Advanced Trauma Life Support for Doctors, ATLS: Student Course Manual. American College of Surgeons, Eighth edition.2008; p.49-55.
3. Durkin A, Sagi H, Durham R, *et al*. Contemporary management of pelvic fractures. The American Journal of Surgery.2006;192, p.211–223.
4. McCormackR, Strauss E, AlwattarB, *et al*. Diagnosis and Management of Pelvic Fractures. Bulletin of the NYU Hospital for Joint Diseases. 2010;68(4), p.281-291.
5. Mohanty K, Musso D, Powell JN, *et al*. Emergent management of pelvic ring injuries: an update. Can J Surg. 2005;48(1), p.49-56.
6. Klingensmith ME, Chen LE, Glasgow SC, Goers PA, Melby SJ. The Washington Manual of Surgery. Lippincott Williams & Wilkins, 5th edition. 2008; p. 381-385.
7. Abenamar M, Najarian S, Michael P, Valenziano M, Carl P. Practice Management Guidelines for the Evaluation of Blunt Abdominal Trauma. The EAST Practice Management Guidelines; 2001.
8. Moore EE, Dunn EL, Moore JB, Thompson JS. Penetrating abdominal trauma index.The Journal of Trauma. 1981;21(6), p.439-445.
9. Haemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27-28 April 2006.
10. Smith J, Greaves I.Crush Injury and Crush Syndrome. A Review
11. Journal of Trauma-Injury Infection & Critical Care. May, 2003; Volume 54, Issue 5, p.226-230.
12. Davis G, Fortune C, Bone J. Compound fractures. Joint Surg Am. Jan, 1943;25(1) p.97-120.
13. Helfet D, Howey T, Sanders R, Johansen K. Limb Salvage Versus Amputation: Preliminary Results of the Mangled Extremity Severity Score. July, 1990; Volume 256.
14. National Trauma Database January 2009 to December 2009, Fourth Report. National Trauma Database And Clinical Research centre, Ministry of Health Malaysia. July, 2011; p. 23-47.

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Case Report
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Osteoradionecrosis (ORN) of the Jaw

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Keywords:

Osteoradionecrosis, ORN, mandibular resection, fibula free flap

Abstract

TA, a 67-year-old male with nasopharyngeal squamous cell carcinoma (NPC) was initially treated with radical chemo-radiotherapy for his malignanacy. Two years later, dental extractions were performed by a community dentist, following which the tooth sockets were reported to be healing poorly. TA developed osteoradionecrosis (ORN) of the jaw and was managed ultimately with a sub-total mandibular resection and fibula free flap reconstruction. This article uses the case above to explore the aetiology, presentation and management of ORN. Furthermore the principles of surgical management using free tissue transfer and mandibular reconstruction are also discussed.

Case Report

TA, a 67-year-old male presented in March 2007 to a teaching hospital with right sided hearing problems, facial numbness and sensory disturbance in the right trigeminal nerve distribution. The patient had a lifelong history of smoking twenty cigarettes per day.

On examination, a right sided neck swelling was noted. Histological findings showed a poorly differentiated squamous cell carcinoma of the nasopharynx, arising from the posterior wall and eroding the skull base. Right side lymph node involvement was confirmed. Tumour staging was reported as T4 N2 M0 Stage IV cancer. Radical chemo-radiotherapy was administered with neoadjuvant Cisplatin and 5-Flourouracil. In addition he received radiotherapy at a dose of 66Gy over 33 sessions. In March 2009, extractions of the molar teeth were performed by the patient's community dentist. The subsequent sockets failed to heal and in September 2009 an Orthopantomogram (OPT) showed osteoradionecrosis (ORN) of the posterior mandible at both sites of tooth extraction (**Figure 1**). This was managed with local debridement and Augmentin was prescribed for symptomatic relief. Secondary infection was treated with Metronidazole and Clindamycin.

An OPT in November 2010 showed a loss in continuity of the inferior cortex of the mandible, as well as a moth-eaten, radiolucency in the alveolar region bilaterally where the mandibular bone has failed to heal (**Figure 2**).

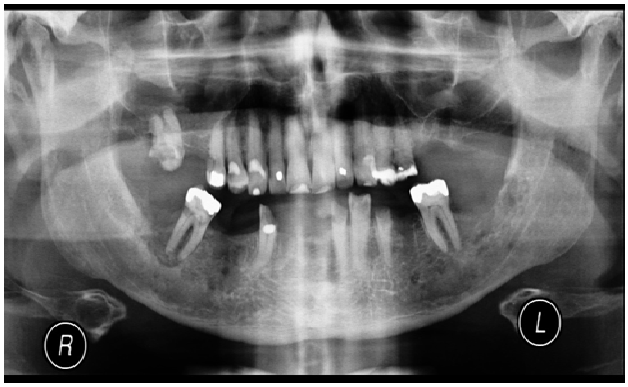

Figure 1: An OPT taken in September 2009

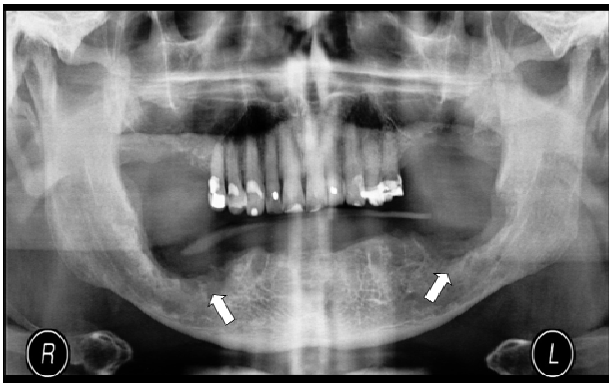

Figure 2: An OPT in 2010 showing advancement of the ORN

In March 2011, surgical management was agreed upon, namely a sub-total mandibular resection with reconstruction using a fibula free flap.

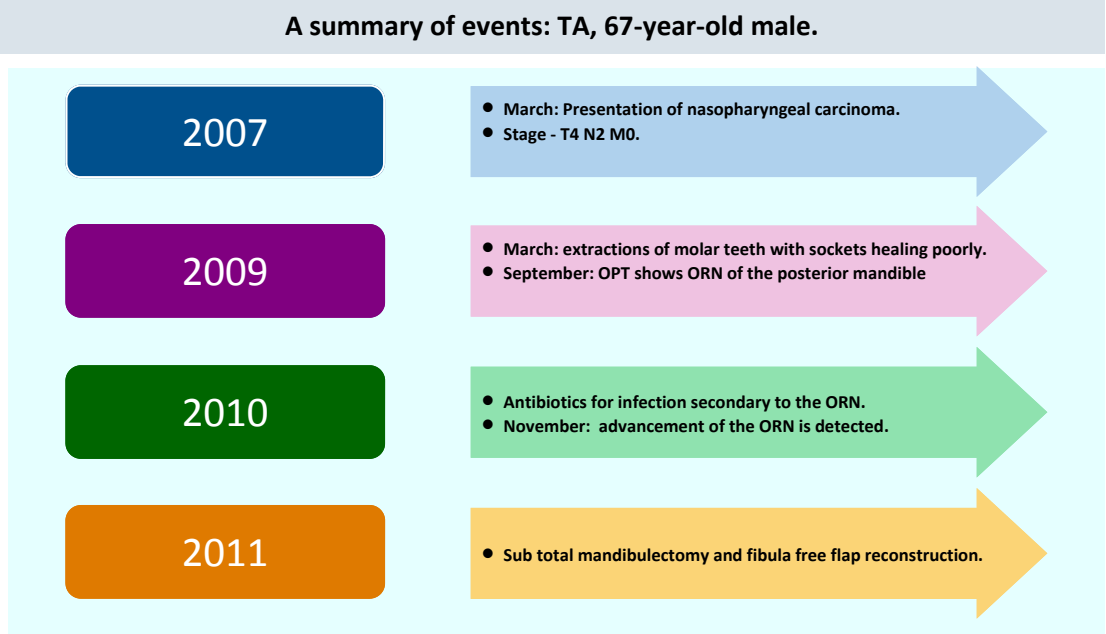

Figure 3: Summary of events in case report

Osteoradionecrosis (ORN)

"ORN is defined as exposed bone tissue that has had previous irradiation and which fails to heal over a period of 3 months in the absence of a residual or recurrent tumour [1]."

ORN usually occurs in patients who have been exposed to more than 60 Gy of radiation. The overall incidence of the disease is hard to determine due to the absence of a formal reporting system, but certain studies have found a reduced incidence of ORN over the past three decades. An approximate value of a 3% incidence has been collated from pooled studies[2].

Pathology

The pathological processes behind ORN have been an issue of dispute for some time. There are three proposals explaining the pathology of ORN. **Figure 4** highlights the principles of the theory of 'Three H's' proposed by Marx.

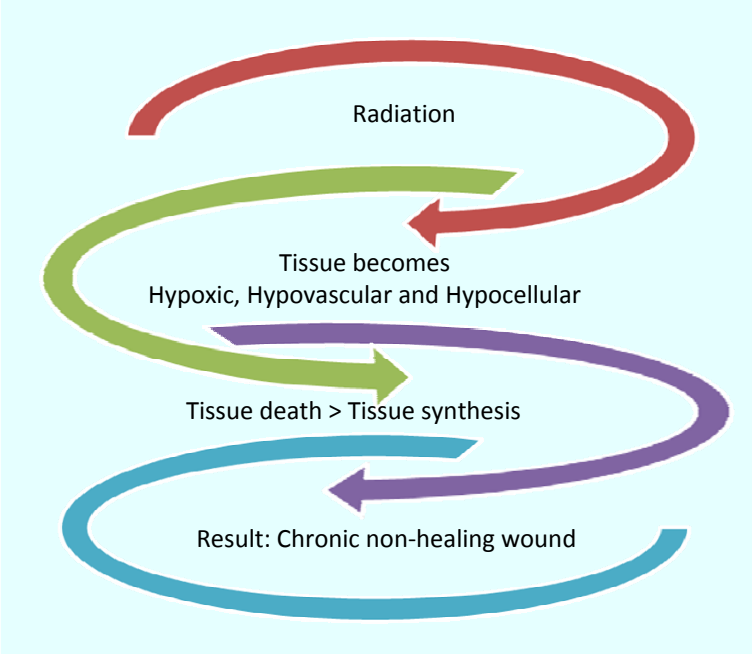

Figure 4*. Marxs' theory of 'Three H's'*

Previous to the 'Three H theory', the pathology was understood as a triad of radiation, trauma (tooth extraction in 88% of cases) and subsequent infection of the devitalised bone. ORN was likened to a disease similar to osteomyelitis secondary to irradiation. Marx disputed this heavily suggesting that infection is superficial and secondary.

Recent work challenges the principle of 'Three H's' and introduces a concept surrounding a radiation induced mechanism of fibro-atrophic tissue formation. The cascade of events proposed by this theory is outlined in **Figure 5**[4].

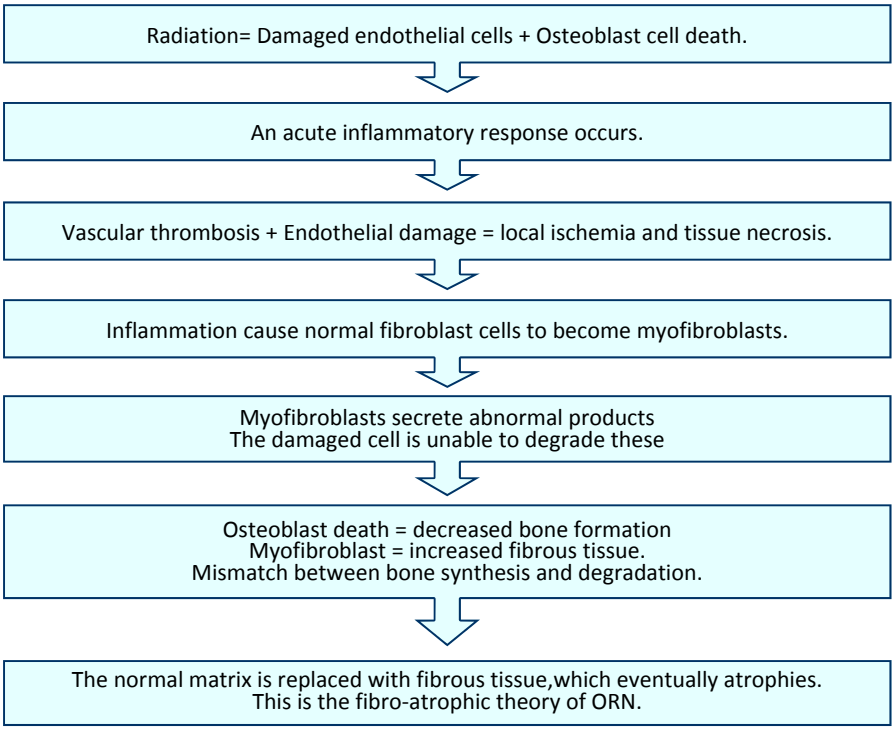

Figure 5: The fibro-atrophic cascade involved in ORN.

Risk Factors and Presentation of ORN

There are several risk factors for developing ORN as well as a number of protective agents. These are explored in **Figure 6**.

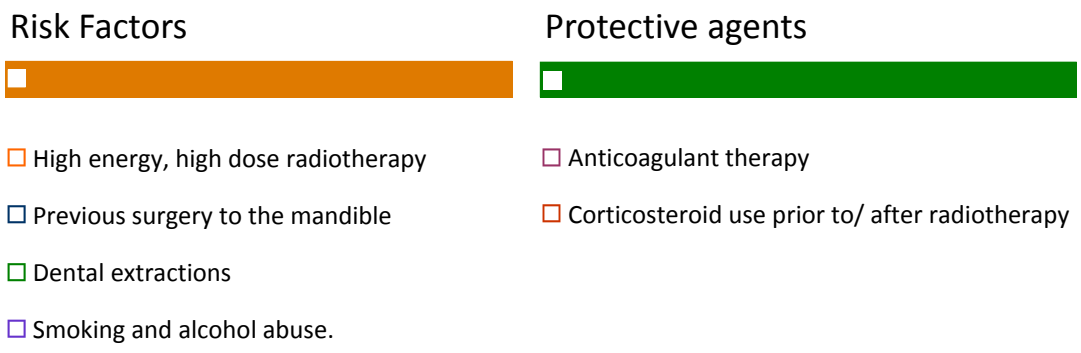

Figure 6: Risk factors and protective factors in ORN

ORN is an extremely disabling disease, not only because it causes pain and swelling in the jaw, but it has the potential to erode through bone and cause fistulation to the mucosa and skin. **Figure 7** outlines the presentation of ORN.

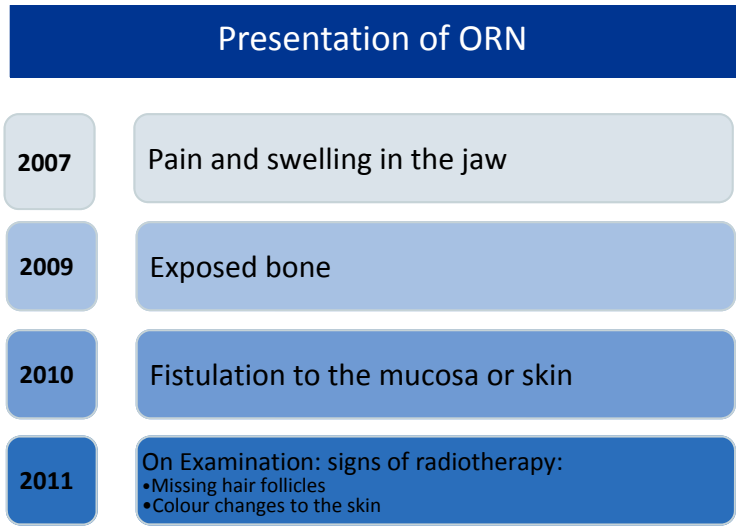

Figure 7: Presenting features of ORN

Diagnosis

Diagnosis is primarily from history and examination. One criterion states:

"The presence of persistent exposed bone after 6 months of conservative management is diagnostic[4]."

Diagnosis is aided by an Orthopantomogram(OPT)) to observe the different densities of bone and soft tissue. Histology can also be used to show necrosis of the bone.

Radiological Features of ORN on OPT
• Moth-eaten appearance • Radiolucent alveolar region • Poorly defined osseous destruction

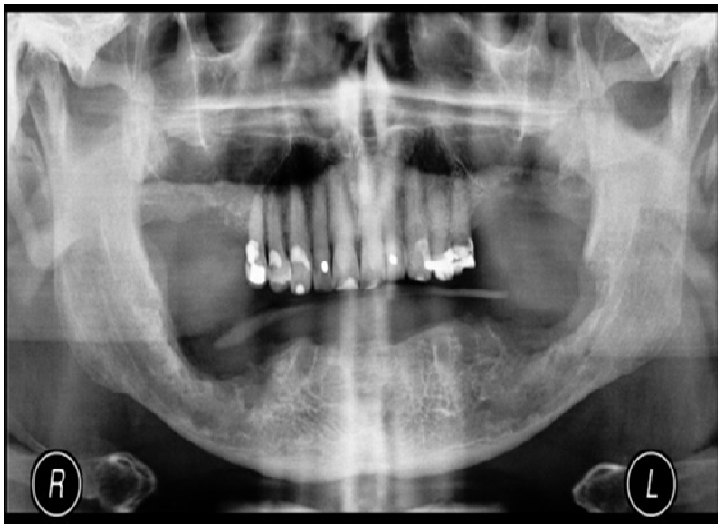

Figure 8: Radiological signs of ORN of the jaw

Management

There are a number of treatment options available for ORN depending on the severity of the disease and individual patient factors.

Prevention

- Preventative extractions of decayed teeth before radiotherapy[6].
- Lifestyle advice- Avoid alcohol and tobacco
- Good dental hygiene.

Medical

1. Pentoxifylline (PTX) 1200mg/day for 6 months- works by counteracting tumour necrosis factor alpha (TNF- α).
2. Alpha-tocopherol- an active form of vitamin E which removes free radicals generated during oxidative stress.
3. Antibiotic therapy-this is not evidence based, but has been found to be helpful.

Surgical

This involves reconstructive techniques such as reconstructive plates, regional flaps and free tissue transfer. Free flaps are the treatment of choice. They enable functional ability to be restored with the best cosmetic result. Donor sites include fibular, radial, iliac crest and scapula. Angiography is used to investigate collateral blood supply at the donor site.

Fibula Free Tissue Transfer for Mandibular Reconstruction

"A free flap is a mass of tissue that is transferred from its donor site to a recipient site, which can be some distance away."

Free flaps can be used to reconstruct large areas and the mass of tissue transferred can include skin, muscle, fat, bone and nerve. The structures that need reconstructing in a mandibular reconstruction are the mandibular bone, the intra-oral lining, underlying soft tissue, lower lip and in some cases the tongue.

The fibula free flap is the treatment of choice. It provides a high quality and quantity of bone and vasculature with a flap survival rate reaching 95%[7]. The lower third of the face is used for many activities, eating, speech and deglutition. The face is paramount in the social context. Thus it is fundamental that a good aesthetic result is achieved along with good levels of function.

Harvesting the Fibula Free Flap and Mandibular Reconstruction

The diagram below illustrates the principles of reconstructing the mandible.

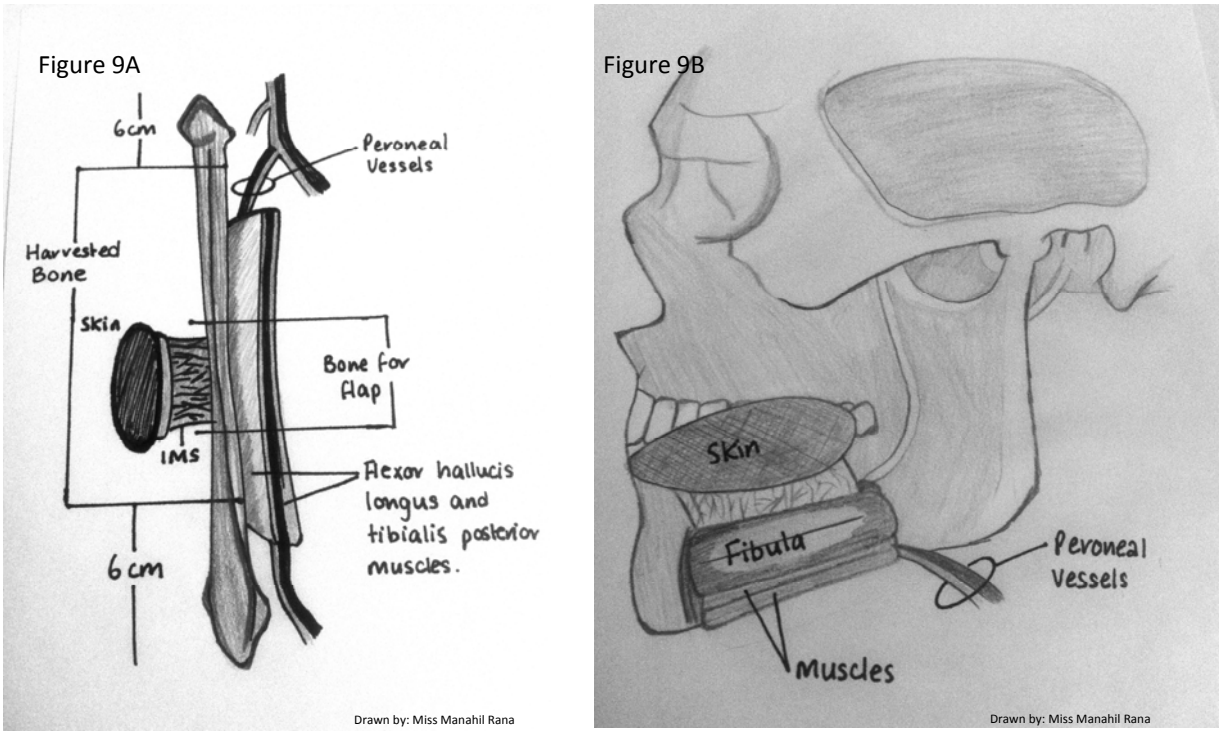

Figure 9: Principles of fibula free flap and mandibular reconstruction.

Conclusion

ORN is a significant complication of radiation therapy to the head and neck. The mandible is a region most at risk, due to its anatomical position which leaves it exposed and also a consequence of the high amount of cortical bone. The pathophysiology of ORN is still evolving and there are a number of theories regarding the molecular changes that occur in the disease process. This case highlights a patient who had undergone previous radiotherapy and went on to develop ORN following tooth extractions. Prevention of ORN can be facilitated by lifestyle changes and adequate dental hygiene.

ORN has a profound impact on quality of life; it can be treated using a number of methods. Pharmacological interventions play a role in counteracting free radical formation occurring in the diseased bone. Antibiotics are useful for symptomatic control and to manage secondary infections. However, in advanced disease, surgical intervention such as a free flap is often required to restore form and function to the jaw.

References:

1. Madrid C, Abarca M ,Bouferrache K. Osteoradionecrosis: An update. Oral Oncol .2010. 46:471–474.
2. Wahl MJ. Osteoradionecrosis Prevention Myths. Int. J. Radiation Oncology Biol. Phys., 2006. 64 (3):661–669.
3. Marx RE. Osteoradionecrosis: A new concept of its pathophysiology. Oral Maxillofac Surg. 1983. 41:203-280.
4. Teng MS, Futran ND. Osteoradionecrosis of the mandible. Curr Opin Otolaryngol Head Neck Surg. 2005. 13: 217—221.
5. Graigner RG, Allison DJ, Adam A, Dixon AK. Diagnostic Radiology A Textbook of Medical Imaging. 4th Edition. London: Churchill Livingstone; 2001.
6. Chrcanovic BR, Reher P, Sousa AA, Harris M..Osteoradionecrosis of the jaws-a current overview-part 2: dental management and therapeutic options for treatment. Oral Maxillofac Surg. 2010.14(2):81-95.
7. Bak M., Jacobson AS., Buchbinder D., Urken ML. Contemporary reconstruction of the mandible. Oral Oncol. 2010. 46(2):71 -6.

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Assessment and Management of Head and Spinal Cord Injuries

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Keywords:

CT scan in head injury, sub arachnoid haemorrhage, extra dural haematoma, sub dural haematoma, spine injury.

A. Head Injury

Case Study

An 18-year-old boy fell and hit his head against the goal post when he was tackled playing football. He was drowsy initially after the fall but soon regained full consciousness and was able to complete the match. However, he started getting headache soon after and hence was taken to the Emergency Department. Whilst waiting to be assessed, he collapsed suddenly and become unrousable.

- *What type of head injury has this boy probably sustained?*
- *What is the term used to describe his fluctuating level of consciousness?*
- *What will the CT Brain most likely show?*

Introduction

The majority of head injuries are a consequence of road traffic accidents, assaults, injuries at home, workplace or during sports. Excessive alcohol consumption is frequently implicated and young males are most commonly involved.

Epidemiology

Head injuries are a major cause of morbidity and mortality in the community. In the UK, it has been estimated that between 200 and 300 per 100,000 of the population are admitted to hospital with head injuries. Of these, 9 per 100,000 are fatal[1]. In Malaysia, head and neck injuries resulting from road traffic accidents account for 85% of major trauma cases, of which approximately 60% require admission to intensive care unit[9].

Pathophysiology of Head Injuries

The brain is a very vulnerable organ encased in a rigid protective skull and cushioned by cerebrospinal fluid (CSF). Trauma to the brain can occur via translational acceleration or deceleration forces, direct focal sharp penetrating or blunt forces. In abrupt deceleration, injuries can be divided into *coup* and *countercoup*[3]. A *coup* injury results from trauma at the site of impact whereas *countercoup* injury is the resulting remote injury away from the site of impact (*i.e.,* the force of injury propelling brain parenchyma to hit the opposite interior surface of the skull). This is why most cerebral contusions occur without skull fractures. On the contrary, patients with skull fractures that look significant usually only sustain minor neurological dysfunction as most of the force is absorbed by the skull after an impact.

Indications for CT Scan

The advent of CT scanning has had a huge impact on the treatment for traumatic brain injury. It is rapid, non-invasive and allows identification of surgically treatable lesions (acute injury) as well as pathological chronic injury.

The following are the criteria for immediate request for CT scan of the head in adults as recommended by the NICE (UK) clinical guideline[2]:

a. GCS less than 13 on initial assessment in the emergency department.
b. GCS less than 15 at 2 hours after the injury on assessment in the emergency department.
c. Suspected open or depressed skull fracture.

d. Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
e. Post-traumatic seizure.
f. Focal neurological deficit.
g. More than one episode of vomiting.
h. Amnesia for events more than 30 minutes before impact

A patient with minimal external signs of injury who is fully alert & orientated with a normal neurological examination and no symptoms other than headache may not need a CT scan. However, they do need close observation for the next 24 hours.

Neurological assessment

Head injuries require thorough on going assessment of the patient. The AVPU scale is a quick and easy method to assess level of consciousness as shown in **Box 1**:

Alert
Responds to **V**oice
Responds to **P**ain
Unconscious

Box 1: The AVPU scale

A more objective way of recording a patient's state of consciousness is by using the Glasgow Coma Scale (GCS). This is usually performed in the 'Disability' component of the primary survey once airway, breathing and circulation of the patient have been secured. **Table 1** describes the GCS scale in detail.

Eye Opening Response	Spontaneous-opens with blinking at baseline	4 points
	Opens to verbal command	3 points
	Opens to pain	2 points
	None	1 point
Verbal Response	Oriented	5 points
	Confused conversation, but able to answer questions	4 points
	Inappropriate response, words discernible	3 points
	Incomprehensible speech	2 points
	None	1 point
Motor Response	Obeys commands for movement	6 points
	Purposeful movement to painful stimulus	5 points
	Withdraws from pain	4 points
	Abnormal (spastic) flexion, decorticate posture	3 points
	Extensor (rigid) response, decerebrate posture	2 points
	None	1 point

Table 1: GCS scale

Scalp laceration

The scalp has a rich blood supply in the dense fibrous layer (**Figure 1**) and hence severe blood loss can result from a scalp laceration. In infants, blood loss from scalp can actually lead to hypovolemic shock. Although scalp lacerations or bruising confirms the presence of a head injury, their absence does not exclude an underlying intracranial haematoma.

Scalp lacerations should be repaired in two layers, with opposition of the galea prior to closure of the skin[3]. This should be done after meticulously debriding the wound. Routine use of antibiotics is not indicated in a clean wound but may be required in a dirty or contaminated wound.

Figure 1: Scalp laceration

Base of skull fracture

Diagnosis is made based on clinical evidence as it is often occult radiologically. Signs of base of skull fracture include periorbital haematomas ('Raccoon eyes'), mastoid haematoma (Battle's sign), anosmia, otorrhoea, rhinorrhoea, or VII and VIII cranial nerve palsies. On CT scan, there is presence of pneumocranium or air fluid levels in the sinuses. Prophylactic antibiotics may help in preventing meningitis. Nasal secretions post head-injury should be screened for beta transferrin ('tau' protein) for CSF. To prevent further leakage due to fistulas, surgery may be required.

Top Tip

Box 2

In elderly, alcoholic and patients on anti-coagulant medications, even minor head trauma can result in devastating intracranial bleeding.

Intracranial haemorrhage

Bleeding within the skull is a life-threatening emergency. Brain damage resulting from accumulated blood volume which in turn increases intracranial pressure (ICP) can lead to permanent neurologic deficit or death. Intracranial haemorrhages (ICH) can be classified into:

a. Subdural hematoma
b. Extradural hematoma
c. Subarachnoid haemorrhage

Subdural Haematoma

This results from tearing of bridging veins between the cerebral cortex and draining venous sinus. They are classified into:

- ❑acute <24hours
- ❑sub-acute 24hours – 2weeks
- ❑chronic >2weeks

Acute subdural haematomas are associated with high-velocity trauma and thus have a poor outcome. The blood follows the subdural space over the convexity of the brain and appears as a concave hyperdense collection (**Figure 2**). Acute subdural haematomas are rapid evolving lesions and early evacuation is mandatory.

Chronic subdural haematomas are most common in infants and elderly. They present with progressive neurological deficit after trauma.

CT appearance varies depending on the age of the lesion[4]. In the acute phase (Days 0-3), the lesion appears hyperdense. As it liquefies (Days 3-14), the lesion is isodense or hypodense as a result of fibrinolysis occurring within the clot. Chronic subdural hematomas, older than 2 weeks, are usually hypodense.

SDH collections can either resolve or increase in size from osmotic effects or repeated bleeds. These clots are evacuated by drilling burrholes over the skull.

***Figure 2*: SDH on CT scan**

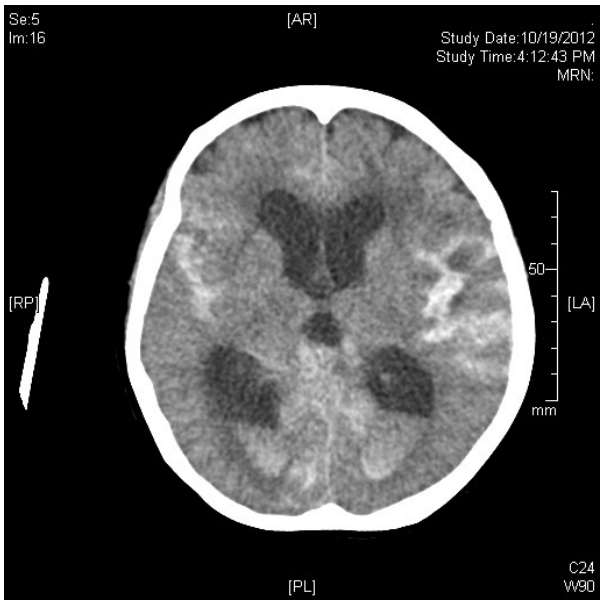

***Figure 3*: EDH on CT scan**

Extradural Haematoma

Extradural haematoma (EDH) is the accumulation of blood between the dura matter and skull, typically occurring after significant blunt head trauma. Fractures of the temporal bone can disrupt the middle meningeal artery and dural venous sinuses leading to high-pressure bleeding within the cranial vault[1]. The potential space between the dura and bone is developed by the expanding haematoma taking on the convex lens configuration inside the cranium (**Figure 2**). Cushing's triad describes the physiologic response to the rapidly increasing intracranial pressure and imminent brain herniation.

EDH is more likely to occur in younger age groups as the dura is able to strip more readily off the underlying bone. Patients will have brief loss of consciousness often accompanied by a lucid interval, headache, drowsiness, dizziness, nausea and vomiting. Rapid clinical deterioration is a significant criterion. An extradural haematoma is a surgical emergency where an urgent craniotomy and decompression is required.

Box 3

Features of Cushing's triad include:

- ❑ Hypertension
- ❑ Bradycardia
- ❑ Abnormal respiratory patterns

Subarachnoid haemorrhage

Subarachnoid haemorrhage (SAH) is bleeding in the area between the brain and the thin tissues that cover the brain (subarachnoid space). Subarachnoid haemorrhage can be caused by bleeding from an arteriovenous malformation (AVM), bleeding disorders, cerebral aneurysms and use of anti-coagulants.

The main symptom is a severe headache that starts suddenly and is typically occipital or unilateral. Patients often describe it as the "worst headache ever" or also known as 'thunderclap headache' which reaches maximum intensity within seconds[6]. Patients may experience photophobia, agitation, drowsiness or become comatosed.

Acute bleeding in SAH appears bright in CT scans (**Figure 3)**. Blood is usually seen in the ventricles, sulci and cisterns. The overall sensitivity of CT is best within the first 12 hours. Sensitivity declines with time. Approximately seven percent of acute SAH will not be visualized on initial head CT, typically because there is a small volume of bleeding[5]. CSF analysis from a lumbar puncture can help with the diagnosis even if the CT scan is normal.

The principal goal of treatment is to prevent re-bleeding by surgical clipping or endovascular techniques. Without treatment, re-bleeding occurs in 50% of patients with ruptured aneurysm within six months[3].

Box 4

Top Tip

Prior to obtaining consent for a lumbar puncture (LP), patients should be warned of post-LP headache as it is common

B. Spinal Cord Injury

Case Study

A 23-year-old lady is brought to the Emergency Department after a road traffic accident. She was the driver of a 3-door hatchback car that was hit from the back by a lorry whilst driving to her workplace. On examination, she is noted to have bruising over her anterior chest wall and tenderness at the upper cervical region. Her GCS is 15 and other physiological parameters are stable. Further neurological assessment reveals weakness in her upper limbs. PR examination is normal.

- *What type of spinal cord injury she may have sustained?*
- *What is the best form of imaging which may be used to diagnose her condition?*
- *What drug(s) should be given to her during the initial phase of injury?*

Introduction

Due to the increase in road traffic accidents, unfortunately, spinal cord injuries have become more common in the modern society. Despite advances in the understanding of the pathogenesis and improvements in early recognition and treatment, it remains a devastating injury, often producing severe and permanent disability. With the peak incidence in young adults, traumatic spinal cord injury leads to widespread impact to the society and the economy.

Epidemiology

In the UK every year, there are around 1,200 people paralysed from spinal cord injuries. There are currently thought to be approximately 40,000 people in the UK living with paralysis. This may be a conservative estimate as this only takes into account patients who have been treated in a specialist spinal cord injury unit and does not include those who have been treated in a district general hospital. It is estimated that the current annual cost of caring for people paralysed by spinal cord injury is more than £500 million. Twenty-one percent of people discharged from Spinal Cord Injury Centres require nursing home, hospital care or other institutionalised settings rather than their own homes. Around 20% of patients leave Spinal Cord Injury Centres clinically depressed[7] .

Common mechanism

The spinal cord can be injured by transection, distraction, compression, bruising, haemorrhage, or ischaemia of the cord or by injury to blood vessels supplying it. These injuries can all result in permanent cord injury and may be complete or incomplete.

Presentation

A complete cord syndrome is characterized clinically as complete loss of motor and sensory function below the level of the traumatic lesion.

Incomplete cord syndromes have variable neurologic findings with partial loss of sensory and/or motor function below the level of injury. These include the anterior cord syndrome, the Brown-Séquard syndrome and the central cord syndrome[8].

Signs & symptoms of acute spinal cord trauma

- Flaccid paralysis below level of injury
- Loss of spinal reflexes below level of injury
- Loss of sensation (pain, touch, proprioception, temperature) below level of injury
- Loss of sweating below level of injury
- Loss of sphincter tone with bowel and bladder dysfunction

Assessment

History

A high index of suspicion of spinal cord injury is necessary in any major accidents, unconscious patients, falls from a height, sudden jerk of neck after rear end car collision, facial injuries or head injuries. Enquire about neck or back pain, numbness, tingling, weakness and ability to pass urine.

Examination

A logroll is performed to assess the patient's spine. Inspect for bruising then palpate for spinal deformity or tenderness. Repeat the neurological examination to determine neurological damage (complete/incomplete) and its progression. Perform rectal examination to asses anal tone. Thorough overall examination for fractures at other sites must be performed to rule out other distracting injuries.

Complete neurological examination

The aims include:

- To determine level of lesion - counted as the lowest level at which neurological function is intact bilaterally

- To determine whether damage is complete or incomplete
- To determine prognosis

This may be difficult until period of spinal shock (flaccidity, areflexia) is over *i.e.,* 24-48 hours after injury.

Imaging

X-rays

- Cervical spine: AP, lateral including C7/T1, open mouth view of odontoid, Swimmer's view or pull arms down view.
- AP and lateral view of other tender areas of spine.

Box 5

Top Tip

Period of spinal shock usually resolves within 48 hours and return of bulbocavernosus reflex signals termination of spinal shock.

CT scan

- Used to show bony injuries
- Provides better visualization of vertebral arches, facet joints and neural canals.
- Differentiation of neural elements from other soft tissues requires intrathecal administration of contrast medium.

MRI scan

To show soft tissue involvement. Any extramedullary compression by disc, haematoma and bone may also be readily apparent.

Management

Initial management

If there is presence of neurological damage:

- Catheterise
- Take note of reduced blood pressure and bradycardia due to neurogenic shock (temporary generalised sympathectomy)
- Rule out hypotension due to haemorrhage elsewhere
- The patient may need treatment with vasopressors, not fluid resuscitation
- Invasive monitoring is required.

Give intravenous methylprednisolone (solumedrol) to reduce inflammation and preserve blood flow to the spinal cord. The dosage regimen is as follows:

- 30 mg/kg over 15 min
- Then 5.4mg/kg/hour over 23 hours or 48 hours depending on time since injury i.e. given over 23 hours(if presentation is within 3 hours since injury) or given over 48 hours(if presentation is between 3 to 8 hours since injury)

Definitive management

The objectives are to preserve neurological function and relieve reversible nerve or cord compression. This is done by stabilizing the spine with surgery via posterior instrumentation or fusion (**Figure 4**). After surgery, patients need to undergo rehabilitation as part of the recovery process.

Box 6

Top Tip

Use of high-dose methylprednisolone therapy for spinal cord injury patients remains controversial. Clinicians should carefully weigh the potential benefits versus the risks of this treatment[8].

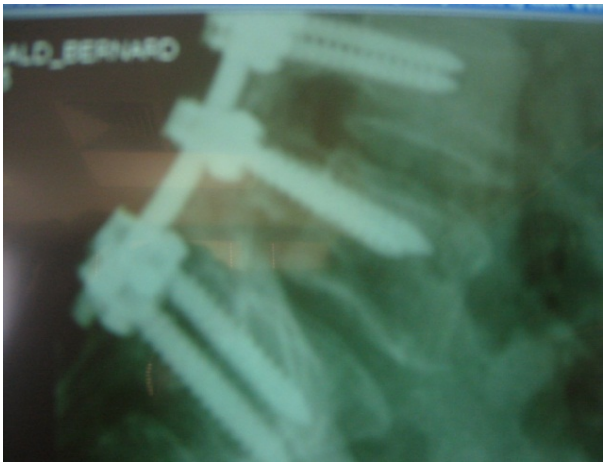

Figure 4: Posterior instrumentation of L3 - L5

Conclusion

Head and spinal cord injuries result in significant morbidity and mortality. Since it commonly affects young individuals, the resulting paralysis and permanent brain damage has a devastating impact socially and economically. Prompt recognition, careful stabilisation and referral to the appropriate specialist unit is thus essential to enhance the possibility of a successful functional outcome.

References:

1. Russell RCG, Williams NS, Bulstrode, CJK.Bailey &Love's Short Practice of Surgery. Arnold, 24th edition. 2004; p. 594 – 605.
2. NHS NICE guideline. Head injury: Triage, assessment, investigation and early management of head injury in infants, children and adults. September, 2007; p. 22-26.
3. Klingensmith ME, Chen LE, Glasgow SC, Goers PA, Melby SJ. The Washington Manual of Surgery. Lippincott Williams & Wilkins, 5th edition. 2008; p. 567-576.
4. Bullock MR. Surgical Management of Acute Subdural Hematomas. Neurosurgery. 2006; 58:S2-16-S2-24.
5. Diringer MN. Management of aneurysmal subarachnoid hemorrhage. Crit Care Med. 2009; 37: p.432-440.
6. Edlow JA, Panagos PD, Godwin SA, Thomas TL, Decker WW. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med. 2008; 52: p.407-436.
7. http://www.apparelyzed.com/statistics.html
8. Gupta MC, Benson DR, Keenen TL. Initial evaluation and emergency treatment of the spine-injured patient. Skeletal Trauma. 4th ed. Philadelphia, Pa: Saunders Elsevier; 2008: Chapter 25.
9. National Trauma Database January 2009 to December 2009, Fourth Report. National Trauma Database and Clinical Research centre, Ministry of Health Malaysia. July, 2011; p. 28-47.

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Future Excellence

International Medical Summer School 2012

University Place, University of Manchester, United Kingdom

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This is an article by Ms Pophali, a final year medical student from Maharashtra University of Health Sciences, India, who was invited to attend the International Medical Summer School as a gesture of appreciation for her winning the best oral presentation award at the Kolkata Annual Research and Medical International Congress, India, 2012.

Ms Prachi Pophali

My week at the Doctors Academy's flagship event, The Future Excellence International Medical Summer School (IMSS) 2012, has been one of the most memorable times of my life. It is a rare opportunity for a student from India like me to attend such a grand event during their undergraduate education.

I got the golden opportunity to attend this school as a result of being judged the winner of the best research paper presentation at the National Indian Conference: the Kolkata Annual Research and Medical International Congress (KARMIC) 2012, which was organised under the auspices of the Indian Medical Students Association.

The concept of an event for medical students to gain an insight into the different specialities and to obtain information and basic skills about the field in medicine that they found most intriguing was something of a novelty to me for the concept was completely unknown for majority medical students in India.

The IMMS took place from 13th to 17th of August 2012 with support from the prestigious organisations such as the Royal College of Surgeons of Edinburgh, Royal College of Physicians of London, British Orthopaedic Association, British Association of Plastic, Reconstructive and Aesthetic Surgeons, and The Royal Society of Medicine was attended by over 200 students representing more than 30 countries from all over the world. Being unsure of the speciality I would like to pursue, the IMMS was tremendously beneficial as it provided me and the other delegates an opportunity to discover what life is like for a doctor in a diverse number of specialties.

On the first day of the IMSS event, we were asked to choose between medicine and surgery and were then allocated accordingly to a particular stream. We were then given a series of talks that provided us a broad overview of the speciality through 'A day in the life of... ' lectures. For example one of the talks was entitled: ' A day in the life of an Acute Physician'. I felt that the second and third days were most exciting, as we were split into the sub-specialities and we were then given more in-depth knowledge about them including current advances and future of the speciality. We also took part in various workshops. The opportunity to learn basic surgical skills was really exciting. We carried out procedural skills like chest drain insertion and common anaesthetic procedural skills which was not only educational but incredibly enjoyable. The laparoscopic workshop using simulators, however, was the icing on the cake!

In the last two days we were given information about audits, research, presentations and publications. The talk I enjoyed the most was by Dr.Swee Ang, a Consultant Orthopaedic Surgeon from St Barts Hospital London, about the role of a doctor in a war or disaster situation. Also, the brain storming session on how to deal with the situation of organ procurement and presumed consent was immensely refreshing.

As a sponsored student from India, I was given the chance to give a talk about the research situation among medical students in that part of the world. To give a talk in front of such a large and varied international audience with some of the eminent doctors of the world sitting in the audience was an incredible experience.

Academic and educational activities consumed the day. During the night, however, there were a number of social events to opt for which allowed us to get to know our fellow students, interact with consultants in a more relaxed setting and cultivate camaraderie.

I wish the week could have lasted longer! At the end of it I was empowered with knowledge about the specialities, about the people from different parts of the world and instilled with plenty of self confidence. The IMSS definitely helped me to understand my affinity for different specialities which will help choose a path in the future.

It was definitely a learning opportunity you really can't afford to miss!!

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Indian Medical Students Association

A report from the "Hyderabad Annual Medical Students' Assembly" (HAMSA) 2012

A STEP AHEAD FOR INDIA

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The state of play of medical education in India today is at the brink of transformation. A decade ago the situation was such that all that was expected was academic excellence and very little emphasis on medical trends and advances in other parts of the world.

However, when students graduated and encountered clinical challenges they felt that something much beyond the margins of their text books was needed. With the technological boom, medical graduates were consequently exposed to advanced and sophisticated medical systems in the Western world, hence piquing their curiosity and instilling a thirst and desire to be as competitive and competent like their counterparts in others parts of the world. This suddenly sparked a revolution in the Indian System of medicine, bringing together students from different parts of the world, with a goal to achieving the transfer of knowledge amongst others.

Keeping in mind the needs of the medical student fraternity and the colossal potential it contains, the Indian Medical Students Association (IMSA) (www.imsaindia.org.in/) was inaugurated. IMSA is one of the largest medical students network in the world connecting medical students all over India. In the past few years since its inception, there has been a tremendous overhaul in the medical education in India. With the burgeoning number of undergraduate research projects in India, the scientific exchange between the students has risen exponentially and there has also been an increase in the number of research gatherings, conferences, workshops and CME's being held in different regions of the country and this subsequently brought out a much needed paradigm shift in the goal to achieve a solid and stellar academic background. In the recent past, India saw the first of the many more to follow, "Hyderabad Annual Medical Students' Assembly" (HAMSA) 2012 (http://www.scribd.com/doc/117581412/IMSA-Activities-Updated). The inception of HAMSA met the urgent need for awareness the importance of Emergency Medicine, considering the expandingurban scenario and the medical complications associatedwith it.This was the first workshop-based conference organised for students and hence HAMSA

Thanks to the guidance from Doctors Academy, UK (www.doctorsacademy.org.uk), we were able to increase the scope of HAMSA to other specialized topics such as Problem Based learning and developing a Curriculum for Resource Independent Medical Practice (CRIMP). We also received unwavering support by the Leiden academy, Netherlands (http://www.leiden.edu/)

Day 1

The 7th October 2012 saw a first of-its-kind gathering of medical undergraduates at Gandhi Medical College, for Day 1 of the first chapter of Hyderabad Annual Medical Students' Assembly (HAMSA).

Close to 700 delegates from all over the country arrived to participate in a series of events scheduled exclusively for them.

First was a session on disaster management. This was conducted by the Indian chapter of International TraumaCare. It highlighted the importance of keeping a clearhead and maintaining equanimity whilst dealing with bomb blast victims: how thefirst-aid should be performed, how to classify cases according to the extent and severity of injuries, and how to treatthem accordingly.

This was followed by an orientation programme for students, aspiring to continue their studies abroad, i.e. USMLE. A banquet lunch was arranged for all the delegates because we were aware that there is nothing more than distracting than an empty stomach and the pangs of hunger that than beckon you!

Delegates then attended the most anticipated episode of the day: the HAMSA Open Medical Quiz. Hosted by two quiz-aficionado medical students, it was a novel take on medical knowledge with new twists on known facts. Fifty teams of two and 35 preliminary questions later, six teams progressed to the thrilling final round.
It invigorated participants and non-participants, medics and non-medics alike with valuable information. The quiz can positively be summed up as: info-tainment!

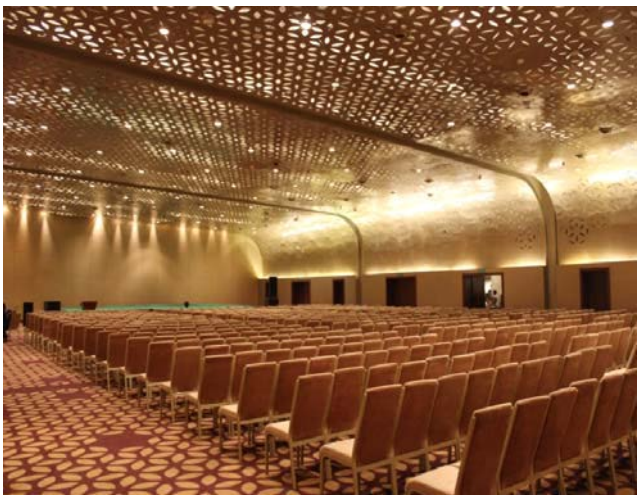
The other high-energy affair of the day was the HAMSA debate on euthanasia: A sombre topic as it was, the topic was given the respect it deserves. Amateur yet determined debaters questioned the pros and cons, the issue of legalization, the social impact, and the role doctors play in euthanasia. The audience was left educated and pondering the implications of mercy killing in our lives. That wrapped up day 1.

Day 2

Day 2 was a mélange of research and academic events. It began with presentations of Research papers and case reports by students from all over the country. This was followed by the much awaited session on Problem based learning by Professor Stuart Enoch from Doctors

academy, United Kingdom. He engaged the participants in an interactive discussion on different patient scenarios. Professor Enoch then went on to a role playing session, by providing simulated doctor – patient interactions by involving the attendingdelegates, which turned to be a consciousness raising session, thanks to his spontaneity and sense of humor. In the afternoon, the delegates were introduced to the concept of CRIMP, an unfamiliar subject in the Indian teaching curriculum. The participants were given a head start to future workshops on CRIMP. The audience was then treated to an enthralling lecture on the subject of geriatrics by Dr. David Van Bodegomfrom Leyden Academy, Netherlands.

The day ended with a poster presentation competition on the topic of Robotic Surgery, which went with the title "I, Dr. Robot: Poised to change the future of surgery…"



Day 3

On day 3, the stage was set for a cultural extravaganza, a day to rejoice for the medical students, a fun and entertaining day full of enticing dance performances and mesmerizing numbers by Music bands. The celebration continued through the night.

The Hyderabad Annual Medical Students Assembly concluded with a promise that was more than just fulfilled. Three days of inspirational events, which will be embedded in the minds of all the delegates and who are already looking forward to the second edition of HAMSA in 2013...

STUDENTS FEEDBACK

"HAMSA was a unique experience when compared to all the conferences I attended because it was more direct, meaningful and provided much needed hands on approach. It audaciously tackled the essential aspect of emergency care in a simple yet comprehensiveand memorable manner. It turned out to be an experience that one would be admonished to forget"

"HAMSA was a novel experience for me! It provided deep insight to the more interesting and informative methods of learning and also a great place to meet likeminded people and a very encouraging platform for beginners. Hope there is much more of these fantastic events in the future! Kudos to the organizers..."

An Introduction to Curriculum for Resource Independent Medical Practice (CRIMP)

16th August 2013, University Place, University of Manchester Campus

Due to a myriad of competing priorities and vested interests of the policies in developing countries, the resources available to provide an equitable and acceptable healthcare to people living in resource-poor conditions in such countries are not set to improve in the foreseeable future. Contrary to the traditional approach of providing resource-poor nations and its people with medical aids that are non-sustainable, the above project aims to provide the healthcare professionals in those countries a structured frame-work and appropriate guidelines to undertake the best practice within the constraints of the available infrastructure and resources. This session will be used to stimulate discussion amongst the 275 participants of the International Medical Summer School, representing some 75 universities from 25 countries. The information gathered from this session will form the basis for developing a robust curriculum that could be validated by appropriate regulatory bodies.

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World University Anatomy Challenge 2012
A Doctors Academy Event

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An article from the winner (joint with Ms Pophali) of the World University Anatomy Challenge 2012, a competition consisting of 219 participants from 116 Universities representing 36 countries

Mr Michaël Ruyssers

Keywords:
International Medical Summer School, Manchester, Anatomy Challenge, Medical Education, Career Opportunities

Regarding the Doctors Academy flagship event the *Future Excellence* International Medical Summer School (FEIMSS) 2012, I have the honour to compose an exposition on my experiences of this event as a student representing the University of Antwerp, Belgium. I immediately state without reservation that it has been a life-enriching experience and it has greatly contributed to shaping my understanding of medicine in the context of a UK healthcare system.

As I was actively searching for a summer school to participate in, I contacted the Belgian Medical Student's Association. They gave me several options but as I was gathering information, there was only one event that really caught my eye; the FEIMSS.

All the information that I required was on the Doctors Academy website, from how to register to what time one was expected to show up on the first day. The faculty made it really easy to arrange accommodation (the halls of residence are situated on Manchester University Campus, which is in close proximity to University Place, the venue for the FEIMSS event) and information is provided on how to go from the airport to the campus. To address individual needs, applicants can choose from more than a dozen disciplines; both surgical as well as medical ones. Moreover, all of this information is available online one year in advance.

The 2012 FEIMSS was an absolutely amazing week . It brought together more than 200 students from over 115 universities representing 36 countries to share the same experience which was truly unique and inspiring. As everybody was being allocated to groups on Sunday evening, friendships were already starting to forge. What made this week so special was how people from different parts of the world gathered together and interacted with one another, talking about and discussing similar interests.

The courses were divided into theoretical lessons and practical classes. A broad range of topics were discussed

by a whole host of guest speakers, each speaker was a specialist in his or her own field. For example in neurosurgery, topics ranged from the first principles in a basic neurological examination to the latest cutting edge developments in brain and spinal surgery. Real time video material is used to explain the process of several operations which makes the cases less abstract and easier to understand. In the practical classes we were taught how to approximate an incision site, how to work with laparoscopic devices, the basics on how to place orthopaedic plates and external prostheses and much, much more. We were constantly learning in an informal setting which makes the acquisition of knowledge an enjoyable endeavour.

Although this event is organized to enhance our medical knowledge and procedural skills, the social aspects cannot be overlooked. To cover the educational arena as well as the social one, there was a perfect balance between classes and free time. During the day we were expected at the school to follow the course and during the evening we were free to participate in the organized social activities or to plan something by ourself. I loved participating in the social events as we went for drinks in traditional English pubs, played footie with the lads in the middle of nowhere, went dancing in one of the best nightclubs in Manchester and much more. These activities provided the perfect opportunity to meet new people and create new friendships. Friendships with people you never thought you would meet.

Moreover, I would like to highlight the World University Anatomy Challenge 2012, the first of its kind. This was a competition that was held during the summer school week, giving 219 participants the unique opportunity to test their anatomical knowledge. And as the winner of this event I was asked to outline the factors that got me to gain the first prize in this competition.

In my humble opinion, the first and most important characteristic for a medical student to win this challenge is a passionate interest in anatomy and how the human body functions. Anatomy always has to occupy some recess in your mind, even when you are watching TV, eating dinner with your family or playing soccer. As they say, you can only really understand the function of an organ and the correlated pathology if you apprehend its anatomical features. And wanting to see the connection between anatomical features and function implies that one has a genuine interest. In this regard I often take time to ponder on what happens during seemingly mundane activities such as during a run; I ask myself which muscles I am using or which way my blood is traveling. Not in an obsessive way, mind you, but in a way that keeps me focused on how anatomy is associated with function. Thus, I repeat my anatomy in a natural manner and make sure I retain it.

The World University Anatomy Challenge gave me the chance to test my anatomical knowledge on an international level and compete with medical students from over 30 different countries. It comprised of questions for which answers can be sought in hundreds of different books, written in hundreds of different languages, but somehow I managed to make a difference. And in that way, it made me realize the purpose of learning and studying about things you are really interested in. And for that I would like to thank the entire faculty at Doctors Academy.

And last but by no means the least I'd like to thank my teammate, Ms Prachi Pophali who represented India, for having been the perfect team mate.

Once again I would like to emphasize how much I enjoyed attending this event and how inspiring the week was. It was a truly unique experience.

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'Doctors Academy Award for Academia and Research'

Preston National Surgical Undergraduate Surgical Conference, 23rd June 2012

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This is an article by Mr Key, a final year medical student from the University of Manchester, United Kingdom, who was invited to deliver a short keynote lecture at the Future Excellence 2012 International Medical Summer School event. Mr Key was invited to speak as a gesture of appreciation for his winning the award for Academia and Research (best Oral Presentation category) at the Doctors Academy 2012 National Surgical Undergraduate Conference which was held in Preston, England. The abstract is published overleaf.

Mr Thomas Key

I was privileged to receive the Doctors Academy award for Academia and Research this year for a presentation I delivered at the 2012 National Undergraduate Surgical Conference which was held in Preston, England. I presented research that I conducted in clinical orthopaedics as part of an intercalated degree in anatomical sciences at the University of Manchester. Doctors Academy provided me with unwavering support at the conference where the presentation sessions were rigorously structured and fairly judged. The award included text books, online resource material, a complimentary place in the highly acclaimed annual final year revision courses in medicine and surgery, and, most importantly, an opportunity to present my research at the prestigious Doctors Academy International Medical Summer School event (http://www.doctorsacademy.org/AcademyCMS/default.asp?contentID=769) at the University of Manchester campus in August 2012.

After winning the award, Doctors Academy liaised closely with me about presenting at the Summer School, both in terms of content and aims of the presentations. I was privileged to be given a half hour slot for two presentations. The first was a presentation of my research findings on orthopaedics and the second was a presentation on conducting research as a medical student. My project supervisor Professor Lennard Funk, an eminent orthopaedic surgeon, was also cordially invited to present on the topic of conducting research as a surgeon and what he looks for in a student seeking a research tutor.

The conference itself was very impressive with over 200 delegates from more than 35 countries. It was obvious an enormous amount of time and effort had been spent to make sure that the five day event delivered a comprehensive curriculum in a very professional manner. It provided an unrivalled insight into aspects of a career in medicine and medical research not covered by the traditional medical school curriculum.

Personally, it was a fantastic opportunity to present my research findings to a large, eclectic and enthusiastic audience of delegates. In addition, I found it a very enriching experience to share my knowledge and insider tips about medical research as an undergraduate, as a journey from the initial conception to national presentations, and finally as a keynote lecture at the International Medical Summer School, which I cannot recommend highly enough. Lecturing at an international conference and publishing the research abstract in the World Journal of Medical Education and Research are golden opportunities, both in terms of gaining invaluable experience and opening doors for your future medical career.

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Research Abstract
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The Use of Geometric Morphometrics as a New Method to Analyse Glenoid Bone Loss after Shoulder Dislocation

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This is the abstract of the presentation that won 'Doctors Academy Award for Academia and Research' (best oral presentation) at the Preston National Surgical Undergraduate Surgical Conference 2012.

Abstract

Introduction

Glenoid bone loss occurs at the anteroinferior and posteroinferior aspects of the glenoid rim in anterior and posterior instability respectively. This morphological change in the shape of the glenoid fossa predisposes to increasing instability. The aim of this study was to use geometric morphometrics to analyse changes to glenoid morphology in traumatic shoulder instability.

Materials and methods

3D models of the surface of the glenoid fossa were created using CT scans from 8 patients with 5 dislocations and 3 controls. Ten landmarks, corresponding to the same anatomical sites between samples were digitized onto the surface of the glenoid fossa. Shape information was extracted from the landmark co-ordinates and analysed for variation in the geometric properties of the glenoid fossa using geometric morphometrics.

Results

The areas of most pronounced variation between the dislocation and control groups were as expected, at the anteroinferior, and posteroinferior glenoid regions. This indicated that geometric morphometrics allows variation in the geometric properties of the glenoid fossa after dislocation to be accurately analysed at a good level of detail in three dimensions. Compared to conventional techniques using single glenoid measurements from 2 dimensional images, morphometrics represents an exciting new avenue for analysing the morphological changes to the glenohumeral joint involved in shoulder pathology.

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An Introduction to Anaesthesiology

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Introducing Anaesthesiology...

The core of anaesthetic practice involves the management of patients in an operative setting and includes skills such as administering general anaesthesia and/or regional anaesthesia and intra-operative monitoring of the patient's vital signs to ensure that the patient's physiological parameters are within normal range. However, there is far more to anaesthesia than just the aforementioned. Indeed, anaesthesia is a broad speciality with plenty of variety and excitement. For instance, anaesthetists are also involved in the provision of intensive care and are experts in the management of pain.

In addition to standard pre-operative assessment on the ward prior to surgery, many patients are now seen in anaesthetic out-patient clinics. Here they are assessed and investigated for cardiac or pulmonary dysfunction. Specialised assessments such as cardiopulmonary exercise testing (CPET) and echocardiography are now being performed by anaesthetists.

Life as an Anaesthetist

A typical day for an anaesthetist begins before 8am and the length of the day can range from a 9 hour shift to a 14 hour shift. There is, however, a great potential for flexibility, depending on the area of the specialty that the anaesthetist is involved in. A significant number of anaesthetists work on a part-time basis and are able to adjust their work pattern to ensure a decent work-life balance.

The first tasks of the day include pre-operative consultations with patients on the surgical wards and preparing the anaesthetic agents and equipment which will be used during the surgery. Throughout the day, the anaesthetist is responsible for the patient's welfare at all times, and works in conjunction with surgeons, operating department practitioners, theatre nurses and ward staff. Following the operation, anaesthetists ensure that the patient has adequately recovered or has been delivered to an intensive care unit where there are provisions for ongoing care. It is the anaesthetists duty to show leadership and to liaise and coordinate with the multi-disciplinary team to ensure a positive outcome for the surgical patient.

Anaesthetists also have an on-call rota.This is variable depending on the work plan and size of the department but there will always need to be anaesthetic cover for emergencies. Many hospitals also run extra operating lists during the weekend and evenings which also require an anaesthetist. Due to the large size of anaesthesia departments compared with other specialties, there is more flexibility in shift patterns, including possibilities for flexible training as mentioned above.

Anaesthesia offers the possibility to sub specialise in a variety of areas including cardiac, neurosurgical, obstetric or paediatric anaesthesia. Some anaesthetists may choose to specialise in adult or paediatric intensive care, and undertake a dual qualification in anaesthesia and intensive care.

There is a great deal of scope for work abroad and outside of the NHS. The anaesthesia curriculum even allows for this to be integrated into training and the higher level training curriculum includes optional modules in remote and rural anaesthesia and anaesthesia in developing countries. Non-governmental organisations and humanitarian agencies such as Medicins Sans Frontiers and Medical Aid for Palestinians are always keen for anaesthetists to be part of their overseas teams and regularly advertise vacancies and job opportunities on their websites.

Training

Anaesthesia is a moderately competitive speciality. There is likely to be increased ST3 competition in the future due to the dual pathways leading to ST3 level which include trainees from both the acute care common stem (ACCS) and the anaesthesia stem. There are over 4700 anaesthetists currently working in the UK.

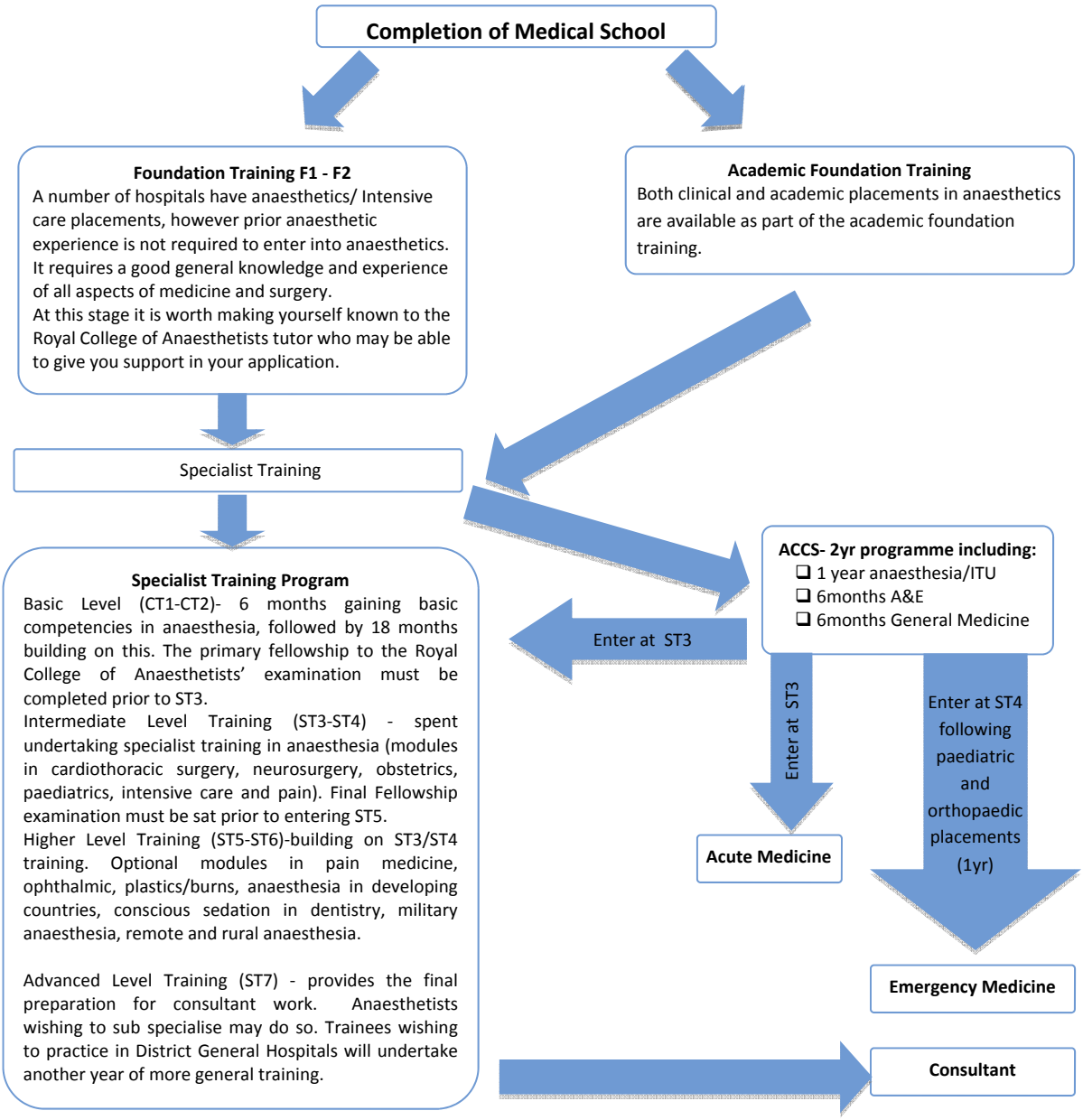
During anaesthetic training, candidates must re-apply at both CT2 and ST3 levels. At ST3 level, candidates must demonstrate that they have passed the MCQ component of the primary fellowship to the Royal College of Anaesthetists (minimum) and also achieved the competencies required from the first two years of training. The primary FRCA is a challenging examination, for which there is a 45-50% pass rate.

The Future

As the population changes, so anaesthesia must evolve too. The classical role of the anaesthetist who is solely involved in theatre has changed dramatically over the last decade and is likely to change further over the next decade.

The increase in numbers of both elderly people and the obese has resulted in a rise in patients deemed to be at high risk for anaesthesia. The role of the anaesthetist as the peri-operative physician is likely to be augmented due to the changes that are occurring in surgical practice. The difficulties encountered with high risk patients has resulted in more anaesthetic led cardiopulmonary exercise testing (CPET) to evaluate individual risk. This is an area in which there is considerable research potential.

Furthermore, the use of ultrasound in anaesthesia has led to changes in practice. Nerve blocks, including spinal blocks, may now be guided by ultrasound which enhances their ease and safety. Echocardiography is also being routinely used by cardiac anaesthetists and is likely to be used more for non-cardiac surgery patients as well.



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An Introduction to General Practice

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Introducing General Practice…

General practice is a unique speciality which carries the sense and indeed excitement of the unpredictable; the sense of, 'not knowing what condition you will diagnose next'. You could see fifteen patients in one clinic and each patient might have a different problem. It is a specialty that demands a broad skill set from its practitioners as you will examine, assess and treat myriad types of people across the age spectrum. This can include inoculating a new-born child with immunisations to assessing and initiating appropriate investigations to determine if an elderly patient with memory problems has developed dementia. The continuity of care of a general practitioner means you can get to know all of your patients and their families, even across several generations during your career.

Life as a General Practitioner

A typical working day begins at 8am and finishes at 6pm although this can vary depending on your patient population and whether you're a 'single-handed' GP or if you work as a locum GP (freelance) between practices:
8-11.30am Morning Surgery
11.30am-12pm Telephone Consultations
12-1pm Home Visits and/or Administration Work
3pm-6pm Afternoon Surgery

How your week is arranged can be very flexible, you can choose how many sessions you work for your practice and how many sessions you dedicate to other things. For example, you could pursue a special interest (the GP with a special interest (GPSI) pronounced 'gypsy'.), work in academic research, health service leadership or become involved with teaching and education. A special interest is a service that you can provide that isn't necessarily expected of a GP. For example rapid access chest pain clinics in Cardiology or providing behavioural therapy in mental health are both potential specialist interests that GPs can pursue. If you wish to have a specialist interest it is possible to start to develop these skills in your foundation rotations. However, your primary care organisation or local trust may offer training if there is a need for the population.

The flexibility that comes with being a GP is really what you make of it, many work part-time, particularly when young children are at home. This also means there won't be any compulsory on-call shifts although from time to time you may wish to work in an out of hours service. This is where you receive phone calls from patients outside of normal surgery opening hours and act accordingly (*e.g.*, telephone advice, review in an out of hours centre, domiciliary visits or admission to emergency services). There is a trend to co-locate out of hours services at the front of A&E so that patients turning up to A&E can be triaged to the right service. The out of hours service usually begins at 6.30pm and finishes at 8am; split into part or full time shifts each with their own allocated rest periods. Amongst all the major specialties, General Practice must offer one of the best work-life balances for anyone with family commitments or extracurricular interests.

General Practice is delivered in the community providing first port of call, or primary care, to its self-referring population and because of this it has its own benefits and drawbacks. Whilst patients will present with a variety of conditions, complex interventional emergency care cannot be safely provided, although many urgent conditions will present and be managed in the primary care setting. Only those conditions that cannot be safely managed in the practice are referred on to hospital specialists. This is not the only interaction with other specialties however. Many patients will often require long-term longitudinal care for chronic illness (from 'cradle to grave') which will involve frequent liaison with many specialties to ensure the best care. This type of work is mainly elective; the role of a GP is to provide holistic preventive care for people with long term conditions to avoid acute deterioration requiring emergency care.

The general practice is the first port of call for the vast majority of patients for preventive, acute and long term health care needs. This provides many challenges. It is the GP's job to determine: what the problem is or could be, whether it needs further action and if so, what that action should be. This makes life as a GP extremely varied, fascinating and complex, but without immediate access to investigations can mean that the GP has to cope with a lot of uncertainty. On the other hand, there is a lot of administrative work and bureaucracy. There will be information from the out of hour's services indicating whether patients need follow up. After each consultation, you will have to write a short summary of everything that happened in the consultation (this normally takes a few minutes) to ensure continuity of care. The majority of lunch can be (but not usually) taken up looking through patient pathology results, updating medical records and writing referral letters.

Most GPs work as independent contractors to the NHS, often within small partnerships. This means that GPs must deliver all of the elements of the GP contract and are paid according to a combination of the number of patients on their registered list, the range of services offered, and the quality of services offered. The quality and outcomes framework (QOF) is a voluntary incentive scheme for practices which measures the quality of services offered to patients. Points are awarded for achieving targets in four domains. These are: clinical care, organisational, patient experience and additional services. Each domain has many specific targets within it *e.g.,* proportion of diabetics for whom good control of blood pressure, cholesterol and glucose is achieved.

GPs in this system are entitled to NHS benefits such as the NHS pension scheme. Practices are mostly run as small businesses so you are not paid a salary but take a share of the profits of the business. Profits for the average GP are in line with the top of the consultant salary scale but will vary according to achievement of the factors listed above and keeping the expense of running a practice (largely staff) down.

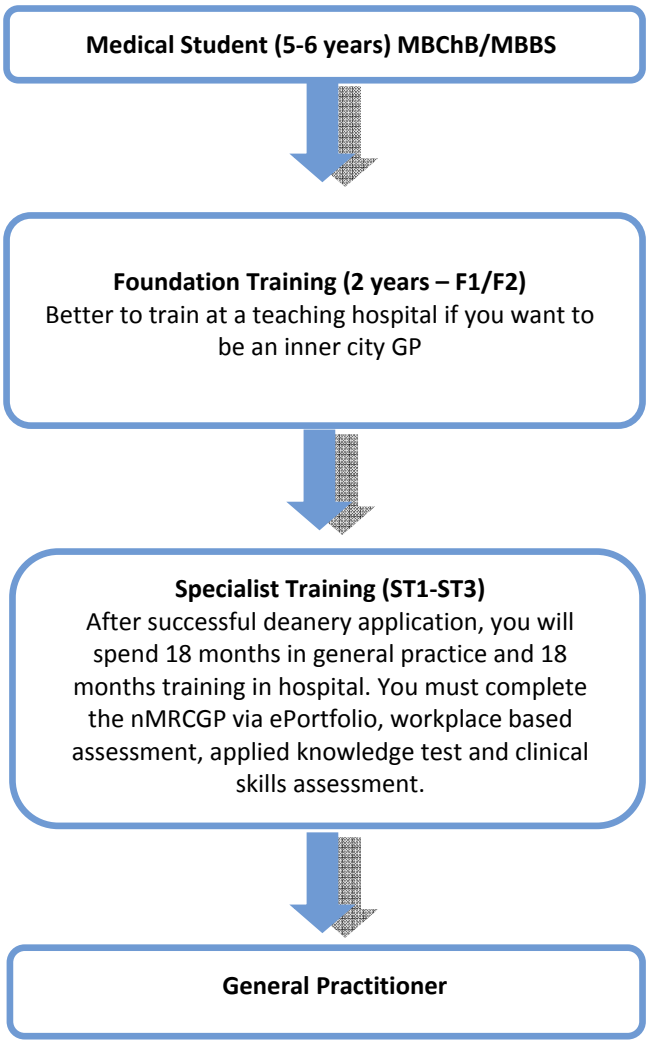
Some GPs work as 'salaried GPs' for a practice and salaries vary between £53K and 81K.

Working in the private sector as a GP in the UK is rare but isn't very different when compared to working within the NHS. This is because the facilities provided are generally the same in a primary care setting. The main differences are seen in the support given. Private practice does not necessarily guarantee the same support for professional development and a full-time private GP does not have access to the NHS pension. As a result, the few GPs who work in private practice only tend to work part-time with the rest of their time spent in standard NHS GP practice.

The application process has three stages once you have completed the foundation programme. There is an electronic assessment which determines eligibility. If successful, applicants are invited to take part in stage 2 assessment against the national person specification to determine if the minimum required standard is met, this is a computer based assessment which includes clinical problem solving and professional judgement. Successful candidates are then allocated to a deanery for the final, stage 3, of selection. This is in the form of a simulation exercise and a written assessment, with a strong emphasis on your communication skills.

The Future

Currently there is a huge reconfiguration within the NHS with plans for reform causing much controversy. The current system of strategic health authorities and primary care trusts distributing the budget will end on 31st March 2013. In its place, a national commissioning board and clinical senates will oversee and fund clinician led clinical commissioning groups (CCGs) who will then manage the budget. A new an important role has therefore emerged for GPs, that of health service leader, commissioner of services and innovation within the NHS. There are also plans to further encourage competition in the provision of services. The rationale behind this change is that the government has recognised a need to make the NHS more efficient and save money due to the economic downturn and an ageing population demographic. This has also raised concerns that GPs will be taking on a responsibility that they don't necessarily want. Furthermore, these changes could lead to redundancies in hospital trusts and shift of services traditionally delivered in hospitals to community (by GPs or often consultants in the community) which could place added strain on GPs ability to maintain a high standard of care.. Encouraging private practice should, in theory, help to drive standards of care by creating competition which may off-set the increased demands but there are concerns that private health organisations will only take the low risk, high profit areas of healthcare leaving the 'traditional' NHS to cope with the rest. These are certainly exciting times to be a GP in the NHS.


Medical Student (5-6 years) MBChB/MBBS
Foundation Training (2 years – F1/F2)
Better to train at a teaching hospital if you want to be an inner city GP
Specialist Training (ST1-ST3)
After successful deanery application, you will spend 18 months in general practice and 18 months training in hospital. You must complete the nMRCGP via ePortfolio, workplace based assessment, applied knowledge test and clinical skills assessment.
General Practitioner

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A Career in Rheumatology

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Introducing Rheumatology

Rheumatology is a medical specialty that is concerned with diseases of the musculoskeletal system the remit of which includesdealing with pathology that affects joints and associated structures as well as muscles and soft tissues. Rheumatic conditions are extensive and challenging to treat not only because of the range of pathological processes involved and the many different ways a disease can manifest, but also because of their significant effects on the patients' quality of life which can render them unemployed and this, in turn, has far reaching consequences (i.e. if they are the sole bread winner for example). Rheumatological conditions can be debilitating illnesses and are a considerable cause of morbidity.

Many of the conditions that a rheumatologist deals with involve autoimmune processes, such as Rheumatoid Arthritis (RA). However, since a lot of rheumatological diseases affect multiple organs, an understanding of the other systems of the body is essential. For example, Systemic Lupus Erythematosus (SLE) has profound effects on the kidneys, skin, heart as well as joints, so it is easy to appreciate how one disease may present in many diverse ways.

Inflammatory conditions are common in rheumatology so understanding and managing conditions that fall under this remit, such as inflammatory arthritis and vasculitis to name but a few, will be frequent occurrences. Also overseeing the care of patients who suffer from metabolic bone diseases such as osteoporosis and soft tissue conditions such as fibromyalgia will also be a rheumatologist's responsibility.

Many genetic conditions such as Marfan's syndrome and heamochromatosis are also encountered by a rheumatologist due to the underlying pathogenesis of these conditions involving the basic components that make up much of the musculoskeletal system. For example, Marfan's syndrome is a disorder of collagen and thus it manifests in various ways such as hypermobile joints which means it warrants rheumatology input.

From the above it is clear how broad the range of diseases encountered by a rheumatologist is and for that reason it could be said that this is one of the enduring fields in medicine where one has the opportunity to practice as a generalist which entails having a holistic approach to looking after the patients.

Life as a Rheumatologist

A majority of the practising rheumatologist's time will be spent working with patients in the outpatient department. Clinics are very busy with both new and follow up patients to see. A rheumatologist will encounter a whole array of conditions that range from Osteoarthritis to SLE. Typically, rheumatologists do 5 - 6 clinics per week with 5-7 new patients or 10-14 follow up patients in each session.

They will also have in-patients on the wards even though most hospitals don't have a ward that is exclusively dedicated to rheumatology. Patients admitted to hospital with new or existing rheumatological conditions that need rheumatological review can be referred to the rheumatology department and they can be seen urgently. Moreover, many cases of Pyrexia of Unknown Origin (PUO) require a rheumatologist's opinion because they are an expert in a whole array of different diseases – much like the cases seen in episodes of the hit TV series "House" and indeed those medics who find the investigative process that is embodied in the protagonist of this series (the so-called 'diagnostician') fascinating need look no further than the field of rheumatology. Some rheumatologists who have undertaken additional medical training usually contribute to the medical on call rota. Thus they are able to provide additional

rheumatological input when required during acute medical admission. Alternatively, patients can be referred to be seen in the out-patient clinics.

Overall, a rheumatologist's day consists of clinics, administrative work, seeing ward referrals, ward round, clinical meetings (X-ray meetings or MDT meetings with colleagues in renal, immunology, or respiratory) and teaching both trainees and medical students.

The vast majority of consultants (in common with consultants in all other specialties) will work considerably longer hours than 9am to 5pm, Monday to Friday.

Rheumatologists work very closely with other specialities and to name just a few they include:

- **Specialist nurses** when collaborating long term care
- **Radiologists** because expert help is needed when interpreting the pathological effect conditions have had on the radiographs of bones and various organs
- **Orthopaedic surgeons** when considering joint replacements, for osteoarthritis for example, when medical therapy has failed
- **Respiratory, dermatology, immunology and renal physicians** when collaborating care of these systems when they have been affected by a rheumatological condition
- **Physiotherapists** if a condition has affected patients in such a way that requires them to obtain help in order to regain mobility or reduce symptoms *i.e.,* ,Ankylosing Spondylitis (AS).

Although working on an outpatient basis means there is a lot of paperwork to deal with, it is no worse than any other speciality. Most of the administrative work is based around referrals to other specialities, contacting patients and their GPs because the chronic nature of many rheumatological conditions requires long term follow up care both in the community and in secondary health care settings.

Given that most rheumatological conditions are chronic, one of the most enjoyable aspects of working as a rheumatologist is the relationship that is built up with patients. The ability to help someone regain their mobility or improve control of their pain can be such a rewarding experience and seeing the dramatic changes in a patient's quality of life is something all rheumatologists relish. Moreover, being in such close contact with many other professionals, keeping up to date with all fields of medicine and connecting (no pun intended!) rheumatology to almost all specialities is another fantastic aspect of this job. Another exciting aspect of rheumatology is the thrill you get from diagnosing rare and confusing diseases and from the problem solving skills that are employed to formulate a diagnosis. For example, the eponymous condition Susac's syndrome is very rare, but when it does present, it is usually with bizarre symptoms such as hearing loss and retinal artery occlusion and a rheumatologist's job is to recognise the pattern.

The opportunity for flexible working in rheumatology is excellent with the possibility of part time work even at a consultant level.

The many new and exciting developments in rheumatology treatments means there is ample opportunity to get involved in research and there is a huge potential to have an international reputation. Should you wish to pursue an academic route, you may be able to work out the underlying pathological processes of diseases, attend international conferences and present research findings and potential novel therapeutics.

Most rheumatologists have a specialist interest that vary from unexplained presentations of rashes to the rheumatic presentation of hepatitis C, but it isn't the norm to exclusively practice these. However, some other specialities such as rehabilitation or sports medicine may be regarded as subspecialties of rheumatology as they also work very closely with musculoskeletal disorders.

One of the advantages of working in rheumatology is that on call shifts are infrequent, but some rheumatologists can spend time on call as part of the general medicine rota if they have additional general medical training. The work life balance for a full time rheumatologist is better than some other specialties which can make it an ideal career for those interested in having a family or who have other commitments outside of medicine.

Earning potential during a career in rheumatology as a consultant is between £74000 and £100000. Although there are some opportunities to work privately, it is not something that is in a lot of demand which is one reason why most rheumatologists don't earn more than the average expected for a NHS consultant.

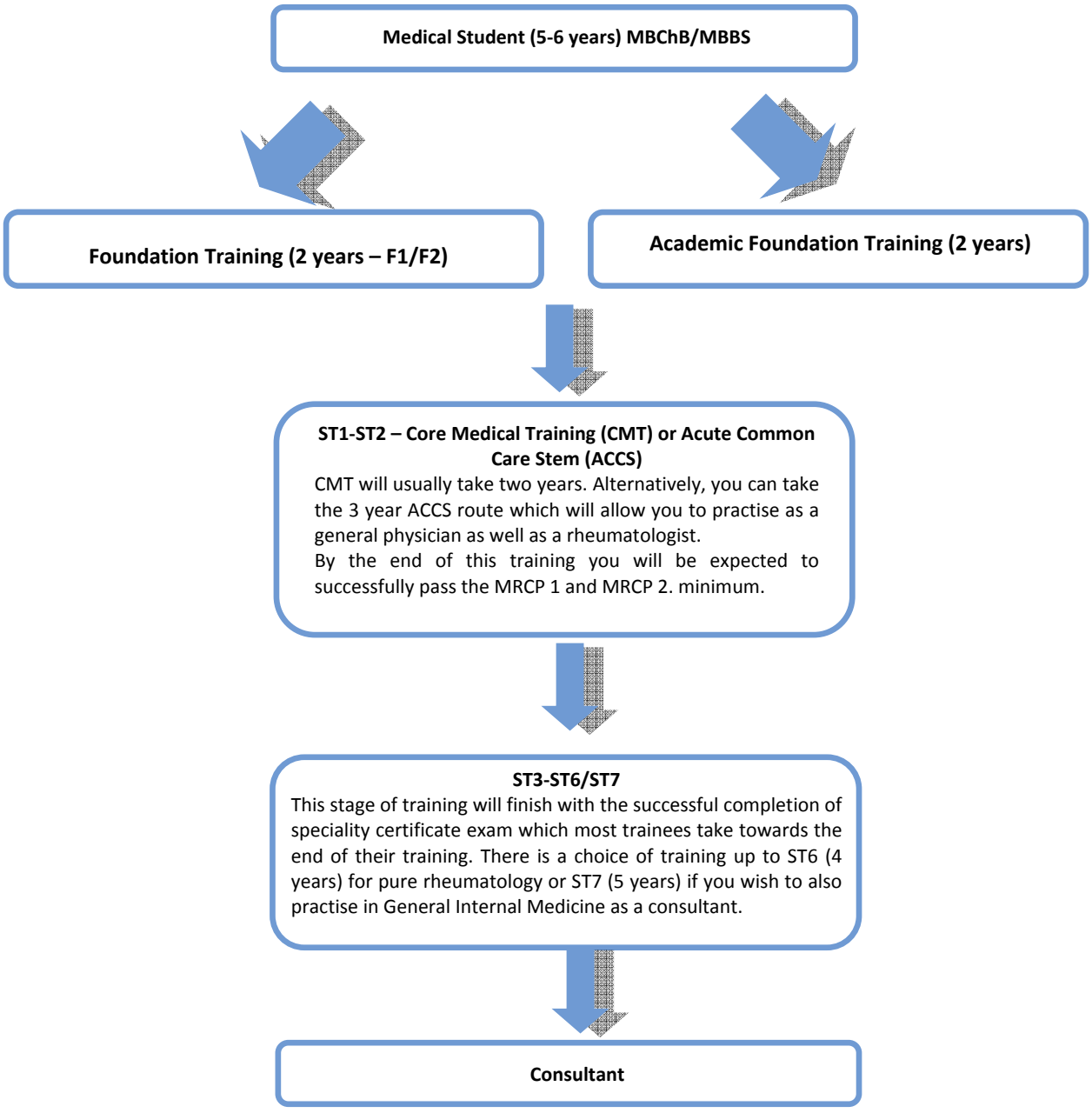
Facts and Figures

There is considerable demand for rheumatology expertise. Currently there are over 470 consultants and 210 trainees working in the specialty and it is one of the rare specialities where there is a relative balance between the number of people training and the number of consultant posts available[5].

Recent and Future Developments

An area in rheumatology that has received a lot of attention in the recent years, due to the potential for controlling many symptoms experienced by patients, is the use of biological agents to treat inflammatory conditions such as RA. One of the major advances that have been made in this field is the use of disease modifying anti-rheumatic drug (DMARD) anti–TNF which have been shown to decrease the inflammatory process that drives many rheumatological conditions. For example, the drugs Infliximab and Enercept are used at the moment for patients who are not responding to disease modifying agents, such as Methotrexate and Sulfasalazine, and so far, these biologics have been very promising. New drugs that are being researched focus on using antibodies to antagonise the key mediators in inflammation and examples include interleukin inhibitors and tyrosine kinase inhibitors. These block the effect and production of many inflammatory mediators and thus combat the underlying pathological problem in conditions such as psoriasis, psoriatic arthritis and AS. The key challenge will be to identify how to integrate these advanced therapies into the clinical setting and tailor the treatment to the specific needs of each patient.

Training



Bibliography:

1. Rheumatology – Approved Curriculum and Associated Assessment System 2010. General Medical Council. Available [online]: http://www.gmc-uk.org/education/rheumatology.asp
2. Speciality Training Curriculum for Rheumatology. Joint Royal Colleges of Physicians Training Board. Aug 2010. Available [online]: http://www.gmc-uk.org/Rheumatology_Curriculum_040510_V0.16.pdf_32486223.pdf_43572851.pdf
3. London Deanery – Rheumatology ST3. Available [online]: http://www.londondeanery.ac.uk/var/recruitment/specialty-recruitment/2012-recruitment-adverts-jun-2012-dec-2012/rheumatology-st3
4. Rheumatology. Joint Royal Colleges of Physicians Training Board. Available [online]: www.jrcptb.org.uk/trainingandcert/st3-spr/pages/rheumatology.aspx

Abstracts from The International Academic and Research Conference

20th August 2012, University Place, University of Manchester

ORAL PRESENTATIONS

Does cardiomyocyte-specific deletion of the Plasma Membrane Calcium ATPase (PMCA) pump alter micro-RNA expression in heart failure?

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Background: MicroRNAs are newly discovered small non-coding RNAs that can regulate hypertrophic gene expression at the post-transcriptional level through targeted mRNA 'silencing' in heart failure. Abnormal Ca^{2+} handling impairs cardiac function and our research group has shown that deletion of the calcium extrusion pump, plasma membrane Ca^{2+} ATPase1 (PMCA1), leads to dilated cardiomyopathy and heart failure. This study aims to determine whether deletion of PMCA1 leads to altered microRNA expression in heart failure.

Methods and Results: PMCA1 cardiomyocyte-specific knockout ($PMCA1^{cko}$) mice were generated using Cre/LoxP technology. A microarray plate revealed a number of microRNA changes in $PMCA1^{cko}$ mice (n=5) compared to $PMCA1^{loxp/loxp}$ (controls) (n=7) which, by reverse transcription and qPCR, confirmed a marked down-regulation ($p<0.05$) of miRNAs let7e (75%), let7i(50%), 101 (76%), 101a(61%), and 93(57%). $PMCA1^{cko}$ and $PMCA1^{loxp/loxp}$ mice were subjected to haemodynamic stress by transverse aortic constriction (TAC) inducing cardiac hypertrophy. After TAC, $PMCA1^{loxp/loxp}$ mice demonstrated a downregulation of mir-101a by 50% ($p=0.06$) compared to sham operated $PMCA1^{loxp/loxp}$ mice but there was an overexpression by 61% (<0.05) in the PMCA1cko mice (n=3). Rcan1.4, a marker of NFAT activity, was upregulated (>300%) in $PMCA1^{cko}$ mice (n=7) under basal conditions.

Conclusions: Deletion of PMCA1 has been shown to directly or indirectly regulate transcription of microRNAs let7e, 7i, 101, 101a and 93, whilst under pathological hypertrophic conditions, deletion of PMCA1 leads to upregulation of miR101 and 101a. Initial studies suggest MicroRNAs 101 and 101a may regulate pathological hypertrophy through suppression of the calcineurin-NFAT pathway, one of the most well characterised pathways in heart failure.

Pioglitazone acts on L-type calcium channels causing vasodilatation in porcine coronary arteries.

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Background: Pioglitazone is an oral hypoglycemic agent used to lower blood glucose in patients with type II diabetes. Pioglitazone activates PPARγ, a nuclear hormone receptor involved in DNA transcription regulation, enabling recovery of insulin sensitivity, particularly in adipose tissue. Moreover, pioglitazone cause vasodilatation which is desirable in diabetics due to their increased risk of atherosclerosis. This investigation looks into the mechanism of pioglitazone-mediated vasodilatation in porcine coronary arteries.

Methods: Coronary artery segments were contracted using a thromboxane mimetic and subsequently exposed to pioglitazone. Vasodilatation was measured using isometric tension recording.

To determine the mechanism behind the pioglitazone-mediated vasodilatation, pathways suspected of being involved were blocked to establish whether this inhibited relaxation. We inhibited PPARγ, potassium channels, NO synthase, AMP kinase, Rho kinase, L-type calcium channels, removed endothelium and removed extracellular calcium.

Results: Inhibition of PPARγ, potassium channels, NO synthase, AMP kinase, Rho kinase and removal of endothelium failed to significantly inhibit the vasodilatation, indicating that relaxation was independent of these pathways. A two-way ANOVA showed that depletion of extracellular calcium significantly inhibited vasodilatation by 36% when compared to a control ($p<0.001$). Moreover, exposure to 0.1µM nifedipine, an L-type calcium channel blocker significantly inhibited vasodilatation by 34% ($p<0.0001$).

Conclusion: Pioglitazone causes vasodilatation by blocking the influx of extracellular calcium through L-type calcium channels.34% of vasodilatation was inhibited indicating that pioglitazone must also act through other pathways. In addition to reducing the risk of atherosclerosis, "off-target" calcium channel blockade makes pioglitazone beneficial to hypertensive diabetic patients since it lowers blood pressure.

Assessment of arterial stiffness indices in stroke survivors

Al-Ansari S; Mistri AK; Robinson TG*
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Background: Arterial stiffness is an independent predictor of stroke and carotid-femoral pulse wave velocity (cfPWV) is considered the best measure of arterial stiffness. PWV can be estimated by simultaneous non-invasive assessment of the arterial pulse waveform at two sites using a cuff-based oscillometric device (Vicorder). PWV is an important determinant of cardiovascular risk. However, only a small number of studies have examined PWV in people with cerebrovascular disease (CVD).

Objectives: This study aimed to establish reference values for PWV in people with CVD, and to compare PWV in this group with a group of age-and sex- matched healthy volunteers (HV)

Methods: Patients with manifest CVD and HV were recruited from outpatient stroke clinics, rapid-access TIA clinics and Acute Stroke Units in Leicester, UK. Casual BP was estimated using the Omron BP monitor. cfPWV and brachio-femoral PWV (bfPWV) were estimated using a standardised protocol (Vicorder).

Results: PWV was measured in 33 CVD patients (mean age 64±8) and 42 HV (mean age 62±8). The mean resting BP was similar (CVD:132/78, ±21/14, HV:130/78, ±15/10). There was no significant difference in cfPWV (CVD:7.66, ±1.73, HV:7.44, ±1.52;p=0.77) or bfPWV (CVD:14.38, ±5.58, HV:11.98, ±3.24;p=0.18) between the two groups.

Conclusion: Although there was no statistically significant difference in PWV between CVD and HV groups, our study suggests that bfPWV may be higher in those with CVD, while the accepted gold standard "cfPWV" was similar in both groups. Further research is warranted to identify if bfPWV is increased in CVD and to clarify the prognostic value of PWV.

An explorative study into the role of midwives in future efforts to eradicate Female Genital Mutilation in Sudan

Anderton C
University of Leeds, West Yorkshire, UK

Background: Female genital mutilation (FGM) refers to 'all procedures involving partial or total removal of the external female genitalia for non-medical reasons.'[1] It is considered a cultural tradition and in Sudan 69% of females are affected[2], with high complication rates. Midwives perform most FGMs in Sudan[3] and many past NGO and Governmental efforts were aimed at midwives. However, progress has slowed, and lack of direction has lead to the gradual abandonment of many of these initiatives.

Methodology: The study was set in Khartoum state, Sudan, May 2012.12 midwives and 6 relevant stakeholders were interviewed using semi-structured one-to-one interviews.

Findings: Knowledge of FGM complications among midwives was high, with most learning from midwifery school or an education programme. Main reasons to practice FGM included income, demand from society and tradition. Barriers to stopping practicing were subsequent lack of income, demand from society and confusion over the current law. Suggestions to support midwives in stopping FGM included changes to the law, provision of employment from the Government, as well as suggestions for NGOs such as micro-finance, and advocacy and raising awareness.

Conclusions: My findings revealed past efforts to educate midwives about FGM have been largely successful, but there are several other influential factors such as income which play an equally large role. Any change in the law is unlikely due to the current political situation. My suggestions are therefore aimed at National and International NGOs and include awareness raising and education of the public, and better support for midwives stopping FGM.

The concurrent association between mood disturbance and disease status in patients with Ankylosing Spondylitis (AS)

Cooper-Moss N; Packham J; Strauss VP*
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Introduction: Depression and anxiety are recognised as common features in patients with chronic inflammatory conditions, such as Rheumatoid Arthritis. Few studies, however, have focussed on the prevalence and overall impacts of mood disturbance in AS. This study therefore aimed to investigate the combined effect of depression and anxiety on several aspects of AS severity.

Methods:605 participants in a UK cohort of patients with diagnosed AS (EASi-QoL) were included. Sociodemographic and disease-related variables were collected [pain (numerical rating scale), disease activity (Bath AS Disease Activity Index), and physical function (Bath AS Functional Index)]. Mood disturbance was measured by the Hospital Anxiety and Depression Scale.

Results: The majority of responders were males (72%), with a mean age 51 (SD 12). 298 patients (49%) reported mood disturbance. Among these, 166 (56%) demonstrated a co-existence of depressive and anxious symptoms; 27 (9%) had depressive symptoms only and 105 (35%) had anxious symptoms only. After controlling for sociodemographic factors, greater disease activity was most strongly associated with mixed anxiety and depression (OR 7.66, 95% CI 4.10-14.30). Similarly, there were significant independent associations of mixed depression and anxiety with poor function (OR 5.91, 95% CI 3.17-10.99) and increased pain (OR 4.76, 95% CI 2.56-8.86).

Conclusion: This study drew attention to the high prevalence and frequent co-occurrence of depression and anxiety in patients with AS. Findings suggested that AS patients with co-morbidity of depression and anxiety had poor disease status. Both anxiety and depression should be considered in planning care for AS patients in clinical practice.

Awareness of Breast Self Examination among Sudanese female medical students January-April 2012

Idris AT; Elhasani FM; Eltom ME; Diab SM; Suliman AM; Abdelgadir EE; Husain NEO
Omdurman Islamic University, Sudan

Together with cervical cancer; breast cancer represents fifty percent of cancer incidence in Sudan. It is detected in late stages due to lack of awareness and screening programs. Breast Self Examination (BSE) plays a major role in early detection of the disease, and hence increasing the chances for survival. Medical students should take part in breast health education in the society.
This study is aimed to explore knowledge, attitude, and practice among Sudanese female medical students towards BSE.

This is a cross-sectional, descriptive, analytical, institutional based study. A stratified random sample of 363 female students from faculties of medicine in Khartoum state were questioned regarding awareness of BSE via a pretested, pre-structured questionnaire by well trained volunteers. Questions related to BSE, breast cancer, and awareness about screening program were asked. Ethical clearance was obtained from the ethical committee of each faculty, and informed consent was taken from each student.

The mean score of knowledge is 6.9/11, (4.6 for juniors, and 8.9 for seniors).There is a significant effect of positive family history of breast cancer on knowledge score (P value =0.001). A number of 187 (49%) students perform BSE, but only 85(23.4%) of them perform it monthly. The vast majority (95.8%) rated BSE as important for early detection of breast cancer.

There is a strong effect of academic experience on knowledge, attitude and practice of BSE among Sudanese female medial students. Awareness about BSE is expected to increase by early introduction of health education in the curriculum.

Clinical and Biochemical features of Sporadic and Hereditary Phaeochromocytomas and Paragangliomas.

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Currently 33% of phaeochromocytoma and paraganglioma are reported to be hereditary .Though genetic testing enables the identification of hereditary patients, various issues have prompted the search for additional ways to help distinguish between hereditary and sporadic cases. In this study, the clinical and biochemical features of sporadic (44) and hereditary (33 mutations in SDHD, B, VHL, RET and NF-1) phaeochromocytoma and paraganglioma patients were compared .Patients were identified via multidisciplinary database searches and assigned to the hereditary group on the basis of a positive genetic test in any of the known susceptibility genes. Whilst, sporadic patients were classified on the basis of a negative family history, no clinical evidence of a hereditary syndrome and a negative genetic test if available. Findings of statistical significance included: a lower mean age of diagnosis (33.2± 18.1 vs 45.1± 19.2) , a higher percentage of bilateral tumours (35.7% vs 3.40%) and a smaller tumour size (59.4±31.5 vs 33.1± 18.6mm) in the hereditary group when compared with sporadic group. Other findings included: higher rates of multiple tumours and malignancy in the hereditary group. Meanwhile a wide range of symptoms and catecholamine phenotypes were reported in both groups but hypertension and hypersecretion of noradrenaline respectively were the commonest.

Overall, these results suggest significant differences in age, tumour size and bilateral phaeochromocytoma do exist between both groups and knowledge of this information may be useful in distinguishing between cases. As for the other features, the trends noted provide general information concerning these rare tumours.

Development of a recombinant virus assay for the evaluation of drug resistance mutations in the reverse transcriptase gene of the Human Immunodeficiency Virus type 2

Folkard S; Willems B; Fransen K; Vanham G; Janssens W; Jones S; Jallow S
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Knowledge of the clinical relevance of drug resistance mutations is vital for optimal anti-retroviral therapy (ART) selection and can be reliably determined only by phenotypic resistance assays. Recombinant virus assays are quick, cost effective and show low inter-assay variability. Whilst these are widely available for resistance testing for HIV-1, none have previously been developed for HIV-2 which is found predominantly in West Africa. HIV-2 infection poses particular problems for therapy, as the virus is intrinsically resistant to both non-nucleoside reverse transcriptase inhibitors and fusion inhibitors. Potential genotypic resistance mutations to antiretroviral therapy have been identified in the reverse transcriptase (RT) gene of HIV-2, but the clinical relevance of these is currently unknown. We aimed to develop a recombinant virus assay using two components: an HIV-2ROD deletion vector lacking the protease and RT regions of the pol gene and a PCR amplicon coding for the protease and RT region containing the mutations of interest. Electroporation protocols were optimised using the HIV-1 molecular clone pNL4-3. Following electroporation of both components into human T4-lymphoblastoid cells, an RT assay was used to determine the success of recombinant mutant HIV-2ROD generation. Such a recombinant virus assay would allow evaluation of phenotypic drug resistance as well as cross-resistance. This would inform the selection of suitable drugs for salvage therapy, further improving the management of HIV-2-infected patients. The clinical relevance of HIV-2 resistance mutations will be increasingly important as RT inhibitor use becomes more widespread following the increasing availability of ART, especially in West Africa.

Effects of sympathetic nerve stimulation on cardiac electrophysiology in Long QT syndrome 1

Gupta A; Brack KE; Ng AG
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Introduction: Long QT syndrome 1 (LQTS1) is a life threatening cardiac condition arising from reduced activity of the slow activating delayed rectifier potassium channel (IKs), where mortality is associated with surges in sympathetic tone. Symptoms occur due to broad complex tachycardia, which degenerate into ventricular fibrillation (VF) and sudden cardiac death. Mechanisms underlying SCD are not understood but may relate to alterations in ventricular repolarisation. The aim of this study was to examine the effects of sympathetic nerve stimulation (SNS) on effective refractory period (ERP) and inducibility of VF in a pharmacological model of LQTS1.

Methods: The novel innervated heart preparations from adult male guinea pigs (n=6, 450-550g) were used. ERP was measured using a single extrastimulus protocol. Inducibility of VF was investigated using ventricular fibrillation threshold (VFT) with burst pacing. ERP and VFT were measured at baseline (BL), and SNS (3Hz,1V) during periods of control and in the presence of the IKs blocker N-[(3R,4S)-3-hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-N-methylethanesulfonamide (HMR1556). Data are mean+SEM, analysed using Students T-Test. * P<0.05 vs. BL and vs. Control

Results: During control, SNS significantly reduced ERP and VFT (Table). In the presence of HMR1556, the effect of SNS on ERP and VFT was augmented.

	Control			HMR 1556		
	BL	SNS	Change	BL	SNS	Change
ERP (ms)	104+5	93+6**	11+2	130+4	101+3**	29+6*
VFT (mA)	4.2+1.2	2.9+0.9*	1.42+0.5	4.2+1.1	1.3+0.5*	3.2+1.1*

Conclusion: LQTS1 is associated with increased susceptibility to VF during SNS, which is directly related to changes in ventricular repolarisation.

A new tool for assessing the pattern of branching of the cerebral vasculature. Relevance for Alzheimer's disease.

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Accumulation of the protein amyloid-β (Aβ) in the brain is a major feature of Alzheimer's disease. Cerebral amyloid angiopathy in AD reflects an age-related failure of elimination of Aβ from the brain along perivascular drainage pathways. In this study we test the hypothesis that the histological profile of basement membranes in cerebral arteries changes with advancing age and disease process.

Immunocytochemistry with collagen IV was performed on 10 sections of brains with AD and 10 age matched controls. The sections were from the frontal and occipital cortices. Slides with human tissue from the Brain Tissue Resource in Newcastle (http://www.ncl.ac.uk/iah/campus/facilities/nbtr/) were used. We then developed image processing tools to automatically differentiate between normal sections and those from subjects with AD.

The immunostaining for collagen IV is more intense in brains with AD compared to controls. There appear to be more branches of the microvasculature in brains with AD. The functional consequences of these changes most likely will result in alterations of perivascular drainage that lead to failure of elimination of Aβ and alteration of the homeostasis, neuronal dysfunction and dementia. We can now differentiate successfully between the images from normal subjects and those with AD. This is achieved by analysis of the cells present in the image and their structures, especially their branching structure.

These results argue well for future development that uses clinical images from patients at differing stages of AD. As such, we have a new approach to analysing the cerebral vasculature with regard to early diagnosis of AD.

Conclusion: Pioglitazone causes vasodilatation by blocking the influx of extracellular calcium through L-type calcium channels.34% of vasodilatation was inhibited indicating that pioglitazone must also act through other pathways. In addition to reducing the risk of atherosclerosis, "off-target" calcium channel blockade makes pioglitazone beneficial to hypertensive diabetic patients since it lowers blood pressure.

A comparative study of quality of life in irritable bowel syndrome and inflammatory bowel disease

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Background: This study aimed to determine the impact of irritable bowel syndrome (IBS), a functional disorder, and inflammatory bowel disease (IBD), an organic disorder, on health-related quality of life (HRQoL), and the mechanisms by which this occurs.

Methods: 187 gastroenterology outpatients (IBS: 96, IBD: 91) completed the measure yourself medical outcome profile (MYMOP) and various disease-specific HRQoL and symptom instruments. Questionnaires were mapped to determine parallel concepts in IBS and IBD and data re-coded to enable comparative analysis. MYMOP, HRQoL and symptom data were compared via Mann-Whitney U or t-tests and proportions of patients with particular symptoms via chi-squared. Logistic regression analysis was conducted to compare differences in HRQoL once other factors had been controlled for.

Results: Overall HRQoL was worse in IBS (mean: IBS=46, IBD=67, $p<0.001$), as was emotional and social HRQoL. Bowel function was similar, with certain gastro-intestinal symptoms more prevalent in IBD. Chi-squared and logistic regression analysis demonstrated that patients with IBS were significantly more likely to report psychosocial problems, such as embarrassment, depression, lack of sympathy from others and diet affected by bowel problems. Patients with IBD were significantly more likely to report physical symptoms, such as incontinence, urgency, difficulty sleeping and bloating.

Conclusion: HRQoL is significantly worse in IBS, with social and emotional reductions accounting for the difference. Despite this, bowel function is equivalent, or slightly worse in IBD. This study has demonstrated that the mechanisms by which IBS and IBD affect HRQoL differ, with GI symptoms alone not accounting for the impacts of IBS.

Validation of 3 letter and 5 letter per line computerised visual acuity measurements using COMPlog against ETDRS measurements in subjects with AMD

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Introduction: Age-related Macular degeneration (AMD) is the leading cause of visual loss in the industrialized world, and its prevalence has been projected to double by the year 2020. AMD affects the macula, often creating a central scotoma.
Accurate and repeatable visual acuity (VA) measurements are important in monitoring disease progression and treatment efficacy. ETDRS charts are considered the 'gold standard' tests for VA and employ 5 letters per line. The COMPlog computerised VA measuring system, relies on a 3 letter per line assessment. Its advantages include the ease of use, shorter test distances, and an automated scoring system.

Aims: We aimed to determine whether electronic COMPlog measurements agree with those of the 5 letters per line ETDRS charts in patients with AMD.

Method: Timed test and retest VA measurements were taken using 3 and 5 letters per line on COMPlog and the ETDRS charts in random order in 50 patients with wet AMD. Bland and Altman methods were employed.

Results: No significant bias and similar test-retest variability was observed in the computerised 3 and 5 letter per line VA measurements compared to the ETDRS chart. Median test times were 92, 71.5 and 131.5 seconds for ETDRS and COMPlog 3 and 5 letters per line respectively.

Conclusions: The preliminary data is suggestive that COMPlog measurements agree well with and are similarly reliable to the ETDRS chart. In patients with AMD, the use of 3 or 5 letters per line did not appear to affect VA scores although test times are shorter with 3 letters per line.

Presence of autoantibodies in patients with glioma

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Gliomas comprise an aggressive group of heterogeneous neoplasms with dismal survival. Vague initial symptoms and late focal onset predisposes delayed diagnosis with subsequent poor prognosis. Invasive biopsy and current diagnostic challenges emphasise the need to identify novel, specific and non-invasive early-diagnostic techniques. The detection of tumour-associated antigens (TAAs) in patient sera well before symptom onset indicates that autoantibodies may prove a promising diagnostic measure.

High throughput (HTP) antigen production techniques were employed to successfully produce 9 new recombinant TAAs. Sera from adult patients with glioma (n=61) and age, sex and smoking status matched normal controls were collected. Analysis of sera by ELISA tested for the presence of IgG autoantibodies against 22 TAAs (the 9 produced in this study alongside a further 13 antigens produced in-house).

Autoantibody responses towards SOX11, SSX-2, HER-2 ICD and MMP-7 were significantly raised in gliomas compared with matched controls. A six antigen diagnostic panel including the four significant antigens alongside SOX9 and SOX13 elicited 31% sensitivity with 94% specificity (n=61). Additionally, a low-grade (n=17) specific panel comprised of p53 and GFAP, demonstrated 29% sensitivity and 98% specificity.

Autoantibodies to some TAAs are significantly raised in individuals with glioma compared with matched controls. The diagnostic panel described has great promise but further validation is warranted. Its future use may be indicated in screening genetically susceptible patients. Validation of the low-grade specific antigen panel and the identification of a high-grade panel would facilitate a more precise grading and prognostic measure.

Temporal and Spatial Distribution of Matrix Metalloproteinase -2 and its Role in the Pathogenesis of Pre-eclampsia

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Background: Matrix metalloproteinase (MMP)-2 and MMP-9 degrade components of the extracellular matrix and have been implicated in impaired trophoblast invasion in pre-eclampsia (PE). The purpose of this study was to investigate expression of MMP -2 and -9 mRNA in placentae from healthy, PE and IUGR pregnancies, and to elucidate the expression of MMP-2 protein in a gestational series of placentae.

Methods: MMP-2 and MMP-9 mRNA were quantitated using real-time PCR in third trimester placental tissue samples from healthy pregnancies (n=37) and those affected by PE (n=22) and IUGR (n=12). Immunohistochemistry and a weighted histoscore method were used to determine the expression patterns of MMP-2 in placentae from 7-17 weeks' and 34-41 weeks' gestation.

Results: There was no difference in levels of MMP-2 (p=0.75) or MMP-9 (p=0.20) expression between control, PE and IUGR placentae. MMP-2 was greater than MMP-9 mRNA expression in all samples. Median fold expression of MMP-2 relative to MMP-9 was 73.8 (95% CI 58.6–91.8).

A negative correlation between MMP-2 protein expression and gestation in endothelial cells (rs=-0.43, p=0.025) and a trend towards a negative correlation between MMP-2 expression in trophoblasts (rs=-0.33, p=0.093) and gestation were observed.

Conclusions: Placental MMP-2 expression appears to decrease throughout gestation. While we did not find evidence of a difference in MMP-2 or MMP-9 mRNA expression between PE, IUGR or healthy third trimester placentae, this may not reflect in situ MMP activity. Reduced trophoblast invasion in PE may depend on the balance between MMP and TIMP expression, an area which warrants further investigation.

Diagnostic benefit of using 6 lead ECG compared to pulse check alone in high risk population with Silent AF

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Background: Atrial fibrillation (AF) is a major risk factor for ischaemic stroke yet the risk can be dramatically reduced if detected and treated with anticoagulation therapy. Up to one third of AF patients may be asymptomatic. Importantly, this silent variant of AF exhibits a similar stroke risk. AF is commonly detected by an irregular radial pulse rhythm. This method fails to detect silent AF and also causes unnecessary ECG referrals due to ventricular ectopy. However, 6 lead ECG detects silent AF and ventricular ectopy yet is less costly and more accessible than 12 lead ECG.

Method: This retrospective study evaluated 6-lead ECG screening in primary care. 7631 patients were screened across 15 practices in Yorkshire. ECGs were analysed by cardiac physicians and confirmed by consultants. The aim was to detect AF prevalence in the over 65 population, particularly in those previously unaware. Furthermore, to compare the AF incidence with ectopy.

Results: Out of 5,733 patients aged over 65, 237 (4.1%) suffered from AF. Of these only 153 were previously diagnosed with AF, therefore 35.45% were newly identified with screening. Also, ectopy was present in 568 (9.9%) patients.

Conclusion: AF screening identified a high number of previously unknown AF cases. Furthermore, the rate of ectopy was great, almost 10%. Hence, 1 in 10 patients would be referred for an ECG for suspected AF, causing anxiety and unnecessary service cost. AF screening using a simplified ECG system not only detects silent AF but also eliminates false positives from pulse checking and therefore allows better stroke prevention.

Cardiac PMCA 1 and 4 are potential targets for future prevention and treatment strategies for heart failure.

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Heart failure is a common and life threatening condition, with a 5 year survival of only around 50%. Plasma membrane Ca^{2+} ATPase (PMCA) genes have been previously linked to human cardiovascular disease, with PMCA 1 recently being linked to hypertension and both PMCA1 and 4 expression being reduced in heart failure. A novel mouse model, cardiomyocyte specific double knockout of PMCA1:4 ($PMCA^{dcko}$), has been generated in order to study the effect of the concomitant reduction of these genes on the cardiac phenotype. To study the role of PMCA1 and 4 in the development of cardiac hypertrophy and heart failure these mice were subjected to pressure overload by surgically constricting the aorta (transverse aortic constriction, TAC) for two weeks.

Normalised heart weight data reveal that the hypertrophic response induced by TAC is attenuated in $PMCA1:4^{dcko}$ mice compared to controls ($p<0.05$), furthermore no signs of heart failure were detected in this group and Masson's trichrome staining revealed reduced fibrosis ($p<0.05$). Molecular analysis revealed that this may be in part due to decreased induction of the hypertrophic Akt pathway ($p<0.05$). This study provides the novel finding that the cardiomyocyte specific deletion of both PMCA1 and 4 in mice protects the heart against TAC induced hypertrophy and fibrosis. This is preliminary evidence for a novel role for PMCAs in the development of heart failure and a potential mechanism in the form of depressed Akt function. These results highlight PMCA1 and 4 as potential targets for future strategies to prevent and treat heart failure.

General Practitioners' experiences of and views towards using ScriptSwitch®: Qualitative study of GPs who trialled ScriptSwitch®

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Background: Increasing prescribing expenditure in the context of limited overall budgets has resulted in general practitioners (GPs) being under pressure to prescribe cost-effectively. The literature shows that GPs increasingly welcome easily accessible drug cost information, identified as a modifiable factor in altering prescribing behaviour.

ScriptSwitch® is an active, electronic decision support tool which delivers "pop ups" within consultations, integrating national and local information including drug costs, cheaper formulary switches, dosage duration optimisation and relevant safety information. Bradford & Airedale Primary Care Trust, which commissions general practice services, recently trialled ScriptSwitch®. This qualitative study seeks to explore GPs experience of, and views towards, using this software to help understand the barriers and facilitators to employing such software to facilitate more cost-effective prescribing.

Methods: A convenience sample of 8 GPs across 5 practices took part in semi-structured one-to-one interviews, which were audio recorded and transcribed verbatim. Thematic analysis was employed to identify emerging themes in the data. Areas covered in the interviews include exploring: the perceived value and influence on prescribing behaviour of the "pop ups"; why ScriptSwitch® use was terminated by some GPs and/or practices; GPs views on potential improvements to such decision-support software to enhance its influence and acceptability.

Results: Full results will be presented at the conference. Early analysis is revealing themes that can be categorised into: contextual; software-related; and impact-upon-consultation factors.

Conclusion: The full results from this in-depth qualitative study will provide insight into the barriers and facilitators to deploying such decision-support software to aid cost-effective primary care prescribing.

Does physical activity improve concentration? A comparison of performance on tasks of sustained attention after active and non-active periods in the school day

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Background: Physical activity has been associated with improved cognitive function in children. The purpose of this study was to investigate if physical activity at lunch breaks and in physical education (P.E.) lessons influence sustained attention of children in school.

Methods: Participants were 20 typically developing children aged 9-10 years recruited from two local primary schools. Each child performed a computerised neuropsychological test measuring sustained attention twice; once after a P.E. lesson or lunch break, and once after an academic lesson. Teachers completed the hyperactivity and inattentive subscale of the Strengths and Difficulties Questionnaire for each participant.

Results: There was a significant interaction between P.E. lessons/lunch breaks and academic lessons ($p<0.05$), showing that physical activity benefits sustained attention. The interaction of sustained attention between hyperactive children with high Strengths and Difficulties Questionnaire scores and less active children with low Strengths and Difficulties Questionnaire scores was approaching significance ($p=0.082$), with physical activity appearing to have a greater benefit on sustained attention in hyperactive children.

Conclusion:Results indicate that physical activity in P.E. lessons and lunch breaks benefit sustained attention in comparison to an academic lesson. Children experiencing hyperactive and inattentive difficulties may benefit from physical activity in these school periods more so than children without these difficulties.

Comparing The Haemodynamic Effects Of Phenylephrine And Pseudoephedrine In Oral Nasal Decongestants, Using Finometry And Pulse Plethysmography

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Background: Sales of oral nasal decongestants containing pseudoephedrine have been legally restricted due to its high abuse potential, regardless of its proven efficacy. Oral phenylephrine was developed as a replacement product, but concerns have been raised over its low bioavailability and hence its value as a nasal decongestant. Both being systemic sympathomimetic drugs, cardiovascular effects are expected upon their administration.

Objective: To monitor the cardiovascular effects of a single dose of Sudafed® (pseudoephedrine, 60mg) and Sudafed® PE (phenylephrine, 12mg) for a revaluation of both efficacy and safety.

Methods: Ten healthy male volunteers ranging from 18-25 years old took part in two sessions; one for the administration of each drug. Administration of either Sudafed® or Sudafed® PE occurred after twenty minutes of baseline recording. The Finometer®, a continuous, non-invasive haemodynamic monitor and the PulseTrace® PCA2 finger plethysmography device were used to record several cardiovascular variables during the baseline twenty minutes and for two hours after drug administration.

Results: On average, pseudoephedrine was found to decrease stiffness index from 6.7m/s to 6.1m/s ($p<0.05$) and increase peak-to-peak time from 277ms to 296ms ($p<0.05$). Phenylephrine increased peak-to-peak time from 240m/s to 259m/s ($p<0.05$) and total peripheral resistance from 1 monitor unit to 1.2 monitor units ($p<0.01$), but decreased heart rate from 65 beats/min to 60 beats/min ($p<0.01$) and cardiac output from 5.5 litres/min to 4.5 litres/min ($p<0.001$).

Investigation into the interaction between Sirtuin expression and Pancreatic cancer

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Aims: The Sirtuin gene family (SIRT1-7) are thought to play a prominent role in cellular ageing and have been associated with cancer pathology. The aim of this study was to establish if there is a correlation between Sirtuin gene expression and clinicopathological factors and patient outcome in pancreatic ductal adenocarcinoma (PDAC).

Methods: Immunohistochemistry was performed for SIRT1-7 on tissue microarrays of tumour cores from 121 PDACs. Statistical analysis was used to compare sirtuin expression with prognostic indicators, and survival analysis was performed to determine association with patient outcome.

Results: Elevated SIRT3 expression was associated with favourable prognostic markers, such as well differentiated tumours ($p=0.012$). In patients who did not receive chemotherapy, low SIRT3 cytoplasmic expression was associated with reduced overall survival (OS) ($p=0.014$,HR 2.23) and disease free survival (DFS) ($p=0.05$,HR 1.95). SIRT4 cytoplasmic staining was higher in low grade tumours ($p=0.022$). SIRT5 expression was elevated in high risk tumours, such as increased tumour stage ($p=0.045$). SIRT7 expression was higher in tumours with low risk prognostic factors, such as low grade and smaller tumour size ($p=0.018$,$p=0.013$). In patients with survival >12 months, low nuclear SIRT7 expression was associated with reduced OS ($p=0.025$,HR 2.07) and DFS ($p=0.014$,HR 2.22). SIRT3 cytoplasmic and SIRT7 nuclear expression were independent of various prognostic markers in influencing survival and recurrence.

Investigating a potential functional single nucleotide polymorphism in the promoter region of the *transferrin* gene; possible involvement with Alzheimer's disease.

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Background: The Oxford Epistasis Project identified an epistatic interaction between single nucleotide polymorphisms at transferrin -2 and hemochromatosis H63D as a risk factor for Alzheimer's disease; causing iron overload, inducing oxidative stress and resulting in neurodegeneration. Whilst hemochromatosis H63D affects blood iron status and transferrin saturation, the functional effect of transferrin -2 remains unresolved. The core promoter region in liver cells is -125 to +1 base pairs.

Methods: Bioinformatics analysis on the sequence flanking transferrin -2 identified our core promoter region of -144 to +89 base pairs, including the single nucleotide polymorphism. This was amplified in homogenous wild type and mutant samples by optimized polymerase chain reaction, cloned into the Dual Luciferase Reporter Gene Assay System and transfected into human brain cells. Measurement of luciferase expression defined promoter activity.

Results: No significant difference was identified between wild type, mutant and negative control activity, indicating that this region did not function as a promoter of gene expression.

Conclusion:Further research identified a region of -164 to +1 base pairs as the core promoter in brain cells, hence a modified system may prove more conclusive; by using an enhancer for less variable results and methods of defining a functional affect on transcription from a translational effect.

The impact of screening on clinicopathological determinants of outcome in colorectal cancer in the West of Scotland

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Background: There has been limited investigation of the tumour pathological and host-related features indicative of adverse survival in screened colorectal cancer patients. It is therefore reasonable to examine these clinicopathological determinants of outcome to assess the role they will have in the stratification of patient survival in the post-screening era.

Methodology: Patients with a positive faecal occult blood test (FOBT) in NHS Greater Glasgow & Clyde were offered colonoscopy where appropriate. The outcomes of colonoscopy were collected retrospectively from the Scottish Bowel Screening Database and socioeconomic deprivation was calculated using the Scottish Index of Multiple Deprivation. Variables were analysed using χ^2 tests for linear trend on SPSS software.

Results: Of 1266 patients attending for colonoscopy, 8% had a diagnosis colorectal cancer. Risk of cancer at colonoscopy was associated with male sex ($p<0.001$) and increasing age ($p<0.001$), but was non-significant for socioeconomic deprivation ($p=0.642$). Early stage (Dukes A and B) tumours accounted for 66% of colorectal cancers. Dukes stage was associated with vascular invasion ($p<0.001$). Advancing T stage was associated with nodal status ($p<0.001$), peritoneal involvement ($p<0.001$) and vascular invasion ($p<0.05$). Vascular invasion was present in 26% of T1 & 44% of T2 tumours.

Conclusion: The widespread adoption of screening has created a substantial stage migration towards earlier presentation. Vascular invasion appears to be an early feature in the natural history of colorectal cancer and may have important clinical implications. There is no association between socioeconomic deprivation and colorectal cancer at the colonoscopy stage of the screening programme.

The Effects of Maternal Hyperglycaemia on Vascular Endothelial Cadherin (VE Cad) in Fetoplacental Vessels

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Introduction: The prevalence of diabetes mellitus in women and pregnancies complicated by it are increasing. Maternal hyperglycaemia in pregnancy increases risks of complications including macrosomia, congenital malformations, miscarriage and stillbirth. Placental structure leaves fetoplacental vessels vulnerable to the environment of maternal circulation. Maternal hyperglycaemia has adverse effects on fetoplacental vessels, characterised by increased angiogenesis and endothelial disruption. Currently, direct effects of glucose on the endothelium of fetoplacental vessels are unknown. The aims of this study are to investigate the effects maternal hyperglycaemia has on:

1. The presence of VE Cad in fetoplacental vessels.
2. Phosphorylation of VE Cad in fetoplacental vessels.

Methods: Having undergone a 3hour placental perfusion with a euglycaemic media (n=3) and a media containing 15mM glucose (n=3), normal human placentae were subjected to immunocytochemistry and microscopy. Differences in VE Cad immunoreactivity intensity and junctional integrity, via tracer leakage studies, were investigated in small and large fetoplacental vessels. Double labelling of phosphotyrosine (PTYR) and VE Cad was performed. Localisation of PTYR and VE Cad and the number of vessels showing presence of both PTYR and VE Cad staining were recorded.

Results: Small and large fetoplacental vessels perfused with 15mM glucose showed significantly increased tracer leakage (2.7% increase ($p<0.05$), 21.7% increase ($p<0.037$) respectively) and down-regulation of VE Cad ($p<0.05$, $p<0.46$ respectively).From the PTYR results, no conclusions could be drawn as to whether phosphorylation of VE Cad caused the down-regulation observed.
Discussion: Effects seen from the inducement of hyperglycaemia can be compared to fluctuations seen in diabetic patients. The results illustrate that even a single hyperglycaemic episode damages the junctional integrity of fetoplacental vessels by causing a down-regulation of VE Cad.

Tip-apex distance (TAD): a comparison between dynamic hip screw (DHS) and Cephalomedullary nail fixation of extracapsular fractures of the hip.

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Background: Tip-apex distance (TAD) of >25mm is a known predictive marker for screw cut-out in fixation of extracapsular hip fractures. This study was performed to compare TAD achieved using a Dynamic Hip Screw (DHS) to that using a Cephalomedullary nail for stabilisation of extracapsular hip fractures.

Methods: From Oct 2009-Dec 2011, 246 patients with extracapsular hip fractures underwent stabilisation using either a DHS or a Cephalomedullary device [Intra-Medullary Hip Screw (IMHS) or Intertan nail using one proximal screw]. TAD was measured on intra-operative images; mean TAD was calculated and statistical analysis performed using a one-way ANOVA to identify any significant differences between the devices. Median follow-up duration was 12 months (range 2-27 months). Implant-related complications and revision surgery were used as markers of fixation failure.

Results: In the 150 patients in whom a DHS was used, mean TAD was 17.1mm (±6.5mm). Mean TAD in 81 fractures stabilised with an IMHS was 15.3mm (±5.2mm), whilst mean TAD in the Intertan group (15 fractures) was 19.2mm (±6.3mm). TAD was suboptimal (>25mm) in 9.3%, 4.9% and 13.3% in the DHS, IMHS and Intertan groups respectively. These suggest that lag screw position achieved using an IMHS is better than that using a DHS ($p=0.084$) or an Intertan nail ($p=0.067$). Complication rates were similar in all groups.

Conclusion: Cephalomedullary stabilisation of extracapsular hip fractures though technically demanding is safe and reliable. Newer implants should be used with caution due to learning curve as shown by a higher TAD in the group with Intertan nail fixation.

Is Old Blood More Dangerous Than New Blood?

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Background: There is conflicting evidence concerning the association between transfusion of 'old' blood (≥14 days) and increased morbidity and mortality in patients undergoing cardiac surgery.

Aims: In the first UK project of its kind, we accounted for limitations of previous studies to determine effects of storage age of transfused red cells (RBC) on clinical outcomes after cardiac surgery. Outcomes measured were early & late mortality and respiratory & renal morbidity.

Methods: Data from the Sheffield cardiac surgery database was examined between March 2007 and June 2010. A total of 828 patients received 1141 RBC units within two days of surgery. Patients who received more than two units were excluded. Subjects were divided into three groups based on the age of the RBC transfused; 1) <14 days ('new' blood), 2) ≥14 days ('old' blood), 3) a mixture of 'old' and 'new' blood. Data was analysed using chi-squared tests and binary logistic regression to account for confounding factors (such as EuroSCORE and ejection fraction). Survival was estimated using log rank and Kaplan Meier plots.

Results: The effect of RBC storage on operative mortality, renal support and advanced respiratory support using binary logistic regression yielded statistically insignificant differences. The Kaplan Meier 3-year survival plots were also similar across the groups.

Conclusion: Using a novel approach with UK data, our results show there is no association between storage age of RBC units and morbidity or mortality after cardiac surgery. The need for a randomised control trial to finally answer this issue of major clinical importance could not be greater.

How is tuberculosis diagnosed? A retrospective review of laboratory- and clinically-based diagnosis in the UK setting

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Background: Early and accurate diagnosis of tuberculosis (TB) is not only important for the individual affected but for public health and infection control measures. We reviewed the diagnostic method in a cohort of TB patients in an urban UK setting.

Methods: 109 adult patients were notified to the Sheffield CCDC over an 18-month period (January 2010 to June 2011). In each case, laboratory results were reviewed and the method of diagnosis determined. Medical records were reviewed for patients who had no laboratory confirmation of TB.

Results: All cases had at least one sample cultured; 61% (66/109) were culture positive for M. tuberculosis. Of the 43 culture negative cases, 4 patients were smear positive for acid-alcohol fast bacilli; a further 12 had histology suggestive of TB on biopsy specimens. Only 60% (39/65) of pulmonary TB cases had 3 sputum samples sent to the laboratory. 25% of cases (27/109) had no microbiological or histological evidence of TB, of which 8 patients had evidence of a positive IGRA or Tuberculin Skin Test; the remainder were diagnosed purely based on clinical and radiological findings.

Conclusions: Despite advances in rapid TB diagnostic methods, targets are still barely achieved for microbiological diagnosis. In pulmonary disease, 3 sputum samples need to be sent to optimise the chance of a diagnosis. For possible non-pulmonary disease, surgeons need to send samples for both culture and histology. IGRAs have limited value in the diagnosis of active TB; patients clinically deemed to have latent rather than active disease should be denotified.

The positive predictive value of postmenopausal bleeding for uterine malignancy

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Background: A systematic review was undertaken to estimate the positive predictive value (PPV) of postmenopausal bleeding (PMB) for gynaecological malignancy to aid decision making in primary care about whom to investigate.

Methods: Six electronic databases were searched from inception to September 2011. Included studies had to be in English and contain a PPV of PMB for uterine malignancy or allow its calculation. Methodological quality of studies was assessed and data extracted by two reviewers. Meta-analysis was performed where appropriate, obtaining pooled estimates of PPVs.

Results : The initial search identified 3089 potentially relevant studies, 33 met eligibility criteria. The estimated PPV for uterine and endometrial cancer was 0.51% (95% CI 0.27-0.75) and 0.47% (95% CI 0.24-0.70) respectively for a community population aged 45-54. The primary care PPV for endometrial cancer was 1.68% (95% CI 1.43-1.93) in those aged ≥ 35 years. Pooling findings from secondary care studies via a random effects meta-analysis resulted in an estimate of 8.4% (95% CI 6.9-9.9) for the PPV for endometrial cancer and 19.6% (95% CI 13.8-25.5) for uterine cancer. Results from secondary care were unable to be stratified by age.

Identifying Biomarkers of Vascular Cell Senescence

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Background: Evidence is mounting of an important role for cell senescence in the physiological ageing of the human arterial wall that, in turn, is a risk factor in the development of vascular damage. Human vascular function declines with age and is associated with increased numbers of senescent and proinflammatoryendothelial cells that express senescence associated secretory phenotype (SASP).

Aims: Gene expression profiling (transcriptomics) to identify novel genomic biomarkers and potential pathways associated with and specific to both forms of senescence; replicative senescence (REPS) and stress induced premature senescence (SIPS).

Methods: To model REPS, human umbilical vein endothelial cells (HUVECs) were grown and subcultured until they reached passage 31 (P31). A younger population of HUVECs at P5 acted as control. P12 HUVECs were prematurely induced into senescence using tert-butylhydroperoxide. Cells were determined senescent by SAβ-Gal staining. RNA was extracted from samples were checked for purity and integrity with RNA integrity numbers between 9.40-9.90. Gene expression profiles were generated using Illumina Microarray HumanHT 12 beadchips.

Results and Analysis: 12,115 and 6556 differentially expressed genes were observed in REPS and SIPS respectively. 3994 genes were found to be common to both forms of senescence. Cystatin SN was found to be upregulated in both forms of senescence whilst transforming growth factor β-Induced and α-L-Fucosidase was upregulated specifically in REPS and SIPS respectively. Potential pathways involved in REPS were found to specifically involve telomere maintenance whilst more metabolic pathways were found to have changed in SIPS.

Discussion: The beginnings of a panel of proteins can be seen with potential use both in vivo and in vitro. Senescence and the resultant SASP has been implicated in pathology. Novel biomarkers can potentially be used to identify individuals with an increased “arterial age” and at risk of developing cardiovascular disease, who otherwise appear well and healthy.

Expression and function of sweet taste receptors in human uterus

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Objectives: Sweet taste perception is detected by G-protein coupled receptor which functions as heterodimer; T1R2/ T1R3.Evidence suggests an association between pre-term delivery and consumption of artificially sweetened soft drinks. It is possible artificial sweeteners may modulate uterine contractility as recent evidence has shown that saccharin augments bladder contraction. We hypothesized that these receptors are present in human uterus and direct activation of sweet taste receptors by artificial sweeteners alters myometrial contractility contributing to pre-term labour.

Materials and methods: 6 uterine samples were collected with informed consent from pregnant and non-pregnant women during surgical procedures such as caesarean section and hysterectomy. Sections of human uterine wall were cut from paraffin blocks and stained by immunohistochemistry (IHC) to determine presence of the receptor proteins. Uterine homogenates were subjected to sodium dodecyl sylfate-polyacrylamide electrophoresis and immunoblotting to quantify expression and molecular weight of each T1R protein.

Results: Expression of T1R2/T1R3 sweet taste receptors is evident in endometrium and myometrium of non-pregnant and myometrium of pregnant human uterus by Immunostaining. Immunoblotting revealed bands at expected molecular weights in human pregnant and non pregnant uterus. Bands expressing proteins for T1R2 appeared to be denser in pregnant myometrium than in non-pregnant myometrium.

Conclusion: Sweet taste receptors are expressed in the uterus and may provide a target for the action of artificially sweetened soft drinks on myometrial contractility. This action may be enhanced in pregnant myometrium due to increased expression of the T1R2 receptor.

Circulating MicroRNAs in the Assessment of Diabetic Nephropathy

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Diabetic Nephropathy (DN) is a common microvascular complication of long standing Diabetes Mellitus. Currently, the Albumin-to -Creatinine Ratio (ACR) is considered the gold standard in assessment of DN. However, measurement of ACR is associated with several known limitations and as such, more sensitive and specific tests are being sought after. Recently, the discovery of microRNA nucleic acids in the peripheral circulation has shown promising clinical utility as disease biomarkers. The aim of this pilot study was to investigate the circulating levels of 3 kidney specific microRNAs (miR-192, -377 and -215) in relation to DN. A total of 48 subjects were recruited; 9 healthy controls and 39 diabetic patients and 2.5mls of blood withdrawn from each. Total microRNA was then extracted, reverse transcribed and levels then quantified by real time-quantitative PCR. A comparative CT method including RNU6B as endogenous reference microRNA, was then used to determine differences in the levels of target miRNAs within and between groups. Mir-192 and -215, but not miR-377, were detected in the circulation of all subjects. A 26.5-fold and 27.9-fold increase ($p=0.002$) in levels of miR-192 and miR-215, respectively, was observed in diabetic patients when compared to healthy controls. No significant difference in the levels of microRNAs was however found between diabetic subgroups. Levels of these microRNAs were additionally found to be independent of a number of clinical parameters (for example age, gender, duration of diabetes etc). Although further work is warranted, this study highlights the potential role microRNAs have in the detection and diagnosis of DN.

Clinical application of shear wave elastography for assessing carotid plaque

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Background: Atherosclerotic plaque in the carotid artery accounts for 15-20% of ischaemic stroke. Hence, there is increasing interest in identifying and characterising high-risk unstable plaques by assessing their mechanical properties. This information will improve patient selection for surgical treatment. Shear wave elastography (SWE), is a new ultrasound based technique that quantifies tissue elasticity in Young's modulus (YM). The aim was to evaluate SWE in assessing elasticity of carotid plaques and to relate YM to cardiovascular risk factors and ultrasonic features; echogenicity, plaque texture and degree of stenosis.

Methods: Patients with carotid plaques underwent carotid ultrasound scans using greyscale and SWE imaging. A longitudinal section of the carotid artery was imaged. Elasticity of plaque was quantified by measuring YM of the plaque. Echogenicity was classified according to Gray-Weale classification, plaque texture was classified as heterogeneous or homogeneous and degree of stenosis was grouped into mild (<50%), moderate (50-69%) and significant (≥70).

Results: Thirty-eight patients (16 males) of mean age 73 ±12 were recruited into the study. Significant correlation was observed between YM and increasing age and hypertension, $p<0.05$. Gray-Weale plaque classification showed significant difference, $p=0.03$.Echogenic plaques had a higher YM compared to echolucent plaques, 162 ±65kPa and 101 ±25kPa ($p=0.004$).

Conclusion:Shear wave elastography can quantify carotid plaque Young's modulus of different types of plaques. Significant difference in YM for echogenicity of plaques was observed showing potential of SWE characterization of carotid plaque. Further work includes histological classification of plaque stability which is showing promising results in correlating with YM.

The Role of SP-D in Health and Disease

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Background: Pulmonary surfactant protein D (SP-D) is a hydrophilic C-type lectin produced by type II alveolar cells. It is needed to maintain lung sterility. SP-D provides a first line defence by modulating immune function. During airway inflammation, SP-D undergoes nitrosylation in the presence of high levels of nitric oxide, leaving SP-D functionless. This deficiency in SP-D can lead to development of neonatal chronic lung disease. Currently SP-D is not included in surfactant therapy.

Aims: To investigate whether nitrosylated SP-D can be used as a biomarker for inflammation by:
1. Developing the current SP-D detecting ELISA so that it can measure the levels of nitrosylated SP-D.
2. Applying the improved ELISA technique; distinguishing between functional SP-D, and modified (Non- functional) SP-D.

Methods: An SP-D detecting enzyme-linked immunosorbent assay (ELISA) will be used. Human endotracheal aspirates and serum from preterm infants will be tested. The total concentration of SP-D and nitrosylated SP-D in tracheal aspirate samples will be calculated and quantified to determine the ratio of normal and nitrosylated SP-D in the samples.

Results: Preliminary results indicate that SP-D can be nitrosylated using a nitric oxide gel filtration column. I have been optimising the ELISA to calculate the concentration of nitrosylated SP-D (NO-SP-D) from my samples.

Conclusion: Preliminary results indicate that there is a potential to nitrosylated SP-D. A suitable dilution factor has been obtained to test the samples. The ELISA will test the clinical samples to quantify the concentration of nitrosylated SP-D and subsequently provide a prognosis for extent of inflammation.

International Study of Student Career Choice in Psychiatry: Preliminary Findings from the UK Arm

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Background: Psychiatry recruitment in the UK has been problematic for more than 40 years, with approximately only 4% of medical students choosing it as a career. Understanding reasons why this is so is crucial to potentially averting a recruitment crisis. The World Psychiatry Association provided a £60,000 grant for conducting this study, which represents the largest worldwide study into the subject.

Methodology: This was quantitative cross-sectional study. All medical schools in UK approached. Ethical approval was obtained. Final-year students and Deans of medical schools completed a survey that included questions about Psychiatry placements, students' career choices, and attitudes toward psychiatry. Questions were taken from the APT- 18 (Attitudes to Psychiatry Scale, a validated tool for use with medical students).

Results: The first 212 responses received (from 8 medical schools) were analysed. The mean age was 23.7, with 63.6% women (n=124). 2% (n=4) of final-year students made a definite decision to pursue a career in psychiatry, with a further 20.7% (n=42) seriously considering it. Personal or family experience of mental illness was cited as a very important factor for choosing psychiatry. There was little difference for experience of physical illness, a doctor in the family, media, and views of wider friends and family. There was little difference in the overall quality ratings of their clinical placement, lectures and small group teaching between those interested in psychiatry and those not.

Conclusion: The findings have implications in informing, understanding and strategizing future direction for improving recruitment rates into Psychiatry.

Urotensin and Urotensin Related Peptide in Acute Heart Failure

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Urotensin II (UTN) and Urotensin-Related Peptide (URP) are cyclic peptides found in human tissue and plasma. They have been shown to mediate a variety of effects including altering vascular tone depending on the vascular bed, positive inotropy of the heart and fibrosis. UTN levels are elevated in a variety of conditions including chronic heart failure (CHF).

Based on their similar ring structures previous studies have been unable to separate them. We have constructed a valid and reproducible solid phase extraction technique to separate the peptides and in-house competitive chemiluminescence assays to measure plasma UTN and URP in patients with acute HF (AHF, n= 335).

Amino-terminal pro-Brain Natriuretic Peptide (NTproBNP) has been established as a gold standard peptide in HF and so is used to compare to the Urotensin peptides.

Levels of all three peptides was significantly raised during AHF when compared to controls ($p < 0.05$). On logistic regression lower UTN on admission was significantly predictive of death at one year (OR 0.55, p= 0.044) whereas lower URP on admission showed a non-significant tendency to being predictive of HF at one year (OR 0.65, p= 0.180). Hence, the two peptides may have a complementary role in HF.

Further work into the role of peptides in a larger cohort with longer follow-up could help to clarify the role of the Urotensin system in HF.

An Investigation Into the Activation and Regulation of the Parkinson's Disease Associated Kinase PINK1

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Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1-2% of the ----population older than 65 years of age. PD is characterised by loss of dopaminergic neurones in the pars compacta of the substantia nigra. Mitochondrial dysfunction is thought to play a large role in the aetio-pathogenesis of this condition. Missense mutations in PTEN-induced kinase 1 (*PINK1*) cause autosomal recessive inherited Parkinson's disease. This gene encodes a Ser/Thr kinase that localises predominantly to the mitochondria of cells. To date, little is known about how PINK1 functions and is regulated in cells, since study and biochemical characterisation of the human enzyme is difficult due to its low *in vitro* kinase activity under basal conditions. This research exploits the recent discovery of an active insect orthologue of PINK1 from *T. castaneum* (TcPINK1) to investigate the effect of the mitochondrial uncoupler, CCCP on the stabilisation and catalytic activity of PINK1. Evidence is presented showing that CCCP induces stabilisation of hPINK1 on depolarised mitochondria, and new data exploring the effect of CCCP-induced mitochondrial depolarisation on TcPINK1 activity is presented. These findings will aid with future studies aimed at understanding how the activity of PINK1 is regulated and how PINK1 functions in cells subject to mitochondrial damage. Hopefully such studies could provide valuable clues as to the complex molecular mechanisms underpinning PD and how mutations in PINK1 result in an early-onset familial form of PD.

The Entrainment Test for Tremor Assessment

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Background: Diagnosing psychogenic tremor is challenging, usually relying solely on history and examination. However, clinicians may disregard the outcome of observational tests; basing diagnoses on history alone. The entrainment test is described as the most useful bedside test but literature suggests variability in its performance and interpretation. This study investigated the influence of history on clinicians' assessment of the test and variability in its performance and evaluation.

Method: 31 clinicians, recruited from specialist movement disorder centres and conferences, answered a novel questionnaire assessing performance and evaluation of the entrainment test. Clinicians watched videos of patients with organic and psychogenic tremors performing the test. After each video clinicians decided whether the test was positive or negative. They were read a fictional history and given the opportunity to change their assessment.

Results: 4 out of 62 initial assessments changed, independent of the history that the clinician heard (χ^2=1.974, p=0.542).
The mean questionnaire score was 6.7 out of 12 (standard deviation 2.3). Those reporting confidence in their knowledge of the entrainment test scored significantly higher, indicating greater knowledge, than those reporting limited confidence (mean=7.8, standard deviation 1.9, 95% confidence interval, 7.0-8.7 vs. mean=5.2, standard deviation 2.1, 95% confidence interval, 4.1-6.4. t=3.658, p=0.001). 5 clinicians did not include pure entrainment when asked for signs signifying a positive test.

Conclusion: History does not exert undue influence over assessment of the entrainment test, except in a minority of cases. Training and published guidelines are needed to standardise entrainment test methodology.

The Role of Caspase-1, as Part of the NALP3 Inflammasome in the Processing of IL-1B in Human Cord Blood

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Background: The inflammatory mechanisms that trigger labour include leukocyte influx into the myometrium, cervix and fatal membranes. In term and preterm labour, IL-1b is activated by caspase-1 and the NALP3 inflammasome is a multi-protein complex that triggers caspase-1 activation. The study aimed to determine the presence of the NALP3 inflammasome and to investigate the role of caspase-1, in the processing of IL-1b in human cord blood leukocytes.

Methods: Leukocytes were isolated from the cord blood of placenta from labouring and non-labouring women. Techniques used to investigate the expression of the NALP3 inflammation in placental leukocytes include Western blotting and immunoflurescence. IL-1b levels released following leukocyte stimulation with LPS±BzATP±caspase-1 inhibitor were measured using enzyme linked immunosorbant assay (ELISA). One way analysis of variance was used to compare IL-1b levels released in response to different treatments. To compare laboring and non-labouring samples unpaired t-tests were applied.

Results: In immunoflurescence in fetal leukocytes were stimulated with BzATP and LPS prior to being stained with anti-NALP3 antibody immunoflurescence was observed (n=2). When placental leukocytes were co-stimulated with bacterial endotoxin and BzATP there was a significant increase ($p<0.05$) in the levels of IL-1b released compared to the control in both labouring (n=6) samples (36.83±34.88 pg/ml) and non-labouring (n=5) samples (20.21±18.31 pg/ml). When pre-incubated with caspase-1 inhibitor prior to stimulation with LPS and BzATP levels of IL-1b released decreased in both laboring and non labouring groups.

Conclusion: When placental leukocytes were exposed to danger signals LPS and BzATP, assembly and activation of the NALP3 inflammation occurred. The decrease in IL-1b release when leukocytes were pre-incubated with the caspase-1 inhibitor demonstates that caspase-1, as part of the NALP3 inflammasome, has a role to play in the release of IL-1b, and potentially the inflammatory pathway that triggers labour.

The Effects of Diabetes on the Patency and Complication Rates of Brachiocephalic Fistulae.

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The development of dialysis has improved prognosis in end stage renal disease patients. Diabetes-induced renal failure has increased significantly over recent years. Achieving a satisfactory form of access for haemodialysis in diabetics could be time challenging. The antecubital fistula is often considered for these patients, as maturation of radiocephalic fistulae is often poor leading to inadequate dialysis and increased number of central venous catheters and their numerous complications. Patency and maturation rates as well as complicated outcomes are key when following up fistulae. The aim of this study was to report patency rates and complications of brachiocephalic fistulae created consecutively in our dialysis population and examine whether there was a difference between diabetic and non-diabetic patients. One hundred and sixty seven brachiocephalic fistula creations were retrospectively identified between January 2007 and August 2011 using patient databases. Mean age was 64.7 ± 14.1 years. Incidence of access-related complications and cumulative patency were analysed. Patency was calculated using the Kaplan-Meier method. Forty-nine patients had diabetic nephropathy as the causal factor. Of the 167 fistulae created in total 62 (29 diabetics, 33 non-diabetics) resulted in complications. The most common complication was thrombosis. The cumulative patency was 85%, 78%, 70% in diabetics compared to 86%, 82%, 75% in non-diabetics at 6,12, 24 months respectively. The patency and risk of access related complications are indifferent in diabetics and non-diabetics with regard to brachiocephaic fistulae. Therefore, vascular access at the antecubital fossa in diabetics will reduce morbidity due to better outcomes associated with this fistula

Nitrergic innervation of vasa nervorum

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Vasa nervorum are small diameter vessels that supply blood to main nerve trunks and ganglia. Vasa nervorum are known to be innervated by autonomic nerves, but the expression of neuronal nitric oxide synthase (nNOS) has not been studied previously. nNOS mediates vasodilation via nitric oxide synthesis. The biphasic degeneration of nitrergic nerves is implicated in the pathogenesis of diabetic autonomic neuropathy (DAN) – it is suggested that diabetes-induced deterioration of vasa nervorum causes microvascular deficit and neurodegeneration in the major pelvic ganglia (MPG) and sciatic nerve (SN) of rats. Clinical implications of MPG degeneration include bladder and erectile dysfunction, and motor/sensory deficits are associated with SN neuropathy. Our aim was to investigate the expression of nNOS in the nerve fibres innervating the vasa nervorum of rat MPG and SN.

MPG and SN were obtained from non-diabetic rats, fixed in paraformaldehyde, frozen and processed for immunohistochemistry. The expression of nNOS, nerve fibre markers (PGP9.5) and blood vessel markers (collagen-IV) were investigated using immunofluorescence. .

The results show that small diameter blood vessels (20-100 µm) are innervated by a rich network of nerve fibres in the MPG, most of which are nNOS-positive. In conclusion, these results suggest that nitrergic nerves innervate small diameter vessels which supply blood to nitrergic neuronal cell bodies. To our knowledge this is the first demonstration of nitrergic innervation of vasa nervorum and presents a novel nerve-blood vessel-nerve relationship. Future experiments will compare nitrergic innervation patterns of non-diabetic and diabetic animals to better understand the pathogenesis of DAN.

Inter-rater agreement of Neurological Signs

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Introduction: An assessment of inter-rater agreement of neurologists regarding diagnoses based on the neurological history and on neurological examination findings.

Methods: In the neurological examination aspect, two neurology doctors examined the same patient and recorded their results using a standardised proforma. In typical case histories part the doctors were asked to assess whether they would thrombolyse the described patient, and for their opinion about the diagnosis. The kappa statistic was used to assess the inter-rater agreement.

Results: The mean age of the patients was 55 years (SD 15). For the neurological examination there was very good agreement for inspection (kappa=0.82) and coordination (0.81), good for cerebellar (0.75) and power (0.63), moderate for reflexes (0.57), tone (0.51) and gait (0.42) and fair agreement for sensation assessment (0.35). There was no overall significant difference between grades of health professional.

Observable clinical signs (0.79) are significantly better agreement than elicitable signs (0.49).

For the theoretical patient histories 94% of the respondents correctly thrombolysed, and 79% of respondents correctly diagnosed the patients.

Conclusion: The most important result of this research is that of the significantly better agreement of Observable signs (inspection, coordination and cerebellar signs), in comparison to Elicitable ones (tone, strength, reflexes, sensation), which are more patient and doctor dependent.

The finding of only moderate inter-rater agreement for some neurological signs is of relevance to the telemedicine consultation, where the assessing doctor is reliant on another's findings. The traditional clinical neurological examination may need to be adapted in light of these findings.

Assessment of the Discriminant Validity of a New Infant Malnutrition Screening Tool with Body Composition Analysis

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Prevalence of malnutrition is high in hospitalised patients and often goes unnoticed and untreated. NHS guidelines now state that all patients should be nutritionally screened on admission; however there is no specific validated tool available for infants. A new tool is recently under development at Yorkhill hospital in Glasgow, the infant Paediatric Yorkhill Malnutrition Score (iPYMS). This tool encompasses four steps, each an established predictor of malnutrition. Each step bears a score, and a total score ⍰2 indicates high risk of malnutrition. The ability of iPYMS classification and another validated screening tool for children and infants (STRONGkids - Screening Tool for Risk on Nutritional Status and Growth) to discriminate between children with high and low fat stores was explored in 181 infants. iPYMS, STRONGkids and measurements of skinfolds and mid-upper arm circumference (MUAC) were carried out and converted to z-scores (WHO 2006). 29.3% were at high risk of malnutrition with iPYMS and 9% with STRONGkids. All anthropometric and body composition indices were significantly lower in those infants at high risk of malnutrition with STRONGkids compared to those at low risk ($P<0.05$); for iPYMS that was the case for all measurements but skinfolds. iPYMS malnutrition risk classification had ~60% concordance with nutritional status classification by body composition (skinfolds and MUAC z-scores cut-offs below the -1.33 SD). Respectively, STRONGkids had ~80% concordance. iPYMS has fairly good ability to discriminate between patients with high and low levels of body fat but needs further improvement before its use in clinical practice.

Producing and evaluating a novel Lentiviral vector for β-thalassaemia Gene therapy

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Introduction**:** β-thalassaemia, a single gene disorder affecting the β-globin gene, results in the formation of defective haemoglobin A. Treatment presently incorporates regular blood transfusions and currently the only option for a 'cure' is with hematopoietic stem cell (HSC) transplantation. Fewer than 30% of affected individuals have HLA compatible siblings, and in light of the characteristic dilemmas surrounding HSC transplantation, β-thalassaemia has become a target for gene based therapies. The approach essentially involves the use of recombinant HIV viruses, known as lentiviral vectors (LV) in mediating gene delivery.

Method**:** Antoniou's group have recently devised a number of "GLOBE" constructs with the inclusion of regions physiologically present within the endogenous human β -globin gene, previously deemed insignificant, and therefore, omitted from all known published constructs to date. The inclusion of a full β-globin 2nd intron (850bp) has been added, yielding the latest generation of LV, GLOBE 4. The aim of this project was to conduct a comparative expression analysis between the GLOBE-2 (control) and GLOBE -4 vectors to evaluate whether the inclusion of the full 2nd intron allows (i) efficient LV production (in contrast with previous findings observed with gammaretroviral vectors) and (ii) increases β-globin mRNA levels. Lentiviral vectors were produced via cell transfection, and subsequently used to transduce our HSC model, the murine erythroleukemia cell (MEL). The quantity of vector derived human β-globin expression was quantified via qPCR and RT-qPCR analysis to determine the level of expression per LV copy.

Results**:** Average viral titres obtained for the GLOBE- 2 and GLOBE-4 constructs were $7.2x10^7$ and $5x10^7$ viral particles (vp)/ml respectively, incurring a 31% variance despite a 600bp difference in size. The relative amounts of β-globin expression adjusted to level of expression per vector copy were 0.869 (± 0.21) and 0.061 (±0.07) for GLOBE 4 and 2, thus revealing greater levels of expression for our novel GLOBE 4 construct.

The effects of hypothermia on hypoglycaemic injury to mouse optic nerve, a central white matter tract

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The high metabolic rate of the central nervous system (CNS) and its reliance on the oxidative metabolism of glucose means that deprivation of glucose or oxygen leads to rapid functional deficits. Research on neuroprotective therapeutics for conditions such as hypoglycaemia and ischaemic stroke have been focussed primarily on grey matter, showing little regard for protection of the myelinated portions of the CNS. Therapeutic hypothermia is neuroprotective in both white and grey matter for conditions of ischaemia; here it is investigated in isolated glucose deprivation.

The objective was to measure the effects of temperature on the recovery of compound action potential (CAP) area following 60 minutes of aglycaemia-induced axonal injury in the mouse optic nerve.
Mice were killed via schedule 1 cervical dislocation and optic nerves dissected out. Axonal function was assessed using evoked supramaximal CAPs.

60 minutes of aglycaemia with subsequent glucose reperfusion lead to a 34.7 ± 3.8% mean recovery of CAP area at 37˚C. Hypothermia and hyperthermia imposed throughout aglycaemia and glucose reperfusion lead to mean recoveries of 91.3 ± 8.1% and 10.3 ± 13.8%. Hypothermia and hyperthermia solely during aglycaemia gave mean recoveries of 73.8 ± 5.9% and 15.6 ± 5.3%. Hypothermia during glucose reperfusion alone gave a 71.3 ± 20.5% mean recovery.

The results show hypothermia to be protective and hyperthermia to be damaging in aglycaemia-induced white matter injury. Hypothermia was neuroprotective regardless of when imposed. The findings here highlight the potential use of TH as a clinical neuroprotective strategy for severe hypoglycaemic episodes.

Student Learning Needs in Psychiatry

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Background: To the authors' knowledge, very limited number of studies has been conducted into what materials medical students use to learn for their psychiatry undergraduate placement. This study aims to explore this area in more detail, and identify any gaps not adequately filled currently. It also explores student interest in psychiatry and whether they are considering pursuing it as a future career.

Method: Medical Students completed questionnaires about their psychiatric undergraduate placement at Manchester University (2010-2011).

Results: 126 out of 144 students responded, giving a response rate of 87.5%. Students spent a mean of 10.1 hours a week studying psychiatry (outside formal teaching) using various materials. Handouts from lectures or tutors were most commonly used (by 95.2% of respondents) with journals and podcasts being the least common (18.5% and 17.5% respectively). Psychiatric textbooks were the most useful for learning about psychiatry.

Students identified the need for better quality, more structured and more frequent teaching (n=58). Specifically they stated they wanted more lectures, small group teaching, mock OSCEs, and interviews with simulated or real patients to aid their learning of the subject. They also identified a need for greater clinical experience and increased availability of resources such as textbooks.

Conclusions: It appears that despite the growing popularity of the internet, students at Manchester still prefer textbooks to audio books and podcasts to learn. However much can be done to improve on the learning needs of students which, if addressed, may help with the recruitment crisis currently facing psychiatry.

Teaching Old Drugs New Tricks: Rationale for the Redeployment of Valproate, an Anti-Convulsant, and Niclosamide, an Anti-Helminthic Agent, as a Combination Therapy Against Multiple Myeloma

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Multiple Myeloma (MM) is an incurable plasma B cell neoplasm. Current best treatments are associated with significant comorbidites rendering the majority of older patients ineligible. Following a screen of 100 licensed, well-tolerated drugs from the BNF, we identify potent selective anti-MM activity of valproate and niclosamide (VaN) combination therapy, mediated through targeting the mitochondria.

MM cell lines and primary MM bone marrow samples were treated in vitro and cell viability, mitochondrial function and levels of oxidative stress response genes measured using flow cytometry, immunofluorescence assays and molecular techniques. Niclosamide demonstrated potent anti-MM activity against cell lines and primaries and induced a significant decrease in free light chain secretion. Niclosamide uncoupled oxidative phosphorylation causing mitochondrial membrane depolarisation and production of mitochondrial superoxide. Valproate had very little anti-MM activity alone, however in combination with niclosamide, enhanced mitochondrial superoxide production by regulating mRNA, protein levels and acetylation status of genes involved in the antioxidant response including SIRT3, a mitochondrial deacetylase, and manganese superoxide dismutase (SOD2) a key regulator of mitochondrial superoxide levels. Importantly, no induction of mitochondrial superoxide was observed in normal donor cells. VaN therapy also showed enhanced activity with the widely used anti-MM agent melphalan.

Valproate and niclosamide (VaN) have potent, selective anti-MM activity at clinically achievable concentrations, mediated by the generation of oxidative stress levels that are lethal for MM cells. These data, taken in the context of the known safety profiles of valproate and niclosamide, provide rationale for their use as a combination therapy in the treatment of MM.

The paracrine effect of mesenchymal stem cell conditioned media on TGF-β1 induced fibroblast to myofibroblast differentiation.

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Hypothesis & Aim: Idiopathic pulmonary fibrosis (IPF) is an incurable fibrotic lung disease where myofibroblasts are believed to play a key role in the pathogenesis. A mesenchymal stem cell (MSC)-mediated regenerative therapy has been proposed. MSC-mediated anti-fibrotic effects have been demonstrated in animal lung fibrosis models; however their effect on myofibroblast differentiation is unknown. This study will aim to determine the paracrine effects of MSC on myofibroblast differentiation.

Method: Human normal lung (CCD-8Lu) and IPF (LL29) fibroblasts were differentiated into myofibroblasts by TGF-β1 (5ng/ml) treatment for 24-hours. MSC-mediated inhibition of differentiation was assessed by co-incubation of fibroblasts with MSC-conditioned media (MSC-CM) and TGF-β1 for 24-hours. Reversal of TGF-β1 induced myofibroblasts was conducted by treating the cells with MSC-CM for 24, 48 and 72-hours. Determination of myofibroblast differentiation was assessed by immunocytochemical detection of α-smooth muscle actin (α-SMA) expression.

Results: Myofibroblast differentiation was achieved in (86.27+2.57%) and (86.69+2.51%) of CCD-8Lu and LL29, respectively. A significant reduction of myofibroblast differentiation was noted in both cell types; CCD-8Lu (56.54+3.67%) and LL29 (51.77+3.01%) following co-incubation with MSC-CM and TGF-β1 vs. TGFβ1 alone ($p<0.001$). A significant reversal of myofibroblast differentiation was observed following administration of MSC-CM vs. serum-free culture media ($p<0.001$). The duration of MSC-CM exposure influenced myofibroblast reversal in CCD8-Lu and LL29 cells; (81.7+0.43%) and (73.26+0.70%) at 24 -hours, (72.15+0.81%) and (60.57+4.27%) at 48-hours, (57.63+4.54%) and (60.65+4.9%) at 72-hours.

Conclusion: MSC inhibits and reverses TGF-β1 induced myofibroblast differentiation through a putative paracrine-driven mechanism. This has exploitative potential for anti-IPF therapeutic strategies.

Identifying characteristics of insulin pump use that predict good diabetes control in patients with type 1 Diabetes

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A proportion of type 1 diabetics fail to achieve glycaemic targets despite continuous subcutaneous insulin infusion (CSII). We examined differences in pump set-up and usage characteristics between patients with target and sub-optimal glycaemic control as well as low and high rates of hypoglycaemia.

198 patients treated with CSII at a single hospital clinic were categorised into those with target [HbA1c <7.5%] and sub-optimal [HbA1c ≥7.5%] glycaemic control. Patients were also divided into those with high [>3 episodes/week] and low [<3 episodes/week] rates of hypoglycaemia [capillary glucose < 4mmol/l].

Patients with target glycaemic control used more basal rates [5.57±2.6 vs. 4.84±1.8; p=0.029] and boluses [6.1±2.1 vs. 5.2±2.1; p=0.004] per day but there were no differences in total daily dose. Every 1 unit increase in basal rates and boluses per day was associated with a reduction in HbA1c of -0.231% (p=0.002) and -0.289% (p<0.0001) respectively. Target glycaemic control was associated with increased rates of hypoglycaemia. Patients with high rates of hypoglycaemia tested blood glucose more often [6.4±2.1 vs. 3.94±2.0; p=<0.0001), gave more boluses [5.75±1.8 vs. 5.15±2.1; p=0.018] and used the bolus calculator more [4.89±2.1 vs. 4.1±2.4; p=0.009] but overrode the bolus calculator more frequently [16.7±19.5 vs. 13.7±20.1%; p=0.02].

Target glucose control was associated with higher number of basal rates and boluses per day suggesting greater engagement with the pump, and more pro-active management of glucose control. Increased hypoglycaemia was associated with more frequent capillary testing, suggesting increased vigilance. Studies exploring CSII use that results in optimal glycaemic control without hypoglycaemia are merited.

Expression of the Splice Variants of ST2 in Placentae from Healthy and Complicated Pregnancy

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Pregnancy complications such as pre-eclampsia (PE) and intra-uterine growth restriction (IUGR) cause significant fetal and maternal morbidity and mortality. ST2 is the receptor for the type 2 cytokine IL-33. IL-33 is an IL-1 family, pro-inflammatory cytokine that stimulates the production of type 2 cytokines from Th2 cells. ST2 has three isoforms including a membrane bound form, ST2L; ST2V, expressed in the gut; and a soluble secreted form, sST2, which acts as a decoy preventing IL-33 signalling. Previous research found higher placental total ST2 mRNA expression in PE compared to healthy pregnancy. The current study investigated relative placental expression of the ST2 isoforms in PE and also IUGR where placental pathology is present but maternal systemic response absent. mRNA expression of the splice variants of ST2 in placentae from healthy (n=50), PE (n=22) and IUGR (n=28) pregnancies was quantified using RT-PCR. sST2 has no unique exon sequence and was estimated using total ST2 minus ST2L expression. Placental total ST2 mRNA expression was significantly elevated in PE compared to healthy pregnancy [2.27 (0.54) versus 1.92(0.41), mean(SD) log mRNA expression relative to control, p=0.021]. There was no difference in ST2L mRNA expression between normal and PE placenta. Estimated sST2 mRNA expression was significantly elevated in PE compared to healthy placenta [2.27(0.54) versus 1.92(0.41), p=0.02]. There was no difference in total ST2, ST2L or estimated sST2 expression between healthy and IUGR placenta. The increased placental total ST2 mRNA expression in PE is due to the sST2 isoform of the receptor and is specific to PE.

How the amount of protein in a maternal diet affects neural stem cell development in 14.5 day old mice embryos.

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Early phases of embryogenesis are susceptible to maternal malnutrition; with an increased incidence of disease in later life. To see whether protein restriction in a maternal diet affects neurogenesis, we examined the effect of a normal maternal protein diet (control; 18% casein), a low protein switch diet (LPS; first 3.5 days: 9% and remainder 18% casein) and a low protein diet (LPD; 9% casein) during gestation.

The pregnant mouse was culled and 14.5 day old embryos brains isolated. The ganglionic eminences neural stem cells were cultured & the numbers of neurospheres counted. These were passaged and secondary neurospheres were counted.

Primary neurospheres showed no significant difference between control & LPS and LPD & LPS; however, a significant difference was seen between the control and LPD groups ($p<0.05$). With the secondary neurospheres, there was no significant difference between any groups.

Neurosphere size within each group was investigated. Primary neurospheres sized 100-199µm, showed a significant difference between all groups; the control had the largest number, followed by LPS then LPD ($p<0.05$). This was also seen in the 200-399µm size range, except between the LPD and LPS groups where there was no significant difference. >400µm neurospheres showed no significant difference between the groups. The size distribution in secondary neurospheres was similar in all groups.

In conclusion, protein restriction in maternal mouse diets has an initial effect on neural stem cells in 14.5 day old embryos. However, this initial deficit is compensated in passaged neural stem cells.

An Old Antipsychotic Drug with New Pharmacology? Investigating Haloperidol's Action on Dopamine D2 Receptor Signalling.

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Background: The dopamine-D2 receptor is a major therapeutic target for antipsychotics which signals through a number of different intracellular pathways. Biased agonists differ from classic agonists/antagonists in that they preferentially signal through one of these pathways. Thus, clarifying the key signal transduction pathways activated by individual antipsychotics may be important in delineating their therapeutic action and side effects in a clinical context. Here, we studied whether the antipsychotic haloperidol and structurally related butyrophenones (droperidol, risperidone, melperone, and domperidone) displayed biased signalling at the long isoform of the dopamine-D2L receptor (D2LR).

Method: Chinese hamster ovary (CHO)-K1 cells expressing an N-terminal SNAP-tagged D2LR receptor and SPAP reporter gene (CHO-ssD2L cells) were used. D2LR inhibition of cAMP production and signalling via β-arrestin were measured indirectly by CRE-mediated SPAP reporter gene and receptor internalization assays, respectively.

Key results: Haloperidol acted as an agonist showing significant internalization ($p<0.05$ using one-way ANOVA and Bartlett's test) in the receptor internalization assay and as an antagonist of quinpirole induced CRE-SPAP responses. Droperidol, risperidone, melperone and domperidone solely acted as antagonists throughout these assays. Dissociation constants for each compound for both assays, pA2 (7.5-10.3) and pKb (7.8-10.2) were derived using Gaddum-Schild analysis, respectively. Differences between these values for each compound were not statistically significant.

Conclusion: This study suggests haloperidol exhibits biased signalling at the D2LR. This characteristic is specific to haloperidol as the other butyrophenones under investigation did not display this.

The Changing Epidemiology of Clavicle Fracture in an Adult Population

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Background: A number of studies have described the epidemiological characteristics of clavicle fractures, including two previous reports from our institution. The Robinson classification system was described in 1998, after the analysis of 1,000 clavicle fractures. We aim to provide a contemporary analysis and compare current clavicle fracture patterns of our adult population with historical reports.

Methods: A retrospective analysis of a prospectively collected fracture database from an institution serving 598,000 was conducted. Demographic data were recorded prospectively for each patient with an acute clavicle fractures including age, gender, mode of injury, fracture classification, and the presence of associated skeletal injuries. Fractures were classified according to the Robinson system.

Results: A total of 312 clavicle fractures were identified, occurring with an incidence of 55.9/100,000/yr (CI 49.8-62.5) and following a bimodal male and unimodal older female distribution. Sporting activity and a simple fall from standing caused the majority of injuries. More than half of simple fall fractures affected the lateral clavicle. Overall, type II mid-shaft fractures remain the most common, but comparison of this series with historical data reveals that the epidemiology of clavicle fractures is changing. We have identified an increase in the average patient age and overall incidence of clavicle fractures in our adult population.

Conclusions: The epidemiological characteristics of clavicle fractures in our adult population are presented. The incidence, relative frequency, and average patient age of type III lateral one-fifth fractures have increased. This epidemiological trend has implications for the future management of clavicle fractures in our region.

Crush Cytology of gastro intestinal malignancy. A cytohistological comparison.

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Introduction: Gastrointestinal malignancies are commonly encountered in medical practice and endoscopic examination and biopsy. Crush cytology of gastrointestinal malignancy is a simple, cheap and readily available technique which increases diagnostic yield and expedites diagnostic work-up of such patients. Compared to biopsy, crush preparations require minute amount of tissues and provide rapid diagnosis.

Material and Methods: All cases of gastrointestinal malignancy of esophagus, stomach and colorectum, which underwent endoscopic examination from January 2007 to September 2011, in Kasturba Medical College and Hospital, Mangalore, India, were included in the study. The diagnosis on crush cytology was compared with histopathological diagnosis, along with review of the patients' records. Diagnostic accuracy, sensitivity, specificity, positive predictive values were calculated.

Results: Total 204 cases of gastrointestinal malignancy were evaluated with endoscopy and crush cytology during this period. Respective histolopathological examination was available in 170 (83.3%) cases. There were 119 cases of histologically confirmed carcinomas with male:female ratio of 2.6 : 1.The most common site of carcinoma was stomach (35.9%) followed by colorectal (29%), oesophagus (26.5%), duodenum and gastroeosphageal junction with 4.3% cases each. Crush smears were inadequate in 5 cases. The sensitivity of crush cytology was 81.1%, with a specificity of 83.7%, positive predictive value 93.4% and negative predictive value of 61%. The diagnostic accuracy of crush cytology was 95.2%.

Conclusion: Crush cytology is a cost effective diagnostic tool with high diagnostic accuracy, specificity and sensitivity, and provides early diagnosis, which is helpful in planning the further management of gastrointestinal carcinoma cases.

The Prevalence of Diverticular Disease in Riyadh, Saudi Arabia

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Background: Diverticulosis is an outward protrusion of the mucosa and submucosa of the colon. Only 5% of patients may develop inflammation of the diverticula (diverticulitis). Life style and eating habits significantly impacts the distributional prevalence of the disease. Diverticulosis is on the rise in developing countries and underreported in countries such as Saudi Arabia. Despite the low complication rates of the disease, immediate intervention is critical due to the severity of the complications once occurred. This is a hospital-based study to assess the prevalence of diverticulosis and its clinical implication on patients.

Methodology: This is a cross sectional study where data were extracted from the colonoscopy medical charts (2006-2011) at the National Guard Health Affairs (NGHA) – Riyadh, Saudi Arabia. Assuming a prevalence of 27%, α= 0.05, β=0.20, and a precision of 0.05, the optimal sample size was 302 subjects. Only 269 charts met the study inclusion criteria and were reviewed. Data was analyzed descriptively to identify both demographic and clinical characteristics of patients with diverticulosis. Moreover, logistic Regression was used to identify significant predictors of "diverticulitis disease".

Results: Diverticular Disease accounted for 7%; it was mainly positioned on the left side (57%). The majority of the patients were male (62%), mean age (63 ±12), mean BMI (29.1± 5.9).The majority of patients were symptomatic (72%), where diffused abdominal pain ranked highest (51%). Use of NSAIDS was the only significant predictor of diverticulitis (P-value: 0.03)

Conclusion: This study act as an exploratory study that can set the ground for future investigational research since it sheds the light on the prevalence of the disease, its clinical implications and possible risk factors.

The effect of socioeconomic factors in the treatment of Multiple Sclerosis

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Background: There are many treatments available for MS; however the fairness of allocation of such has been questioned. Research has shown that access to the Disease Modifying Treatments (DMTs) such as Beta Interferons is influenced by our postcode. The study assesses whether deprivation also plays a role in allocation of the newest MS treatments mainly Tysabri.

Methods: Data was collected from 1,263 MS patients whose MS was managed at the Queens Medical Centre, Nottingham. A binary logistic model was constructed to assess any correlation between treatment allocation and deprivation together with sex, age, MSSS score and time in years between onset and diagnosis.

Results: The results showed that deprivation does not influence treatment of Tysabri, Beta Interferons or Copaxone, which contradicted the previous research. They also showed that as age of MS patients increased, the likelihood of receiving DMTs was reduced.

Conclusion: We can assume that the reduced inequalities in treatment are due to the NHS actively trying to reduce health inequalities, and that as MS drugs have become more established, disparities in their allocation have been reduced. Also the lack of Tysabri allocations may be due to the possible adverse effects such as the risk of progressive multifocal leukoencephalopathy and so physicians are wary about such treatments. Further research is however needed in order to generalise such assumptions to the rest of the UK.

Staged management of complex low birth weight tetralogy of Fallot

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Appropriate management of low weight infants with complex tetralogy of Fallot is often fraught. We present a 2.8kg infant with Di George syndrome and spelling tetralogy with non-confluent pulmonary arteries, the left pulmonary artery being supplied by an aberrant ductus arteriosus from the left common carotid artery. This is truly unique anatomy, never documented before. We performed a pioneering management regime, which included stenting of the outflow tract and the ductus to allow this patient to progress towards an elective surgical correction. This surgery was undertaken 11 months after the initial stenting procedure and was successful; the infant is now growing, and thriving.

Management of complex neonatal tetralogy of Fallot is has multiple approaches and there is no overall consensus as to the best strategy. The use of neonatal outflow tract stenting has added a potential temporizing procedure to our armamentarium. This case illustrates the extremes of complex Tetralogy with the left pulmonary artery supplied by an aberrantly arising ductus arteriosus; providing a major management dilemma in a low weight infant. The pioneering management strategy has made a condition previously incompatible with life, compatible with life until the infants weight and size allows a corrective surgical procedure. This management strategy has the potential herald a new and successful regime for low weight infants whilst they grow to a weight compatible with surgery.

A cadaveric study of subpatellar nerves in relation to incisions used for total knee arthroplasty

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A midline incision (MI) for total knee arthroplasty provides good access to the knee but damages the infrapatellar branch of the saphenous nerve and medial cutaneous femoral nerve causing lateral skin dysaesthesia in 55-100% of cases and occasionally painful neuroma and complex regional pain syndrome. The anterolateral incision (ALI) seeks to prevent this by penetrating the skin in an area of sparse neurovasculature.

A skin and subcutaneous fat flaps were reflected in 12 cadavers (mean age 82.8 ±SD10.3 years) in order to reveal the subpatellar nerves. Following this, the position of both ALIs and MIs were marked to determine the quantity of nerve branches crossing each incision, as well as the number of terminal nerves void of supply. Measurements between the most superior and inferior nerves to cross each incision, as well as the distance from the inferior border of the patella to the tibial tubercle were taken for inter-cadaver analysis of desensitisation.

No significant difference was seen between the numbers of nerve branches crossed by each incision; however, the ALI crossed the nerves further from their origin reducing the likelihood of neuroma formation. The ALI blocked the supply to significantly less terminal nerves ($p=0.026$), which would reduce the area of numbness experienced compared to a MI. Furthermore, the ALI permits faster wound healing as less vascular damage occurs, enabling earlier flexion after surgery without strain on the wound.

An ALI could provide a good alternative to a MI in cases where normal skin sensation takes precedence over incision size.

Recurrent intestinal volvulus In midgut malrotation as a cause of acute bowel obstruction

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Background: Intestinal malrotation occurs when there is a disruption in the normal embryological development of the bowel rotation, elongation and fixation. The majority of patients present with clinical features in childhood, though rarely a first presentation can take place in adulthood. Recurrent bowel obstruction in patients with previous abdominal operation for midgut malrotation is mostly due to adhesions but few cases have been due to recurrent volvulus.

Case: We present the case of a 22 year old gentleman who had laparotomy in childhood for small bowel volvulus and then presented with acute bowel obstruction. Preoperative CT scan showed small bowel obstruction and features in keeping with midgut malrotation. Emergency laparotomy findings confirmed midgut malrotation with absent appendix, abnormal location of caecum, ascending colon and small bowel. In addition, there was small bowel volvulus and a segment of terminal ileal stricture. Limited right hemicolectomy was performed with excellent postoperative recovery.

Discussion: Midgut malrotation is a rare cause of intestinal obstruction in adult life and only few of such cases have been reported in the literature. Recurrent intestinal obstruction is even rarer in adults who have been previously operated for gut malrotation and few of such cases have been reported.

Conclusion: Midgut malrotation is a rare but an important cause of bowel obstruction in the adult population. The most dreadful and life threatening complication of intestinal malrotation both in children and adults is gut volvulus with possible ischaemic changes and associated high mortality.

Pseudoaneurysm in a patient with Tuberous Sclerosis complicated by multiple renal angiomyolipoma and pulmonary lymphangioleiomyomatosis: A rare manifestation

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Coexistence of renal angiomyolipoma (AML) and pulmonary lymphangioleiomyomatosis (LAM) associated with Tuberous Sclerosis (TS) is extremely rare, first described only in 1994. Spontaneous haemorrhage of renal AML may lead to pseudoaneurysm formation and can be life-threatening. A literature search reveals just four cases of pseudoaneurysm associated with renal AML and TS. This appears to be the first example of renal pseudoaneurysm in a case of TS with renal AML and concomitant LAM.

This case report describes a presentation of a pseudoaneurysm complicating renal AML in a patient with TS with LAM. Previously undocumented, it is important to describe this interesting condition and the treatment choices made in order to improve understanding of its management.

A 46 year old female was admitted with pyrexia, shortness of breath, right-sided loin pain and frank haematuria. Renal US showed bilateral multiple AML and a large solid mass in the lower pole of the right kidney. MRI confirmed it to be a 85mm haemorrhagic mass. CT angiogram showed a 33mm x 27mm pseudoaneurysm contained within this. Due to coexisting lung disease, she was unsuitable for nephrectomy and consequently underwent embolisation. Following this, she developed persisting pyrexia and worsening renal function which eventually settled with conservative treatment. She was discharged and continues to be followed up in the clinic.

This case report is a unique chance to discuss the management choices made for this young woman suffering from a rare presentation of complications arising from Tuberous Sclerosis.

Investigating the Efficacy of a Current Subcutaneous Insulin Regimen during Nasogastric Feeding using Continuous Glucose Monitoring

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Post-stroke hyperglycaemia is associated with detrimental clinical outcomes. Glycaemic disturbances may be exacerbated by nasogastric (NG) feeding. A feeding-specific protocol has been designed for patients with type 2 diabetes (T2DM): intravenous (I/V) sliding scale insulin on Day 1, followed by subcutaneous (S/C) insulin (soluble and intermediate-acting insulin at start of feed; intermediate-acting insulin halfway through feed) on Days 2 and 3. Our aim is to determine whether this regimen achieves good glycaemic control in stroke patients.

Study 1 was a retrospective audit of 19 patients with T2DM requiring NG feeding following stroke. In Study 2, an iProTM2 Continuous Glucose Monitoring device was fitted to 4 prospectively-recruited participants for 3 days to assess glycaemic control.

In Study 1, 13 patients received S/C insulin during feeding (4 followed protocol, 9 received alternative regimens), Most patients (15.4% on Day 2, 25% on Day 3) did not achieve ≥80% of glucose measurements within target (4-10 mmol/L) while receiving S/C insulin. Glycaemic outcomes with S/C insulin were inferior to I/V insulin, with respect to proportion of measurements within target ($p=0.006$) and mean glucose ($p=0.002$). In Study 2, the S/C insulin regimen has maintained good glycaemic control in 2 out of 3 patients with T2DM, without inducing hypoglycaemia (<4mmol/L). The non-diabetic patient remained normoglycaemic.

Current practices are highly variable and failing to attain glycaemic targets. A standardised protocol may establish tighter control during NG feeding. In clinical practice, this requires insulin dose adjustments in response to feeding changes, and optimising transition from I/V to S/C insulin.

Risk Factors for Mortality in Patients with Tuberculosis in a Rural Area of Malawi.

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Background: Tuberculosis (TB) is a major cause of morbidity and mortality in the developing world, despite the widespread availability of effective treatment. The rise in the incidence of HIV infection in sub-Saharan Africa over the past 20 years has led to a rapid increase in the incidence and mortality of TB infection. This indicates a need to identify the risk factors leading to TB deaths and to evaluate the impact of HIV infection on TB patients. This will enable the implementation of TB control measures which aim to reduce the mortality of TB infection.

Methods: Data was collected from existing TB registers containing information on patients who registered with TB at Nkhoma Hospital, Malawi, between January 2008 and August 2011. Several factors including age, gender, TB classification & sub-type, HIV status, ART status and CPT status were evaluated for their effect on TB mortality using Pearson Chi-square analysis and crude and adjusted odds ratio calculations.

Results: Out of 917 patients, 220 (24.1%) of patients died during the course of TB treatment. Using multivariate analysis, independent risk factors for TB mortality were old age; male gender, miliary TB, meningeal TB, abdominal TB, and pericardial TB. HIV positive patients who had not started ART during the course of TB therapy were also significantly at risk of death.

Conclusion: These findings suggest that, improved coordination of TB and HIV services, and more effective diagnosis and treatment of extrapulmonary TB could help reduce TB related morbidity and mortality rates in this area of Malawi.

Continuous Infusion Analgesia In Thoracic Surgery (CIATS) Reduces Morphine Usage In Patients Who have Empyema And Undergo Open Decortication.

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Objectives: Continuous infusion analgesia in thoracic surgery (CIATS) used for post-thoracotomy pain control. CIATS consists of a catheter in the wound topped up with 10 mls of 0.25% chirocaine and connected to continuous infusion of 0.1% chirocaine 5ml/hr. We reviewed the impact of CIATS in thoracic surgery in decortication patients.

Methods: 15 cases that had undergone thoracotomy for decortication were retrospectively analysed. 8 had CIATS with morphine PCA (Group1), 7 patients had only morphine PCA (Group2). Patients had supplementary analgesia consisting of paracetamol, tramadol, di-hydrocodeine, and non steroidal inflammatory drugs. Post-operative pain scores, amount of morphine used and length of hospital stay (LOS) were measured.

Results: Mean morphine infused, mean duration of PCA, mean post-operative pain scores on day 1-2 and mean hospital stay recorded in Table1.

Supplementary analgesia utilised in group 1; 3 patients required 1 extra drug, 4 required 2, and 1 required 3. Supplementary analgesia utilised in group 2; 4 patients required 2 extra drugs, 3 required 3, while 1 required 4 different drugs.
Better pain scores and reduced morphine usage in CIATS but not significant. There was statistical significance between the 2 groups in mean duration of PCA usage (p=0.05).

Conclusions: CIATS is efficacious in the management of post thoracotomy pain.

	Group 1(CIATS + PCA)	Group 2(PCA)	P values
Mean total morphine infused (mg)	92	112	p=0.29
Mean duration of PCA used (hrs)	44	66	p=0.05
Mean post-operative pain score D1	2.2	2.4	p=0.37
Mean post-operative pain score D2	1.8	2.7	p=0.22
Mean hospital stay (days)	7	7	p=0.5

From Behcet's Disease to Dilated Cardiomyopathy: A Patients' Journey

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Behcet's disease or the silk route disease is a rare, multi-systemic, autoimmune disease of unknown aetiology. This vasculitic syndrome initially presents with mouth and genital ulcers and later on affects the eyes, intestines and central nervous system. The current rate of prevalence in the United Kingdom is 0.64 per 100,000.

This case study highlights the journey of a 26 year old Caucasian showroom assistant from Liverpool who started developing mouth ulcers in his early teens. Aged 21, he developed genital ulcers which he described as 'tender, open wounds' lasting a few weeks. All possible sexual diagnoses were excluded and he was referred to rheumatology where a pathergy test confirmed the diagnosis of Behcet's disease.

Soon after the diagnosis, he reported constant palpitations and shortness of breath after little or no exertion. A 24 hour electrocardiogram (ECG) showed that he had supraventricular tachycardia, P wave morphology with ventricular ectopics. A diagnostic transthoracic echocardiogram confirmed left sided heart failure and dilated cardiomyopathy with an ejection fraction (EF) of 33%. There was moderate global hypokinesia of left ventricle along with reduced left ventricular systolic function. He was treated with a beta-blocker, an ACE inhibitor and a loop diuretic which improved his EF to 44%. He requires treatment from time to time for episodes of pyelonephritis, epididymitis and recurrent E.coli infections.

In conclusion, dilated cardiomyopathy in a Behcet's patient is a rare presentation with only a few reported cases and symptoms of heart failure should be promptly assessed by echocardiography.

Vitamin B12 and Vitality: A questionnaire study to determine patient perceptions of B12 effect on vitality

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B12 deficiency is common: prevalence ranges from around 4% in young adults to 12.6-14.5% in older adults. Short-term failure of treatment impacts quality of life. A 3-monthly B12 injection is the most popular treatment method, however guidelines on treatment frequency are not evidence-based, and patients report a return of symptoms before receiving their next injection.

Primary care patients receiving B12 injections were identified by GPs and postally surveyed to determine symptom recurrence. The survey was also available for completion via the NACC website. 465 responses were received by April 4th 2012. In the week before injection, over half of the sample reported tiredness, energy levels, concentration, bodily aches and mood as 'Poor' or 'Terrible'. More than 5 symptoms are affected in 54.8% (95% CI: 50.3-59.4) participants. 31% (95% CI: 26.5-35.5) experience symptom onset more than one week before injection. 58.0% (95% CI: 53.5-62.5) participants want the injection more often. A small proportion (15.8% (95% CI: 12.4-19.1)) would prefer oral B12 to an injection.

In conclusion, a substantial majority of participants experience multiple symptoms, often more than a week before their next injection is due. Further studies are required to establish an evidence base for treatment frequency, to minimise symptom recurrence. Oral B12 may be trialled in a primary care setting for those patients that would prefer it.

Case series: Deep peroneal nerve compression in 2 patients caused by an osteophyte arising from the 2nd tarso-metatarsal joint.

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Background: Compression neuropathies of the foot and ankle are uncommon and may be underdiagnosed and underreported in the literature. Deep peroneal nerve (DPN) compression typically causes pain or dysaesthesias in the first dorsal webspace, discomfort at the site of compression and night pain. Compression of the DPN typically occurs beneath the inferior extensor retinaculum. We report two cases of DPN compression recently encountered in our institution. In both cases, the compression was caused by an osteophyte arising from the 2nd tarso-metatarsal joint. This is an unusal presentation of midfoot arthritis that could easily be misdiagnosed. The authors aim to raise awareness of this pathology as a cause of DPN compression in the foot.

Methods: A literature review was performed using medline and pubmed databases. No case reports of DPN compression secondary to osteophytosis of the 2nd tarso-metatarsal joint were found.

Results: Conservative management with orthotics failed in both cases. Patient 1 has recently undergone surgery and is awaiting review. Patient 2 has not yet undergone surgery.

Discussion/Conclusion: Successful management of foot and ankle compression neuropathies is entirely dependent upon identifying the precise site of nerve compression. Recent advances in electrodiagnostic and imaging modalities have increased our understanding of the pathologies associated with these conditions. Sound clinical examination skills are essential and an awareness of all possible causes of foot pain/dysaesthesia is required in order to request the most appropriate investigation in the first instance. The authors feel that midfoot arthritis deserves recognition as a cause of DPN compression.

Characterstics of gestosis in partureints with heart disease

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Background: Heart disease can complicate pregnancy due to increase stress on heart, one of the most common complication is late gestosis of combined form.So in this complex problem particular importance is the further improvement of tactics in term of preservation of parturients and fetus.

Objective: Study of outcomes and characteristics of gestosis in parturients with heart disease.

Materials and Methods: We analyzed 15 parturients with heart disease, aged 19 - 40 years with primigravida - 7 and multigravida - 8. Acquired heart diseases occurred in 10 (66.7%) and congenital in 5 (33.3%). In acquired heart diseases most common being mitral valve insufficiency - 8 (80%) and mitral stenosis - 2 (20%) . Pregnant with compensated heart diseases were 66.7% and cardiac decompensation occurred in 33.3% of pregnants.

Result: Appearance of gestosis in the second half of pregnancy were observed from 19-22 weeks in 10 parturients, from 28 weeks - in 5 parturients. In 7 cases - 1st stage of gestosis in the form of oedema, in 6 cases - in the form of edema and arterial hypertension and in 2 cases in the form of oedema and proteinuria of up to 0.033% were present.
Other obstetrical problems in these parturients were anaemia - 76%, chronic feto-placental insufficiency - 100%, intrauterine growth restriction - 24%, risk of pregnancy termination - 48%.
Delivery related complications like delayed rupture of membranes - 16.8 % of cases, primary and secondary uterine inertia - 38.5%, hypoxia and birth asphyxia were noted in 27.1%. Episiotomy was performed in 44.4% of cases.

Conclusion: Only correct outpatients observation early detection of sub clinical stages of gestosis and their adequate correction to avoid severity especially in parturient with heart disease can ensure a women to the happiness of motherhood.

Counselling of Women in Preterm Labour: Exploring Current Practice and the Benefits of Additional Written Information

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During antenatal counselling in preterm labour, the possible risks and outcomes of early delivery are explained to parents. Current standard practice offers verbal counselling alone to women who are likely to deliver below 35 weeks of gestation.

This study assessed effectiveness of antenatal counselling in preterm labour, and evaluated benefits of providing additional written information.

25 mothers who delivered between 26+0 and 34+6 weeks gestation were recruited, in two consecutive cohorts, at a single hospital. The first cohort received standard verbal information, and the second, additional written information in the form of a newly designed leaflet. Questionnaires were given within one week of delivery, to assess efficiency of counselling, changes in perceived understanding and preparedness, and opinions on the quality of information provided.

The counselling process improved maternal understanding equally in both cohorts with 75% of mothers understanding "a fair amount" or more after counselling. Preparedness was significantly improved post-counselling (p=0.02) with a higher proportion in the leaflet group showing an improvement (75% vs. 43%). More mothers in the leaflet group also felt well-informed (78% vs. 64%), and fewer in this group wanted further information (56% vs. 80%). 100% of those who received the leaflet found it helpful.

Findings suggest written information, as an adjunct to verbal counselling, is beneficial to parents. Participants felt leaflets were useful, as they added to understanding and could be used as a reminder of information. Doctors at the study site have now adopted the leaflets as part of their standard practice.

Health beliefs about preschool immunisations; an exploration of the views of Somali women resident in Birmingham

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Background: Preschool immunisations significantly reduce child morbidity and mortality. Successful immunisation depends on the attitudes of mothers towards vaccinations. The Somali community in Birmingham forms a significant proportion of the growing Black African ethnic group, which has the lowest levels of preschool immunisation. There is no existing evidence regarding the perceptions towards preschool immunisations dominant in this community.

Aim: To explore the health beliefs of Somali women resident in Birmingham regarding preschool immunisations with the intention of assisting healthcare providers to deliver services in a manner sensitive and complementary to the Somali culture.

Methods: Designs: Semi-structured interviews. Setting: Third-sector organisations providing services to Somali women in Birmingham. Recruitment: Somali women who are mother of at least one child under five years old. Analysis: Thematic analysis concurrent with data collection.

Results: Data were collected from 23 participants. General attitudes towards preschool immunisations were positive. However, beliefs were affected by mothers' perceptions of their child's susceptibility to infection as well as a fear of side effects, including Autism. There was evidence of a fatalistic outlook on health, shaped by religious beliefs. Many mothers also feared, and sometimes refused, immunisations due to the belief that they contain gelatine.

Conclusions: Results suggest increased education is needed to improve knowledge and decrease suspicion of immunisations. Time should be taken by clinicians to ensure understanding of the purpose of vaccination in order to reduce fear and speculation. Religious advisers should be updated on the ingredients of immunisations so that they can accurately advise the Somali community.

Brody's Syndrome with autosomal dominant inheritance: An extraordinarily rare case of muscle cramping.

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Brody's syndrome is a rare inherited myopathy affecting just 1 in 10 000 000 births, characterised by exercise-induced impairment of muscle relaxation. Inheritance is typically autosomal recessive, and a significant number of these cases harbour mutations in ATP2A1 which encode SERCA1, the fast twitch fibre isoform of sarco/endoplasmic reticulum Ca2+-ATPase. Rarer autosomal dominant cases have been reported; however, genetic aetiology remains undetermined.

We present L.W., a 49-year-old, female company director, who presents with exercise-induced muscle cramps which exacerbate in the cold. Symptoms date back to early childhood. She has never been able to run and describes difficulty sustaining muscle activity sufficient to ascend a set of stairs. L.W. reports several episodes of prolonged cramps and myalgia associated with pigmenturia, consistent with rhabdomyolysis. Throughout her adult life several differing rheumatological diagnoses have been postulated. Neurological examination was remarkable for mild proximal weakness. Repetitive exercising induced cramping activity that was electrically silent. Creatinine kinase was elevated at 1100IU/L. There is an interesting and complex family history which is likely to reflect an autosomal dominant inheritance spanning three and possibly four generations.

This case represents only the fifth autosomal dominant case of Brody's syndrome reported in the literature. So far, attempts to define a genetic locus have been unsuccessful. This family may elucidate genetic and molecular processes underlying this heterogeneous condition. Such insight may help guide more targeted therapeutic options. This case also exemplifies the formidable diagnostic challenges of rare inherited muscle disease presenting with non-specific musculoskeletal symptomology.

Churg-Strauss Syndrome in a Patient with Allergic Bronchopulmonary Aspergillosis – A Diagnostic Challenge

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Few instances of Churg-Strauss syndrome co-existing with Allergic Bronchopulmonary Aspergillosis (ABPA) have been reported in the literature.

This is the case of a 62-year-old man presenting with shortness of breath, lethargy and weight loss of two stone in three months. He had a history of ABPA, asthma, bronchiectasis, emphysema and unilateral deafness.

Examination findings were normal save a cachectic appearance and a slight right radial nerve palsy. The initial working diagnosis was an exacerbation of ABPA. A full blood count revealed a Haemoglobin count of 9 g/dl and an eosinophil count of 7.91 x109/l. Serum urea and creatinine were 8.3 mmol/l and 133 µmol/L respectively.

Computed Tomography of the chest showed emphysema, bronchiectasis and a ground-glass appearance. A gastroscopy, colonoscopy and subsequently a bone marrow biopsy revealed no cause for the normochromic, normocytic anaemia. Nerve conduction studies showed no sensory response in the right medial and ulnar nerves. The urine albumin:creatinine ratio was raised and there was some microscopic haematuria. He was found to be pANCA positive, with a raised anti-myeloperoxidase titre. He was subsequently treated with oral steroids which led to an improvement in his breathing and renal function, with the neuropathy showing signs of amelioration over the following weeks.

Complex patients with vague symptoms often present a challenge to medical teams caring for them, particularly when no unifying diagnosis is forthcoming. This case highlights the need to approach such patients holistically in a systematic fashion, involving other specialties early to avoid overlooking aspects of patient care.

An unusual presentation of testicular torsion in a young patient

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Testicular torsion is a surgical emergency commonly occurring in childhood. This case highlights an unusual presentation whereby the diagnosis was made after three admissions and thirty hours from symptom onset.

A fourteen-year-old boy presented with gradual onset severe abdominal pain with a one-week history of feeling unwell, diarrhoea and vomiting. On examination he was uncomfortable, apyrexial and tender over the right renal angle, right iliac fossa and suprapubic region. Initially both testes were fully descended, of normal lie and non-tender. Six hours later his left testis was high-riding and slightly enlarged. After another hour his right testis was high-riding and horizontal, lobulated but non-tender. Physical examination was otherwise normal. An ultrasound scan showed heterogenous enlargement of the right testis with no blood flow. Surgical exploration followed by right orchidectomy and left orchidopexy was performed. Right testicular torsion was confirmed, predisposed by bilateral bell-clapper deformity.

Sudden severe scrotal pain and other characteristic features were absent, except for abnormal lie of both testes. This caused unnecessary delay in diagnosis and subsequent intervention, thus necessitated the removal of an extensively necrotic testis that could have been salvaged otherwise by detorsion. Research and guidelines advocate urgent surgical exploration if an acute scrotum is suspected, as increased waiting time and ensuing tissue damage reduce testicular salvage dramatically.

Management of this patient could have been improved by tackling communication with teenagers, relative inexperience of junior doctors, strict adherence to guidelines, and the essential need to recognize that patients do not always present with archetypal 'textbook' symptoms.

Retrospective Study of a Type B Aortic Dissection Population In The University Hospital of Antwerp (UZA)

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Background: Acute complicated dissections are mostly treated via open surgery or with TEVAR. The golden standard for the acute uncomplicated AD's is conservative treatment with rest and antihypertensiva. Retrospectively we explored if this approach can be extrapolated to the UZA-population.

Methods: We collected data from 2003 until 2011 and a total number of 50 patients were included. Using the hospital's database we gathered all useful information concerning type B AD's.

Results: From the total of 50 patients, 23 were complicated and 27 uncomplicated. The male gender clearly overbalanced counting 40 men and 10 women. Most dissections were seen between the age of 50 and 70. Four Marfan patients were included. Thirty-four patients were initially treated conservatively from whom 26 were uncomplicated and eight complicated. Eight patients had open surgery and all of them showed one or more complications. Eight patients were treated with TEVAR, seven were complicated. From the conservative uncomplicated 23 survived, however 3 of them developed a complication obliging open surgery. In the conservative complicated group 5 patients survived from whom 3 eventually underwent open surgery. Five patients survived in the open complicated group and one was lost to follow up (LTFU). The complicated type B AD's treated with TEVAR held 2 survivors and 2 were LTFU. The one uncomplicated who was treated with TEVAR was LTFU.

Conclusion: UZA also considers conservative treatment in uncomplicated type B dissections as the golden standard. We can also notice that there is no advantage in trying to treat complicated type B AD's on a conservative base. Furthermore our data imply that the prevalence of type B AD's is higher in men. The factors responsible for this probable correlation need to be explored in the future. In case of a complicated type B dissection an open approach seems to have a better outcome.

Auto-antibodies in SLE: Is Antigen Microarray the Future in Autoimmunity Diagnosis?

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The successful diagnosis of Systemic Lupus Erythematosus (SLE) is based on clinical presentation as well as multiple autoantibody serological testing; both of which are expensive and time-consuming. This study aimed to optimise and henceforth illustrate the potential use of antigen microarray to detect various autoantibodies for the purpose of screening as well as disease monitoring. Serum samples were obtained from SLE patients (n=19) and healthy controls (n=7). The serum was analysed by antigen microarray technology to detect 8 known SLE antigens, a Rheumatoid Arthritis (RA) antigen and several positive control antigens. Optimum results were obtained when antigens were printed in trehalose PBS-Tween onto aminosilane slides (Nexterion ®). The lowest background and highest signal-to-noise ratios were obtained when serum was diluted in antibody diluent (Dako). The main finding of this study was that patients had significantly higher autoantibody presence in 3 of the SLE antigens tested: Nucleosome, Ribonucleoprotein and Ribosomal P ($P<0.001$, $P<0.001$, $P<0.005$), in addition to the RA antigen CCP2 ($P<0.001$). Furthermore, antibody levels from patients on treatment correlated with disease improvement. These results suggest that microarray is an efficient technique to monitor and detect a wide variety of antibodies in multiple patients simultaneously, doing so at a relatively lower cost then current methods. This demonstrates the need for further development of this technology due the potential for providing a means of mass screening, early diagnosis and reliable monitoring of autoimmune disease including, but not limited to, SLE.

Vaccination uptake and timeliness on the Bijagos Archipelago

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Uptake and timeliness of childhood vaccination on the Bijagos Archipelago, Guinea-Bissau: a cross-sectional community-based study

Background: Vaccination uptake and timeliness are important for protection against childhood infectious diseases, especially in Guinea-Bissau where childhood mortality is high. This study assesses vaccination uptake and timeliness for a population in Guinea -Bissau and identifies predictors of full and timely immunisation.

Methods: A random 60% household sample identified 872 participants; data were collected by a cross-sectional community-based survey using an abridged validated questionnaire. Uptake for each vaccine was calculated by eligibility. Kaplan-Meier time-to-event analysis was used to show vaccination timeliness. Binary logistic regression was used to identify predictors of fully immunised status. A linear regression model identified predictors of timely vaccination, which was defined using a score.

Results: Vaccination uptake ranged from 50.4% (OPV1, 95% CI 48.2-52.6) to 92.9% (Pentavalent 1, 95% CI 91.8-94). 18.3% (95% CI 16.6-20) participants had received all recommended vaccines by one year of age. Only 10.7% (95% CI 9.3-12.1) of participants received all vaccinations within the recommended time periods; timeliness ranged from 39.5% (Yellow Fever vaccine, 95% CI 37.7-41.6) to 63.5% (BCG, 95% CI 61.4-65.6). Maternal tetanus immunisation and proximity of participants' village to hospital were significant predictors of fully immunised status; the latter was also predictive of timely immunisation, as was access to a private latrine.

Conclusion: Coverage varied between vaccines but in general was reasonable, surpassing latest national estimates. Timeliness was poor; a large number of children were unprotected for several months before vaccination. Efforts are needed to improve timeliness; these should include community outreach nursing and health education, guided by qualitative research.

An Evaluation of the Management of Child and Adolescent Anorexia Nervosa by CAMHS Fife: A qualitative Study of Views of Healthcare Professionals

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Background: Anorexia Nervosa (AN) is a severely debilitating and dangerous disorder that requires a prolonged, multidisciplinary approach to overcome it. In females, it has the highest mortality rate of any other psychiatric disorder. Despite this, the evidence base for the best treatments is weak and there is a patchy distribution of specialist, outpatient services throughout the UK. This research aimed to evaluate Fife's model of service provision for adolescent AN sufferers. Furthermore it aimed to gather healthcare professionals' perspectives on this service and the new models used, and discuss any changes which could benefit the current service.

Methods: A qualitative approach was used. Semi- structured interviews were carried out with nine healthcare professionals involved in the management of child and adolescent AN in Fife. The results were transcribed and Framework Analysis was used to analyse the results.

Results: Fife provides an outpatient service for AN patients. Less ill patients are treated by two specialist Eating Disorder (ED) nurses. The more severely ill patients are treated by a multidisciplinary team. This team supplies intensive, community based therapy to all acutely ill psychiatric patients with the ethos of avoiding, where possible, inpatient care.

Conclusion: Fife has a well structured and effective AN service which fulfilled almost all the NICE guidelines. Although a solely specialist multidisciplinary ED service would be 'gold standard', there is insufficient funding to provide this throughout the UK. Fife's model seems a pragmatic compromise which may be a good template for other regional CAMHS services to adopt.

Pre-operative liver function predicts survival and recurrence after hepatectomy for hepatocellular carcinoma (HCC) arising from non-cirrhotic/non-fibrotic liver: a European perspective

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Background: In western countries, most HCC cases occur against a background of cirrhosis. This study evaluated outcomes and prognostic factors following hepatectomy for HCC arising in non-cirrhotic/non-fibrotic livers.

Methods: Patients undergoing hepatectomy for HCC were identified from a prospectively maintained database. Patient demographics, pre-operative biochemical and haematological factors, intra- and post-operative clinical details, and tumour pathology were analysed against overall survival (OS) and disease progression-free survival (PFS).

Results: 57 patients underwent hepatectomy for non-cirrhotic/non-fibrotic HCC. Median PFS was 33 months and OS was 37 months, with 3- and 5-year OS of 48% and 39% respectively. 42% developed recurrent HCC. In univariate analysis, the ratio of AST or ALT to the upper end of the normal range affected both OS and PFS [$p<0.001$ (survival), $p<0.001$ (recurrent)]; whereas pre-operative bilirubin ($p=0.04$), percentage lymphocyte count ($p<0.03$) and neutrophil/lymphocyte ratio ($p<0.05$) were related to PFS. Excluding non-hepatic recurrence, pre-operative liver enzyme ratio were significantly elevated among patients whose disease recurred ($p<0.01$). There was a non-significant trend towards poorer survival for patients with poorly differentiated tumours ($p=0.07$). Tumour size, number of tumours, resection margin, micro-vascular invasion and capsular involvement were non-significant for both OS and PFS. Using multi-variate analysis, pre-operative liver enzyme ratio was an independent factor related to OS and PFS after hepatectomy.

Conclusions: Pre-operative liver function may be a prognostic factor for OS and PFS after HCC resection in non-cirrhotic/non-fibrotic livers.

The administration of prostin during the induction of labour at a district general hospital

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Induction of labour (IOL) is carried out when further duration of pregnancy could put the mother and/or the baby at risk. IOL is associated with risks including uterine hyperstimulation and therefore, pregnant women undergoing induction should be managed with care.

At St Peter's Hospital, one cycle of prostin is inserted vaginally to induce labour. This is given based on the patient's Bishop score, which is assessed by performing a vaginal examination. According to trust guidelines, after six hours the woman's Bishop score is reassessed and, if less than ten, further prostin is given.

I looked at whether women being induced were given a further dose of prostin if their second Bishop score was below ten. I analysed the labour notes of 61 women undergoing IOL between January and February 2012. I recorded the first Bishop score, the time of first prostin, the time of second Bishop score assessment and whether prostin was given.

Twenty women out of a total 52 (38.5%) with a second Bishop score below ten were not given prostin. Seven of these women were given prostin further into the induction. The average time between first and second prostin in this group of women was 19 hours 54 minutes.

The administration of the second dose of prostin at St Peter's hospital is not consistently carried out according to trust guidelines. This can lead to an unnecessary lengthening of the IOL process. As a result, the trust has applied for a license to induce labour using slow release prostin.

An audit of peripheral intravenous cannulation technique in the Emergency Department: improving infection control practice using the Accuvein AV300

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Background: Peripheral intravenous cannulation is one of the most common procedures performed in the Emergency Department (ED), aiding investigation and treatment1. Clinical audit was used as a tool to examine the technique and performance of this skill in the ED of Leicester Royal Infirmary - highlighting areas for improvement.

Methods: Guidelines facilitated the development of audit criteria and standards2. As a result, a proforma was designed to observe 100 adult patients requiring peripheral intravenous cannulation in the majors area of the ED. All data collected were coded and entered into a spreadsheet for analysis, and an initial recommendation for change was made. A further 100 patients were observed in the re-audit (200 patients in total).

Results: The first audit cycle highlighted deficits in the overall performance of the procedure including: inadequate drying time after skin cleaning (43%); re-palpation at the insertion site (41%).
The use of the hand-held infra-red vein illuminator AccuVein AV3003 was chosen as a novel approach to improve these deficits and was subsequently evaluated in the second audit cycle.There was a significant reduction in the rate of re-palpation (down from 41% to 24%). All other criteria improved, but remained similar.

Conclusion: This audit has raised awareness of peripheral intravenous cannulation technique in the ED. The use of the AccuVein AV300 significantly improved infection control at the cannula insertion site, enhancing patient care and safety. A tailored inter professional education package has recently been established to promote the introduction of the device into daily clinical practice.

References:
1. Ortega, R., Sekhar, P., Song, M. *et al* 2008, 'Peripheral intravenous cannulation', NEJM, 359(21), e26
2. University Hospitals of Leicester (UHL), 2007, 'Intravenous Peripheral Cannulation: Policy and Procedures, Leicester
3. AccuVein LLC, 2009, 'AccuVein AV300 Operating Guide', New York

Investigating the role of Fascia Iliaca blocks in the preoperative management of hip fracture patients-a junior doctor service

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About 75,000 hip fractures occur annually in the UK and the incidence is expected to increase. Acute pain control, traditionally managed with systemic analgesia, is crucial to outcome. Often there is a delay in pain-relief administration. Furthermore, there is a risk of systemic side effects. We performed a prospective case-control audit to analyse the role and efficacy of alternative forms of analgesia like fascia-iliac blocks (FIB).

One hundred and four consecutive hip fracture patients were prospectively recruited and equally divided into; cases (patients receiving FIB) and controls (patients receiving systemic analgesia). Adequately trained junior doctors performed all blocks. The outcome measures included the time of initial analgesia, total pre-operative dose of analgesia, regularly measured pain scores from admission to 24 hours pre-operatively and any complications.

The pain scores were significantly lower ($p=<0.05$) in patients receiving FIB at 2, 8 and 16 hours pre-operatively. The timing of initial analgesia was also quicker in patients with FIB (25 compared to 40mins). FIB patients required fewer doses of systemic analgesia. The block was successful in 83% patients. There were no complications.

The implementation of European Working Time Directive, Hospital at Night, shift-system and the reduction in the number of medical staff has increased the burden on Emergency Departments. Junior doctors are often at the forefront of service delivery and can actively contribute to adequate pain management of hip fracture patients. FIB, performed by junior doctors, is not only safe and effective analgesia but also provides an opportunity for junior doctors to improve current clinical practice.

Assessing the timeliness and completeness of the discharge summary within a community hospital: A clinical audit of 158 patient cases

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The discharge summary allows for effective dissemination of patient information between the hospital and GP, ensuring for the continuity of care that a patient receives subsequent to discharge. However, given the increasing concerns that hospitals are failing to deliver discharge summaries in a timely and complete manner, the present audit examined the quality of current discharge summary practice within a Merseyside community hospital. Assessment was done by systematically selecting 158 discharge summaries from 8 medical consultant teams over three months. The extent to which discharge summaries were generated in a timely and complete manner were analysed according to current local and national guidelines respectively. Only 42% of discharge summaries overall were typed up within the current local guideline period with only one of the eight consultant teams being able to do so consistently. There was also considerable variation amongst consultant teams regarding the completion rates of discharge summaries with regards to medications on discharge, follow-up instructions and past medical history in particular. In conclusion, to consistently ensure for a timely and complete dissemination of patient information a more standardised format is required. Given the potentially disruptive nature of introducing an electronic discharge summary platform, at least in the short term, this audit recommends a standardised dictation template to slowly phase in the benefits of a standardised discharge summary process. The author has developed a template which is currently being implemented across the hospital which may ultimately pave the way towards a fully integrated electronic discharge summary process long-term.

An Audit of Medication Review in Palliative Care

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Background: Medication review is an integral part of good medical practice. It is of particular importance when treating the elderly and end of life patients to avoid polypharmacy and thereby reduce side effects, reduce medication burden and improve concordance in these vulnerable patients.

Method: The medical notes of all patients admitted during a one week period were retrospectively reviewed to identify how frequently medication reviews at admission were carried out. Following liaison with the Medication Safety Department a ward-specific proforma was devised to assist in carrying out medication reviews at admission. The proforma was then introduced and trialled in the department to be used on admission of every patient. A second assessment of medication review on admission was completed after four weeks of trialling the proforma.

Summary of results: The initial audit identified that only 37% of patients had a documented medication review on admission. Following introduction of the proforma, 100% of patients had a medication review.

Conclusion: Junior doctors frequently omitted patient medication reviews at admission to hospital. The introduction of a proforma to assist with medication review on admission resulted in complete compliance. It is also proposed that a clearer medication review (and therefore clearer documentation) will assist with communicating changes in medication to primary care on patient discharge.

Investigating the effectiveness of an indoor residual spraying programme in reducing the public health burden of malaria in a Malawian community

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Introduction: The global health burden of malaria is vast and Malawi is particularly badly affected; thus an effective method of malaria control is badly needed. In 2009, an indoor residual spraying programme (IRS) was commenced in the Nkhoma, Malawi. A population of 60,490 were targeted by the programme which aimed to reduce malaria incidence in the region by 25%.
This project was designed in order to evaluate the effectiveness of the programme.

Methods: Two different study designs were used. A retrospective cohort study compared outpatient malaria cases in in sprayed and non-sprayed areas (the catchment areas of Chimbalanga and Matapila health centres respectively) during selected monthly periods between December 2008 and March 2012.
In addition, a case control study analysed data from a parasitaemia survey of 148 randomly selected children <5 years to observe the relationship between living in a sprayed home and contracting malaria. Both used secondary data held by Nkhoma Hospital Public Health Department.

Results: The cohort study showed that the introduction of IRS to Chimbalanga had coincided with a reduction in malaria incidence in children <5 years and adults. Insufficient data were available to produce any findings regarding malaria incidence in pregnant women. The parasitaemia survey revealed that children who lived in a sprayed home were 24.26% less likely to contract malaria.

Conclusion: The introduction of IRS appears to have contributed to a reduction in malaria incidence in the Chimbalanga region. Living in a sprayed home offers protection from malaria for children <5 years.

Steroid Reduction Adherence in Post Renal Transplant Patients

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The aim was to assess compliance with the steroid reduction regime in renal transplant patients. Renal transplantation offers patients improved mortality, morbidity and quality of life compared to renal replacement therapy. It is beneficial to slowly dose reduce steroids in transplant patients accepting that altering immunosuppression therapy carries a risk of acute rejection.

Standards:

1. Patients received triple combination immunosuppressant therapy. Standard Expected 100%
2. Post-renal transplant patients are on prednisolone. Standard Expected 100%
3. Corticosteroids were dose reduced in 5mg increments over the 6 post-operative weeks. Standard Expected 100%
4. Patients with acute rejection were given high dose methylprednisolone. Standard Expected 100%

Method: Retrospective case note audit of 45 consecutive patients transplanted between April and October 2011. Data was recorded on a spreadsheet.

Results: Combination immunosuppression therapy: mycophenolate mofetil, tacrolimus and prednisolone was used for all patients.

Appropriate steroid reduction to 5mg was only achieved in 56% (n=25), compared to an expected performance of 100%.

Performance level for treatment of acute rejection was 100% (n=6).

Conclusion: Overall performance levels were desirable; all patients received correct immunosuppression therapy with acute rejection episodes treated appropriately. Many patients received higher doses of prednisolone for longer than expected. Steroid reduction has not achieved a desirable performance level with factors contributing to the poor performance being easily modifiable.

Paediatric Day Case Tonsillectomy a Safe, Feasible and an Economical way to treat patients –Yorkhill Experience

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Introduction: Day case surgery is widely encouraged as it has many benefits. In this study we evaluate the feasibility of paediatric tonsillectomies as day cases surgery procedures in a tertiary paediatric centre.

Methods: The outcome of paediatric tonsillectomy performed as day case procedures were studied for four months. We recorded complication rates in comparison to the standard in-patient practise

Results: 23 paediatric patients were included in this study. The age of the patients ranged from four to 11 years, with mean age of 6.5. No patients suffered postoperative complications within the first 24 hours. Two patients were re-admitted due to a post-operative complication (8.6%) and one patient for a non-operative cause (4.3%) beyond the initial 24 hours.

Conclusion: Paediatric Day Case Paediatric Tonsillectomy is a safe, feasible and an economical way to manage patients.

Ophthalmic uses of Botulinum Neurotoxin

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Background: Botulinum neurotoxin (BoNT), a neuromuscular inhibitor used in the management of facial dystonia and strabismus, provides symptomatic relief from the unwanted effects of abnormal muscle contracture. Research or audit into its use is poor, related to the lack of benchmarks from published data and the low clinical importance often given to the conditions treated. Greater awareness of clinical governance, and the need to standardise patient care has raised the importance of these conditions and their treatment. Evaluation of current practice is now considered a priority in order to establish new guidance, set standards, monitor clinical practice, and patient satisfaction with their care.

Aims: To identify
- Ocular conditions requiring BoNT treatment
- Factors influencing treatment outcome
- Patient perceptions of efficacy
- Need for change in practice

And additionally, publish and dissemination findings to improve quality of patient care.

Methodology: Without a diagnostic code-index or clinical database, patients were identified from a strabismus clinic logbook and prospectively for dystonia clinic attendees. Retrospective data collection was then carried out from patient records.

Results: One hundered and sixty eight patient records were identified. Diagnostic categories of Dystonia patients clearly formed two main groups: blepharospasm and hemifacial spasm. 90% of dystonia patients showed identifiable and treatable exacerbating factors, however few triggers were adequately treated. Most strabismus clinic patients received BoNT to plan surgery. 24 patients (40%; 95% confidence interval, 29% to 53%) were corrected to the level expected post-operatively.

Conclusion: Exacerbating factors including psychosocial issues influence diagnosis and treatment outcomes in dystonia. Similar conditions are reported in strabismus patients. High volume treatment clinics do not allow the time to identify or manage these. This particularly in dystonia patients may influence success and need for treatment. In strabismus patients this oversight affects quality of care.

An audit of the implementation of NICE and Health Protection Agency guidelines for the investigation, management and notification of TB and study into relationship between vitamin D levels and MTB for UK and non UK resident patients.

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Introduction: Literature of functions of vitamin D has demonstrated a potential immunomodulatory role for response to Mycobacterium tuberculosis (MTB) infection. There is potential use for vitamin D for prevention and treatment of MTB. There may be a link to vitamin D levels and country of origin as a large proportion of MTB patients are of non-UK origin.

Aims: To study MTB epidemiology and measure time between arrival in UK to diagnosis of infection for non-UK residents. To measure levels of vitamin D and its biochemical markers in infected patients. To assess the implementation of NICE guidelines in MTB management.

Method: A retrospective study analysing records of 75 MTB infected patients, who were treated in the Infectious Disease department (UK) between 2007- 2011. The audit tool was devised from NICE guidelines (2006).

Results: Fifty one patients were non-UK origin; 47 % developed disease within 2 years of arrival in UK and 25% within first 5 years. Extra-Pulmonary MTB is more common in immigrants from Asia and the Middle East. All patients, 63% had some biochemical evidence of vitamin D deficiency. Those tested for vitamin D deficiency all had significantly low levels. Audited standards for diagnosis by sputum analysis and x-ray were met by 54% and 26% respectively. 82% had correct duration of treatment. 42% had notified the Health Protection Agency (HPA).

Conclusion: The results show a potential significant relationship between vitamin D and MTB. Comparison of results with vitamin D levels in uninfected UK and non-UK origin patients would prove valuable.

How reliable is the wells criteria as a screening tool for pulmonary embolism in a district general hospital?

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Background: The Wells Criteria is a 7-criterion screening tool developed in Canada to help screen patients with a high probability of having a Pulmonary Embolism (PE). This helps the clinician decide if the patient merits further investigations such as a Ventilation-Perfusion Scan or a Computed Tomography Pulmonary Angiogram (CTPA) which whilst being the gold standard for PE diagnosis, can be extremely costly and also exposes patients to significant radiation. Our retrospective analysis aimed to determine the sensitivity & specificity of Wells Criteria for diagnosis of a PE.

Methodology: The notes of all patients who had a CTPA in 2011 were identified and the relevant data extracted. Data was then analyses using the SPSS Statistical Software.

Results: There were 44 patients who had a CTPA in 2011. A Wells Score of more than 4 indicated a high likelihood of PE whilst a Wells Score of 4 or less indicated a low likelihood of PE. Results are summarised in the table below.

		CTPA		
		Positive (PE present)	Negative (no absent)	
WELLS SCORE	>4	13 patients	4 patients	Positive Predictive Value = 76.48%
	≤4	2 patients	25 patients	Negative Predictive Value = 92.59%
		Sensitivity = 86.67%	Specificity = 86.21%	

Conclusion: The Wells Criteria had a sensitivity of 86.67% & specificity of 86.21%. This suggests that if used in combination with clinical judgement, the Wells Criteria can be a reliable screening tool for exclusion of PEs. This certainly will be helpful in smaller hospitals where financial resources and radiological expertise may not always be available.

Severity Scoring and Chest Radiograph Interpretation - Improving the Quality of Care for Hospitalised Community Acquired Pneumonia

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Introduction: Worldwide population-based studies of community acquired pneumonia (CAP) requiring hospitalisation have reported overall incidence between 1.1 and 4 per 1000 population per annum.[1] CAP is associated with high and variable mortality rates; in the UK this has been reported between 5.7 and 14%.[1] The management of CAP is therefore an important issue.

Method: A 70 day prospective casenote review between March and May 2011. The audit included all patients admitted to the respiratory wards via the Acute Medical Unit (AMU) with CAP. Hospital and national guidelines were reviewed and audit standards set.

Results: Data was collected on 47 patients, 24 male, mean age 74.9 years.100% had chest radiographs, 74.5% interpreted by AMU doctor, respiratory specialist and radiologist. There was common agreement in radiograph interpretation in 68.6% of patients. 100% had FBC, 97.9% U&Es, 63.8% LFTs and 57.4% CRP. Severity according to CURB65 was scored in 39 patients (82.9%), correctly scored in 27 patients (69.2%). According to assigned CURB65 scores, 47.5% had blood cultures, 40% had sputum cultures, 33.3% had atypical serology sent appropriately. Mortality rate was 21.3%. 62.5% of patients that died had incorrectly scored severity.

An audit of temperature on arrival to recovery and availability of intra-operative warming in operating theatres

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Inadvertent perioperative hypothermia is well-known and preventable consequence of anaesthesia, which is associated with negative patient outcome. These include greater intraoperative blood loss, increased rate of infection, possible cardiac events, pressure sores and longer stay in hospital. Hence, maintaining normothermia perioperatively can modify these adverse outcomes.

This was a prospective audit of peri-operative temperature and availability of intra-operative warming. The data was collected by a FY1 doctor based in the main recovery of ARI theatres for five days. All patients who came into the main recovery post-operatively were included. A total of 196 patients' temperature was taken on arrival to recovery and availability of warming in theatre was obtained from the anaesthetics chart.

The results showed only 7% of patients had temperature less than 36 degree. Theatre 6 (ENT) and theatre 11 (trauma) had the highest percentage of hypothermia with 23% respectively. The procedure was shorter than two hours in 92% of the hypothermic patient. Fluid warmer and forced air warming were available almost 50% of the time while temperature probe are only available 34% of the time. 61.5% of patients with core temperature <36 did not have fluid warmer and 77% did not have forced air warming.

This audit shows that some patients were becoming hypothermic in theatre, even those having short procedures and this may be detrimental to their recovery. The authors recommend that temperature should be taken routinely prior to induction, monitored in the theatre, and patients actively warmed if their temperature falls even during short procedures.

Hygiene Behaviours and Trachoma on the Bijagos Archipelago, Guinea Bissau.

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A Cross-sectional Study Investigating Hygiene Behaviours in Communities Hyperendemic for Trachoma on the Bijagos Archipelago, Guinea Bissau, West Africa.

Trachoma, a neglected tropical ocular infection, is a major public health problem on the Bijagos Archipelago, Guinea Bissau. The World Health Organization endorsed the 'SAFE' (Surgery, Antibiotics, Facial cleanliness, Environmental improvements) strategy to eliminate blinding trachoma; this has yet to be implemented effectively in this region.

Methodology/results: A cross-sectional household survey examined associations between hygiene behaviours and the presence of trachoma. Data were gathered from 186 households using observations, a hygiene behaviour questionnaire and examining children less than 10 years of age. Presence of trachoma in a household was revealed by collaboration with an on-going prevalence survey.

Multiple logistic regression found households are more likely to have trachoma if they contain children with ocular discharge (OR 1.88; 95%CI 1.21-2.93) or if they report removing ocular discharge from a child's face using a towel (OR 6.93; 95%CI 2.35-20.42) Households are less likely to have trachoma if parents (OR 0.20; 95%CI 0.050-0.77) or the mother and child together (OR 0.19; 95%CI 0.045-0.80) are responsible for a child's face washing. The greater the volume of water stored in a household for hygiene purposes, the less likely that household was to have trachoma.

Conclusion: Associations between hygiene behaviours and trachoma in a household contribute to understanding the disease in this environment. A household hygiene promotion campaign is recommended to aid implementation of the 'F' and 'E' components of the SAFE strategy and improve hygiene practises. Qualitative research and an in-depth risk factor study are recommended to further understand trachoma in this under-researched environment.

Evaluate the effect of intravitreal Bevacizumab (AVASTIN) injection for diabetic macular oedema

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Introduction: Bevacizumab is an anti-VEGF (vascular endothelial growth factor) agent and it has originally been licensed for the treatment of metastatic colorectal cancer. However, it has also been used as an off-label drug for the treatment of diabetic macular oedema (DMO). This audit is to evaluate the effect of intravitreal Bevacizumab injection for DMO in Raigmore Hospital.

Method: This audit was done retrospectively. It involves all patients (total of 6) with DMO who have had intravitreal Bevacizumab injection over a state of 15 month period (from 15/04/2010-15/07/2011). All those patients had failed laser photocoagulation treatment before. The main outcomes was measured in terms of the changes in the best corrected visual acuity(BCVA) and central retinal thickness(CRT) by optical coherence tomography(OCT). The changes in BCVA were measured by comparing the mean baseline BCVA with the mean final BCVA during the 15 month period. Similarly, the changes in CRT were measured by comparing mean baseline CRT with the mean CRT in final OCT during the 15 month period.

Results: This audit involved 6 eyes (6 males; average age 68). All patients received average of 3 treatments during the 15 month period. BCVA has worsened from mean baseline BCVA of 0.625(logMAR) to final BCVA of 0.763(logMAR). Meanwhile, CRT has worsened from baseline CRT of 546μm to final CRT of 578μm.

Conclusion: Intravitreal Bevacizumab injection was not effective in treating DMO in Raigmore Hospital.

The Real Spectrum of Migraine

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Background: Perhaps surprisingly to those who have escaped the wrath of migraine, the WHO regards this condition as the most disabling illness, comparable even to the likes of highly stigmatized conditions such as quadriplegia and dementia. Diagnosis and management not only require clinical aptitude, but also the ability to apply basic concepts in neuroscience; such skills remain suboptimal for a number of physicians, with almost 50% of patients remaining undertreated or undiagnosed. Here, we present two case reports, one to demonstrate the atypical way by which this disorder may present and the second to provide evidence for the re-emerging continuum model of migraine. The latter rather boldly refutes the existence of tension-type headache (TTH) as a clinical entity, regarding it instead as a milder form of migraine.

Case Summaries: A 16-year-old male patient suddenly collapsed whilst playing football. He had been experiencing severe dizziness for the preceding few months with nausea and a mild headache. A cardiology review did not elicit a cardiac cause and he was eventually commenced on migraine-specific therapy. A 15-year-old male patient complained of recurrent headaches, which began with severe neck pain followed shortly by a headache, localized to his right temporal area. There were no other symptoms of significance and he did not respond to TTH-specific therapy.

Conclusion: With almost a third of neurology outpatient referrals comprising of headache complaints, it is clear that migraine is greatly misunderstood by the medical profession. Embracing the continuum model of migraine may lessen the impact of this disabling condition.

POSTER PRESENTATIONS

Audit into the Safe Mechanical Ventilation of Critically Ill Patients

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Background: The use of large plateau pressures and tidal volumes in the ventilation of critically ill patients has been shown to cause further damage through excessive pulmonary stretching and barotrauma. The ARDSnet protocol1 set out guidance to decrease the incidence of ventilation induced lung injury. AIM: To ascertain whether ventilation pressures set by Intensive Care Unit (ICU) staff were in accordance with the ARDSnet protocol. METHOD: This was a pilot observational study in which 7 patients admitted to the ICU in February 2011 were monitored over a period of 2 weeks. Their Peak Pressures, Tidal Volumes, Positive End -Expiratory Pressure (PEEP) , Fraction of Inspired Oxygen (FiO2) and Respiratory Rate were recorded whilst the patient was on Bilevel Positive Airway Pressure (BIPAP) and Continuous Positive Airway Pressure (CPAP). Any pathology as a result of high pressures was recorded. RESULTS: In 5 out of 7 patients on BIPAP and 4 out of 7 patients on CPAP, mean tidal volumes exceeded the recommended 6 mL/kg. PEEP and FiO2 values were matched adequately in 5 out of 7 patients on BIPAP and only 1 patient on CPAP. Peak pressures of more than 30cm H2O were recorded in 12.5% of readings in total. CONCLUSION: Ventilatory pressures in excess of the set guidelines were used but there was no evidence that any harm was caused. ICU staff should be educated as to the risk of using high ventilatory pressures and the importance of compliance with the standards set by ARDSnet protocol.

Discrepancy Between Estimated Fetal Weight and Actual Birth Weight

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Extremes of birth weight (<2500g, >4000g) are associated with fetal and maternal complications. Accurate prediction of growth abnormalities can reduce morbidity and mortality by up to 15%. In the UK, ultrasonography is the most widely used method of birth weight estimation.

Maternal diabetes is commonly associated with macrosomia (birthweight >4000g). Accordingly, diabetic patients have serial growth scans from 28 weeks to aid prediction of this abnormality. Thus, this cohort provides data in determining the accuracy of ultrasonographic weight estimation.

This study aims to quantify the discrepancy between ultrasonographically estimated fetal weight and actual birth weight, and compare results against accepted error (±10%). It is a retrospective case note review of 41 diabetic antenatal patients identified from November 2011- March 2012 at Sunderland Royal Hospital. Data collected was analysed by $\chi 2$ test. A $p<0.05$ was deemed statistically significant.

Mean study age was 30.8 years. Of the 41 patients, 60.6% had gestational diabetes, 30.3% type 1 DM and 6.06% type 2 DM. Mean BMI was 29.3. Mean birth weight was 3507g. Mean percentage error was 8.5%. However, 12 birth weight estimations (36.4%) had a percentage error >10%. The average birth weight of these 12 babies was 3538.9g. On closer analysis, birth weight above 3500g was found to be associated with significant error ($p = 0.048$). On average, estimations were 20% less than actual birth weight in this group.

It can be concluded that ultrasonography is a generally accurate tool in estimation of fetal weight, but is inaccurate in the prediction of macrosomia.

Audit of all open cases of Emerge looking at previous involvement with core CAMHS

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Background: There is growing evidence to demonstrate the fact that adolescence is a time of significant stressors. UK surveys illustrate the fact that developmental disorders of childhood are super ceded by mood and anxiety disorders. Adolescence is also a common time for previous and continuing mental health difficulties to be exacerbated, which during this volatile time can lead to poorer clinical and social outcomes. In addition to this it is a difficult time with regards to staying engaged with mental health services as it is the transition between childhood and adulthood. It would therefore be useful to know whether these problems are occurring within CAMHS (Children and Adolescent Mental Health Services) by looking at levels of disengagement by children and adolescents.

Method: This is an audit of all 267 case notes open to Emerge, a CAMHS service specifically for 16-17 year olds in Manchester. The aim is to find out how many adolescents had previous engagement with CAMHS.

Results: Notably, 44.6% of all patients open to Emerge were found to have had previous involvement with CAMHS, this figure rising to 61% in the least affluent areas of Manchester.

Conclusion: This audit showed a significant proportion of adolescents had disengaged from CAMHS despite continuing mental health problems showing issues regarding continuity of care are a significant difficulty. It illustrated disparities between affluences, showing that the less affluent areas of Manchester were less likely to engage with services perhaps implying there is poorer access to care for the more vulnerable adolescents.

Audit in general practice: uptake of the seasonal influenza vaccination (2011) among pregnant women registered at an inner city GP practice

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Pregnant women are at an increased risk of serious complications due to the influenza virus, and therefore are eligible to receive the free seasonal flu vaccination in the UK. Evidence of the safety and efficacy of the vaccine is strong, but despite this, uptake rates among this patient group were only 38.0% in the winter 2010-2011.

This audit analysed the records of 93 patients at an inner city GP practice who were identified as pregnant between 1/10/11 and 31/12/11. Results showed that 38.7% were vaccinated against influenza, a figure which is very similar to national rates.
On investigation into the strategies used by the practice for recruiting pregnant women to have the vaccine, letters were shown to have no positive influence over the likelihood of vaccination. Meanwhile, face-to-face encounters were shown to be very effective.

Therefore, in the action plan for improving the uptake rates next year, the main recommendations are: re-writing of the invitation letters; improving rates of opportunistic vaccinations by midwives (by re-education, re-training and policy-making); and introducing a text/phone invitation service at the beginning of the 2012-2013 flu season.

The Diagnosis of Pancreatitis in Paediatric Patients with Immune disorders at a Tertiary Centre

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Background: Paediatric pancreatitis is rare with an incidence of 10/100,000 per year. Higher incidences exist in children with immune disorders who are predisposed to pancreatitis due to immunosuppressant use and autoimmunity. The disease is enigmatic, differing in aetiology and presentation to that in the adult population. Diagnostic difficulty is perpetuated by the current lack of national diagnostic paediatric guidelines.

Standards:Great Ormond Street Hospital modified adult British Society of Gastroenterology and American Gastroenterological Association guidelines state a diagnosis of pancreatitis is made by: amylase/lipase >3 times upper normal limit, abdominal pain, blood tests (albumin, calcium, bilirubin, and CRP), and radiological findings of pancreatitis.

Aim: To determine whether the above diagnostic criteria are being adhered to at this tertiary centre and to assess suitability of the modified adult guidelines in paediatrics.

Method: Retrospective review of clinical and laboratory records of 50 patients with immune disorders presenting with amylase/ lipase >3 times upper normal limit from 2004-2011.

Results: 38% of patients presented with abdominal pain. 100% of patients' bloods were tested for amylase/lipase, and albumin levels. Not all patients had calcium (94%), bilirubin (88%), and CRP(82%) tested. 83% of patients had radiological investigations. Aetiology was determined in 58% of patients, with the major cause being drug-induced (50%).

Conclusions: This centre follows the modified adult guidelines in most cases, but paediatricians must maintain a high index of suspicion for pancreatitis as children present atypically. 100% of patients with raised pancreatic enzymes should receive blood tests and ultrasound scans. Closer drug monitoring is required in patients with immune disorders to reduce incidence of drug-induced pancreatitis.

MINERVA: A Patient Safety Tool

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Background: MINERVA is a patient safety tool used to cover 11 domains of patient care. The acronym represents MEWS (modified early warning system) score, mobility, invasive devices, nutrition/fluid status, estimated date of discharge (EDD), results, resus status/level of care, venous thromboembolism (VTE) prophylaxis, antibiotics, analgesia and appropriate handover. MINERVA is intended to make it easy for junior doctors to produce a structured ward round review which addresses the common management issues and highlights potential risks for each patient.

Methodology: An audit was completed analysing documentation of the MINERVA criteria for 60 patients on 6 medical wards at Aintree University Hospital. MINERVA stickers were then used twice weekly by the junior doctors for a period of 2 weeks on the day before a consultant ward round and prior to a weekend. The documentation was then re-audited.

Results: The stickers were able to increase documentation within the last 5 days for mobility from 49% to 97%, nutritional state from 44% to 96%, resus status from 5 to 96% and EDD from 21% to 70%. MINERVA was unable to affect documentation of daily ward round entries.

Conclusion: The stickers were able to markedly raise documentation of the 11 MINERVA domains. In doing so issues of patient care were identified early and could then be highlighted to the senior team in a timely fashion. This improvement in record keeping is able to highlight the need for a multi-disciplinary team approach and could relate to increased patient safety and reduced length of stay.

Screening for hearing defects in children with Cystic Fibrosis receiving frequent IV aminoglycoside treatment: A Service Evaluation

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Background: Patients with CF are frequently treated with aminoglycosides because of their effectiveness at fighting off bacterial infections. They do have important side effects which includes ototoxicity. The literature notes that children with cystic fibrosis who receive systemic or inhaled aminoglycosides have a higher risk of sensorineural hearing loss. Consequently in the consensus guidelines for antibiotic treatment in CF, it is recommended that "an annual pure tone audiogram should be considered for patients receiving frequent courses of an intravenous aminoglycoside

Methods: The medical records of all Cystic Fibrosis patients registered to paediatricians were reviewed between October 2010 and December 2010.

Results: Only 7 (35%) of the 20 children that had received frequent IV aminoglycoside treatment had received hearing tests whilst 4 children had been referred for hearing assessments. Of these 11 children: 8 (73%) had normal hearing (two children had Eustachian tube defects); 1 needed reassessment; 2 children had hearing loss (18%). Both children with hearing loss had received IV aminoglycoside treatment. Only 2 from the group of 11 children were scheduled for an annual reassessment.

Conclusion: CF patients are not receiving annual hearing evaluations despite being at a higher risk of aminoglycoside induced hearing loss. 2 of the 11 patients who had received a hearing evaluation were found to have hearing loss, and this could be linked to the frequent aminoglycoside treatment they received. The department now intends to rectify this situation by arranging hearing assessments at annual review for those children who failed to receive one.

Community Acquired Pneumonia- Are we prescribing correctly?

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Introduction: Community Acquired Pneumonia is a serious illness which causes both significant mortality and morbidity amongst patients. It is also an illness which junior doctors often find themselves managing. The CURB-65 Score is an important tool which allows clinicians to decide on antibiotic treatment and the need for community or hospital management of patients based on different parameters.

Aims: To audit documentation of the CURB score. (2) When a patient was documented as confused, to audit if this was measured objectively by Abbreviated Mental Test (AMT). (3) To audit the prescribing of antibiotics and whether this was in keeping with current trust and British Thoracic Society (BTS) guidelines.

Methods: In this audit I looked at patients that were being admitted through the acute admissions unit at North Staffordshire Hospital over a two month period. After the patients had been diagnosed with Community Acquired Pneumonia by consultant review, I analysed whether the CURB-65 score was documented, and how confusion was measured, as well as if the patients had been placed on appropriate antibiotic therapy. For patients who did not have the CURB score documented I calculated it. Insufficient prescribing was when patient were started on oral antibiotics when the CURB score indicated they should be placed on intravenous antibiotics, excessive prescribing was when intravenous antibiotics were incorrectly prescribed when oral antibiotics were sufficient, or when two oral antibiotics were used, when one was sufficient. Incorrect prescribing was the omission of macrolide (clarithromycin) cover, when it was required.

Results: Of twenty four patients in total; seven (29%) were female and seventeen (71%) were male. The average age of female patients was 73 years (range 68-77years), whilst the average age of male patients was 67 years (range 38-86 years). Four patients (17%) had significant co-morbidities. Three patients (12.5%) died.

CURB Score was documented in two of the patients (8.3%) and only one patient was documented as confused (4.6%) although there was no documentation of how this confusion was measured. Thirteen patients (54%) had correct antibiotic prescribing according to BTS and local trust guidelines, whilst eleven patients (46%) did not. Of these eleven patients; seven (64%) had excessive prescribing of intravenous and in one case oral antibiotics. One patient (9%) had insufficient prescribing, and three patients (27%)had incorrect prescribing

Systematic Improvement of Outcomes in Critical Care: Small Changes in Daily Review Sheet Design Improves Best Practice Standards in Dynamic Environments.

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Background: Daily review sheets in intensive care are simple but powerful tools in delivering safe standards of patient-centred care. Intensive Care Units (ICUs) are dynamic environments where patient needs are diverse; staff and clinical situations change frequently. Checklists and bundles are now commonplace and associated with improved patient outcomes and reduced length of stay. To reduce human error, patient review sheets should be reliably completed with no variability amongst staff. Evidence suggests that bundles work optimally with 95% completion rates; this was our 'gold-standard' target for best practice. This audit measured 'Daily Review' sheet completion among doctors working in North Bristol ICU.

Methodology: The audit had two phases. Phase one audited 138 sheets. Each week, over eight weeks, patient sheets were retrospectively audited. In phase two, a re-designed sheet was then re-audited over six weeks to measure quality improvement.

Discussion: Phase one had an average completion of 92%, with considerable weekly variability (86-97%). Of greatest concern was the lack of doctor's signature and accountability; only 65% were signed. The sheet was improved to engage doctors in a shared responsibility for quality of care. To date, re-auditing the new sheet in phase two has demonstrated an improvement towards 97%.

Conclusion: Delivery of ICU care requires effective communication between staff, daily patient goals and use of evidence-based care bundles. Accurate record keeping and accountability is a Good Medical Practice requirement for delivering high quality patient care. Making small modifications to documentation can make a big impact towards improving systems of patient care.

Audit of High-Dose Antipsychotic Drug Monitoring at Arrol Park Resource Centre In-Patient Unit

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Background: In 2006 the Royal College of Psychiatrists released a Consensus Statement[1] on high-dose antipsychotic medication and in it detailed how cardiac side-effects, in particular, are dose related and recommend repeated audits to ensure that patients are being monitored correctly.

Method:
Five standards were formed from the guidelines[2] –
1. 100% patients on high-dose anti-psychotics should be identified
2. 70% of patients should have an ECG done on admission
3. 70% of these patients should being having their FBC, U&Es, LFTs, blood lipid levels, weight, fasting BM and BP measured, and an Electrocardiogram done before starting on a high dose
4. 70% should have these measurements repeated after three months of treatment
5. 70% should have them repeated every 6-12 months.

The audit was carried out by first identifying which of the current in-patients were being prescribed high doses of anti-psychotics, then looking at the patients' notes to find evidence that monitoring had been carried out, finally comparing the data to the standards set.

Results: Standard 1 was the only one met to 100%, while the rest all failed at 0%. Of the two patients found to be on a high dose neither had all measurements done at the correct time or continued on, though some measurements were done sporadically.

Conclusion: The small sample size of only two patients makes it hard to tell if the standards are truly not being met or if these patients have both just missed out on the introduction of the recommendations of the early 2000s. However, recommendations can be made about the continuation of yearly checks. When normal results were collected several years in a row then tests were stopped. A system needs to be put in place to ensure that if this is the case that monitoring continues at set intervals thought appropriate by the consultant psychiatrists.

Combined Pacreaticoduodenectomy with Venous Resection and Reconstruction using Non-autologous Vein.

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Pancreatic cancer is difficult to diagnose and often presents too late for surgical resection. However, in selected patients, radical surgery including resection of adjacent structures may make cure possible.

A 36-year-old male presented with epigastric pain. Investigations revealed a neuroendocrine tumour of the pancreatic head with portal vein (PV), superior mesenteric vein (SMV), and transverse mesocolon involvement. A decision was made to proceed with a Whipple's procedure, incorporating portal venous resection. This venous resection involved excision of the tumour and a significant length of the extrahepatic PV. A donor iliac vein graft was utilized for reconstruction. Intraoperatively, the extent of the tumour necessitated an additional right hemicolectomy. Postoperatively, apart from a period of ileus, the patient made excellent recovery. The pathology report confirmed an R0 resection.

Pancreatic head resection combined with venous resection remains controversial. It offers the possibility to achieve complete oncological resection of the extended malignancy and thus improve long term survival. The already high rates of morbidity and accompanying mortality following a conventional Whipples resection and the poor prognosis associated with pancreatic cancer, has led many centres considering venous involvement a contra-indication to resection.However, in selected cases, aggressive surgery involving an extension to the customary Whipples resection is warranted and can offer these patients satisfactory long-term outcomes, especially when performed by experienced surgeons in high-volume centers.

Portal vein involvement should not be a contra-indication to pancreatic resection. This case demonstrates this notion and provides an opportunity for change in the surgical practice for pancreatic cancer treatment.

Secondary angiosarcoma of the breast after radiotherapy to the contralateral breast

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Introduction: The shift towards breast-conserving surgery (partial mastectomy) followed by radiotherapy for primary breast carcinomas has unforeseen implications. We present a rare and unusual case of secondary angiosarcoma in the contralateral breast.

Case report: An 87-year-old woman with a history of right invasive ductal carcinoma was treated with a partial mastectomy, axillary clearance, radiotherapy and tamoxifen in 2001. In 2009 she underwent a completion mastectomy following angiosarcoma caused by the radiotherapy.
She now presents with a suspicious left breast lump. Mammography revealed a 40mm mass in the upper outer quadrant of the breast. Our initial assumption was a primary left breast carcinoma. However, despite no skin changes on the left breast, a biopsy of the lesion revealed a low-to-intermediate grade angiosarcoma. The patient will undergo a left-sided mastectomy.

Discussion: Angiosarcoma can be a rare consequence of radiotherapy, normally occurring where the radiotherapy was administered, as seen in the patient's right breast. This is the first time anyone in our specialist breast team has encountered contralateral angiosarcoma post radiotherapy. We believe this unusual occurrence has been caused by scattered radiotherapy.

Conclusion: Due tothe increase in breast-conserving surgery, early recognition and understanding of long-term effects of subsequent radiotherapy are essential.

Is hospital an accessible environment for visually impaired patients?

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Background: In the UK, 370,000 people are registered as blind or partially sighted. Blindness is conventionally defined as best corrected visual acuity less than 3/60 and partial sight as 6/60 or less. This project aims to experience how low vision affects navigation in a hospital and recommend ways to support patients' independence.

Methodology: The vertical width (cm) of first letter on the signposts in Ninewells Hospital was measured. To simulate visual acuity of 6/60, 3/60 and 1/60, a convex +2, +4 and +8 lens was employed respectively. The distance (m) required for accurate interpretation of the signposts was measured.

Discussion: The majority have letters that measure around 4cm. They can be read correctly with a distance up to 3m in patients with 6/60 vision. This is reduced by half in 3/60 and further halved in 1/60 vision. This becomes problematic if the signs are way above the eye level. This makes navigation like attending clinics for appointments difficult. Practicality of having big letters across hospitals needs to be assessed but signs should be located at least at a height that patients could reach to read.

Conclusion: Loss of visual acuity contributes to deficits in hospital navigation and orientation. Improvements should be made by understanding the relationship between signpost design and visual disability. Furthermore, reinforcements can be achieved through raising awareness and recognising the access implications of Equality Act. Further work is mandatory so that recommendations can be formulated to transform hospitals into a more accessible environment for the visually impaired community.

An E-Learning Package for Medical Students on Genocide & Public Health

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Internationally, genocide is a major health problem being the leading cause of preventable death. It has long-term health consequences for survivors. Although the role of health professionals in preventing genocide has been acknowledged, there is little coverage of this topic in undergraduate health courses. The aim of this project was to develop an e-learning package providing an overview of the topic to undergraduate medical students and evaluate its pedagogical value as a learning tool as measured by usability, learner engagement, knowledge and attitude outcomes.

An e-learning package was designed and evaluated by a sample of 96 self-selected second-year medical students. Questionnaires integrated within the package were used to compare pre- and post-intervention knowledge and attitudes. A control group of 89 first-year medical students was used to compare baseline knowledge/attitudes.

Among the respondents in the intervention group 45% gave a 9/10 score for the e-learning package design and 97% preferred it as a learning mode over traditional lecture based. Post-intervention 93.7% of second-years agreed that genocide is a public health issue as opposed to 23.5% at baseline. The intervention group showed statistically significant positive changes in knowledge and attitudes post-intervention ($p<0.001$) when compared to the control group.

The e-learning package was found to be an effective learning tool in terms of usability, learner engagement, influencing positive change in knowledge and attitudes relating to genocide prevention. Due to the multi-disciplinary nature of genocide prevention, it has the potential to be useful in other courses.

Pulmonary embolism is associated with a high rate of idiopathic recurrence

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Background: Pulmonary embolism (PE) is a common and potentially fatal event with a tendency to recur. Following PE, decisions regarding risk of recurrent venous thromboembolism (VTE) and anti-coagulation duration are guided by whether the event was idiopathic or precipitated. We tested this assumption on a large cohort of patients managed under a single protocol.

Methods: Patients were identified from a prospectively-assembled database collecting 262 cases of a first PE presenting to the acute admissions unit at a single university teaching hospital. PE was classed as idiopathic or precipitated. Precipitating factors were defined as: surgery, active malignancy, long-haul travel and pregnancy.

Results: The first PE was idiopathic in 127 patients (45%) and precipitated in 135 (55%). Rate of recurrence following idiopathic PE was 27%. Of these cases of recurrence, 91% were idiopathic. Rate of recurrence following precipitated PE was 20%. Of these recurrences, only 60% were precipitated
Recurrent VTE was PE in 87% and isolated deep vein thrombosis in 13%.

Conclusions: Despite a PE precipitated by a transient risk factor, these patients remain at significant risk of recurrence. Following idiopathic PE recurrent VTE was also idiopathic in the majority of cases, as expected. However following precipitated PE, recurrence was equally likely to be precipitated or idiopathic. The recurrent thrombotic event is highly likely to be a further PE, irrespective of the risk factors of the first event. More clinical information is required over and above the risk factors of the thrombotic event when deciding anti-coagulation duration.

Complement Activation by Metabolic Acidosis: A Mechanism for Progressive Tubulo-interstitial Damage During Proteinuria in Chronic Kidney Disease (CKD)

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In addition to being a marker for chronic kidney disease (CKD), proteinuria is recognised as a cause of tubulo-interstitial damage and CKD progression. Activation of complement leaking into tubular lumen during proteinuria is a possible mechanism. Complement activation products have been demonstrated in urine of CKD patients and are reduced by bicarbonate therapy.

Complement activation products (C5a and C3c) were measured by enzyme-linked immunosorbent assays (ELISA) and immuno-blotting in human and mouse plasma incubated in vitro at pH 7.45 or acidic pH 6.8 (to mimic pH in proximal tubular lumen).

Acidic incubation generated significant C5a even in human plasma diluted 1/200. C3 activation was also detected by immuno-blotting, and confirmed by demonstrating C3c deposition on zymosan-coated plates. A mean 38% increase in C3c deposition occurred at plasma dilutions from 100% to 3% when conditions favoured Alternative Pathway (AP), but not when Classical (CP) and Lectin (LP) Pathways were selectively favoured. However, even when all pathways were blocked, a 17% acid-induced increase still occurred.
Incubation of Wild-type and knock-out mouse sera lacking AP (properdin deficient), LP (MASP-2 deficient) or CP (C1q deficient) all showed a marked acid-induced increase in C5a.

Incubation with immortalised proximal tubular cells (HK-2) demonstrated that acidic pH significantly enhanced cytotoxicity of human plasma (assessed using MTT).

It is concluded that at low plasma protein concentrations and low pH that occur in tubular lumen during proteinuria, significant complement activation occurs, potentially inducing tubular injury, and is therefore a potentially important site for therapeutic intervention to slow CKD progression.

Perinatal depression in Bangladesh: a qualitative study to explore the knowledge and practice of healthcare workers from different sectors in both an urban and rural area.

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Background: Perinatal depression is a significant and treatable cause of ill-health in Bangladesh, with a prevalence estimated between 9-30%. It is associated with poverty, marital violence and lack of social support. Perinatal depression profoundly effects on both maternal and child health. Evidence is scarce regarding this disease in Bangladesh.

Aim: Through qualitative research to explore the knowledge and practice of healthcare workers who work with pregnant and newly delivered mothers in Bangladesh.

Methodoloy: 15 semi-structured interviews were undertaken in May 2012. Participants were identified through purposive sampling of maternal healthcare facilities. Private, government and non-governmental organisation staff from urban and rural areas were included. Data was analysed using thematic content analysis.

Results: Results show low understanding of the term perinatal depression but some awareness of symptoms and causes. Nurses and community health-workers have limited knowledge regarding the complications of perinatal depression, whereas doctors have a better understanding. Most participants regard perinatal depression as a problem, but feel they lack awareness of the disease. Practice is mostly limited to counselling and referral.

Conclusion: Perinatal depression is a significant problem in Bangladesh. This research has shown low awareness and lack of screening and treatment. Further training is needed across all healthcare workers, as is the development of national guidelines emphasising screening.

Research into the Development of a Universal Cell Vaccine for Acute Myeloid Leukaemia

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This research is part of the development of a universal cell vaccine for acute myeloid leukaemia (AML). Trials with CD80 (B7.1)/IL-2 immune gene therapy, using the patient's own leukaemic cells, are underway and K562 cells expressing GM-CSF have been investigated as a leukaemia cell vaccine. This indicates that a leukaemic cell line could provide a universal vaccine, avoiding the difficult and expensive strategy of creating patient specific AML cell vaccines.

Three new cell lines were produced in this experiment from the transduction of K562, K562-A2 and U937 with a lentivirus containing an IL-2/B7.1 fusagene. These new cell lines, K562 (IL-2/B7.1), K562-A2(IL-2/B7.1) and U937(IL-2/B7.1), were then analysed with the original three cell lines for HLA, B7.1 and IL-2 expression using FACS and ELISA. B7.1 and IL-2 expression were measured to calculate the effectiveness of transduction of the IL-2/B7.1 fusagene, and to compare this to B7.1 and IL-2 expression in the original cell lines. Expression of HLA-A*201 was also measured, since its expression would circumvent HLA mismatch stimulation in HLA-A*201 positive patients.

K562(IL-2/B7.1), K562-A2(IL-2/B7.1) and U937(IL-2/B7.1) all expressed large quantities of both B7.1 and IL-2, and K562 and K562-A2 also expressed small quantities of B7.1. K562 and K562 (IL-2/B7.1) lacked HLA expression, while K562-A2, K562-A2(IL-2/B7.1) U937 and U937(IL-2/B7.1) all expressed HLA-ABC.

The cell lines produced and analysed in this experiment can now be used in experiments to provoke an immune response against unmodified AML blasts. If these experiments are successful, these cells could provide the basis of a universal cell vaccine for AML.

K-Ras mutation in colorectal cancer sensitises cells towards cell death, through inhibition of autophagy

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Background: A critical problem in the amelioration of colorectal cancer (CRC) is the occurrence of K-Ras mutations. Patients with K -Ras mutations have bleak clinical outcomes, with tumours being more proliferative, aggressive and often treatment resistant. Understanding the mechanisms behind this will lead to improved patient outcomes. One method cancer cells use to potentiate proliferation and survival is to uncouple autophagy, a cell survival pathway, from activating cell death. In this study, the potential link between K-Ras mutations and autophagy was investigated.

Experimental Design: Extracts from nutrient deprived and/or inhibitor treated cells were analysed by Western immunoblotting for markers of autophagy, cell growth, proliferation and death in isogenic CRC cell lines that harbour either wildtype or mutant K-Ras. Alterations in cell morphology were monitored using phase-contrast microscopy.

Results: K-Ras mutant cells showed upregulation of the Ras/MEK/ERK pro-growth pathway, uncoupled from receptor control. Inhibition of this pathway led to cell death and provided evidence of novel cross-talk with the PI3K/AKT/mTORC1 pro-growth pathway. K-Ras mutant cells also had greater autophagic activity in response to nutrient stress and were sensitised towards cell death following inhibition of autophagy with chloroquine.

Conclusion: Upregulation of the Ras/MEK/ERK pathway independent of receptor activation explains the increased proliferation and resistance to therapies, which often target receptors. Targeting the Ras/MEK/ERK pathway above the level of cross-talk but below receptor level could be of potential therapeutic benefit. Furthermore, the increased autophagic activity observed and potent pro-death response following autophagy inhibition suggests targeting autophagy may be effective in treating K-Ras mutant CRC.

The Assessment of Bone Micro-Architecture and Composition using Micro-MRI and MRS in Individuals with Growth Hormone Deficiency and Hypogonadism

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Although bone health is usually assessed by measuring bone mineral density (BMD) by dual X-ray energy absorptiometry, BMD is not a very sensitive or specific predictor of fractures, especially in those with chronic disease. There is a need to explore alternative bone health indicators that provide information on bone micro-architecture and lipid content. This study assessed the feasibility of using micro-MRI and MR spectroscopy (MRS) to compare bone micro-architecture and lipid content in young adults with suspected mild bone disease compared to healthy controls.

The study sample comprised of 10 cases with growth hormone deficiency (GHD) and/or hypogonadism and 10 age and sex matched healthy controls. A 3T MRI scanner performed a MRI scan of the right tibia and obtained 0.2mm and 0.3mm resolution images. Four parameters of micro-architecture were calculated; apparent trabecular number (appTbN), spacing (appTbSp) and thickness (appTbTh), and apparent ratio of bone volume:total volume (appBV/TV). MRS was performed in the lumbar vertebrae; lipid and water peaks from the bone marrow were acquired and used to calculate %-fat fraction (% FF).

The 0.3mm resolution images reported a lower median appTbN (10.3%, p=0.03), and a higher median appTbSp (14.0%, p=0.02) in cases compared to controls, but there was no significant difference in appTbTh or appBV/TV. MRS reported a 17.3% higher median %FF (p=0.006) in cases compared to controls.

Race, bullying and self-esteem at the transition between primary and secondary school

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Background: Studies from the US have suggested that children who experience racial discrimination have higher rates of depression, anxiety, behavioural disorders, and lower self-esteem. Children are particularly vulnerable at the transition from one school to another.

Design: Children from the Avon Longitudinal Study of Parents and Children (ALSPAC) were asked to define themselves by skin colour aged 12 years (n=7017). Logistic regression analyses, adjusting for gender and maternal education, investigated associations with bullying and racial discrimination, behavioural difficulties, friendships, mood and self-esteem.

Results: 94.2% defined themselves as white (n=6607), 3.6% as mixed race (n=255), and 2.2% (n=155) identified with a specific ethnic minority group. There was no association between race and bullying at 8 years. At 12.5 years the prevalence of racially motivated violence was 10-13%, and was 31-33% for name-calling. Ethnic minority but not mixed race children were more likely to experience overt bullying (OR 2.98; 95% CI 1.38 to 6.42). Mixed race children were more likely to retain friends of different races after the transition to secondary school (OR 1.89; 1.32 to 2.71). At 13.8 years, mixed race and ethnic minority children were more likely to feel unhappy (OR for mixed race 1.87, 1.31 to 2.68; OR for ethnic minority 1.76, 1.09 to 2.86).

Conclusions: Ethnic minority children were more likely than white children to experience bullying at the transition to secondary school. Ethnic minority and mixed race 13 year olds were less happy. Strategies for bullying prevention should be targeted at this vulnerable group.

Investigating the direct and indirect effects of VEGF-188 on pericyte differentiation

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Pericytes provide stability to developing vasculature and are linked with resistance to vascular disrupting treatments in targeting tumours. Our group has found that mouse fibrosarcoma cells expressing only a single isoform of VEGF-A i.e. matrix-bound VEGF-188, are associated with pericyte-rich blood vessels, when grown *in vivo*. Here, we hypothesise that VEGF-188/9 impact upon pericyte differentiation directly or indirectly via endothelial cell stimulation.

Using the mesenchymal cell line C3H/10T1/2 (10T1/2) to model pericyte precursors, cells were co-cultured with mouse fibrosarcoma cell lines expressing VEGF-188 or VEGF-164 isoforms, or alternatively with human umbilical endothelial vein cells (HUVECs). Pericyte markers of differentiation including PDGFR-b, NG2 and a-SMA were investigated in the 10T1/2 cell line using western blotting and immunocytochemistry, with transforming growth factor- b1 (TGF-b1) used as a positive control for pericyte differentiation.

TGF-β treated cells displayed an upregulation of PDGFR-β and NG2 proteins through western blotting. Additionally, a clear increase in the expression of NG2 in TGF-β treated 10T1/2 cells was found through immunofluorescence staining. Furthermore, immunofluorescent staining of cells detected clear changes in distribution of a-SMA after TGF-β treatment. VEGFR-2 expression was also found to be markedly upregulated by TGF-β.

Upregulation of VEGFR-2 in this cell line is a novel find and thus can potentially be used as an additional positive marker of pericyte differentiation in future investigations. However, no similar changes in marker expression were detected in 10T1/2 cells co-cultured with fibrosarcomas or HUVECs, suggesting that VEGF-188 does not directly stimulate pericyte differentiation.

"How the Bangladeshi community in West London, uses and understands their Traditional medicine/ services and how this relates to their use of conventional Western medicine/ services"

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Background: Our objective was to explore the indigenous health beliefs and traditional practices of Bangladeshis resident in the U.K. When and why they are practiced and how they integrate these beliefs and practices with mainstream services.

Design: An exploratory qualitative study that used semi-structured interviews to explore the participant's personal medical history and how traditions and beliefs influence their choices between Traditional Indian (TM) and conventional Western medicine (CWM). Inductive thematic analysis was the chosen data analysis method.

Participants: Purposive sampling was used to recruit 11 Bangladeshi individuals from the community in West London.

Results: Data analysis revealed the importance of religion, culture and family in healthcare beliefs and practices of Bangladeshis in the U.K. The majority of participants viewed illness and well-being to be predominantly determined by God, and the use of prayer, talismans and herbal food-therapy were pervasive themes in the data. In some cases, participants reported a desire to use TM for chronic or psychological problems and conventional care (GP) for acute illness. Concomitant TM and CWM use was also common, though participants reported a reluctance to discuss this with their GPs.

Conclusion: Analysis suggests TM is used by most participants. Though its use is related to socio-cultural factors, it appears not to detract from CWM use, except in some cases of chronic or psychological illness, when TM (when including prayer) seems to take precedence. The findings highlight the importance of providing culturally appropriate care for this group and provide a useful starting point for further research.

Urinary Metabolomic Profile as a Predictor of Minor Cerebrovascular Incidents

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Minor ischaemic stroke and transient ischaemic attacks (TIAs) can be difficult to diagnose. Brain imaging often supports the diagnosis but even magnetic resonance imaging (the most sensitive technique) only has a sensitivity of 83% for detecting acute ischaemia and less for TIA. Through quantifying the small molecule components of metabolic pathways, metabolomics may help with diagnosis, even when brain imaging is negative.

In a retrospective study we used liquid chromatography-mass spectrometry to compare the urinary metabolite profile of cases (patients with recent ischaemic stroke or TIA) to high cardiovascular risk controls.

Sixty-four cases (mean age 69 years, 20 TIA, 44 minor stroke) and 42 control subjects (mean age 67 years) were studied. The urine of cases was characterised by increased levels of 2-deoxy-2,3-dehydro-N-acetylneuraminic acid (DANA); [FA dioxo(8:0)] 4,7-dioxo-octanoic acid; suberic acid; 2-keto-4-hydroxybutyrate; 2-dehydro-3-deoxy-L-rhamnonate and 3-ethylmalate and by decreased levels of allantoin; p-benzenediol; dihydroneopterin; hippurate; threonine-alanine-alanine; methanesulfonic acid; alanine-asparagine-aspartic acid and 4,6-dihydroxyquinoline.

Using K-Nearest Neighbour analysis we developed a multi-marker classifier to predict patient diagnosis. It contained the metabolites: allantoin; suberic acid; p-benzenediol; hippurate; DANA and dihydroneopterin and differentiated ischaemic stroke from control with 84.1% (76.4%, 91.8%) sensitivity, 85.7% (78.3%, 93.1%) specificity (AUC of 0.80 (0.72, 0.91) on ROC analysis).

This study demonstrates the potential of a metabolomic classifier to assist with the diagnosis of minor cerebrovascular events. As the metabolites studied have putative roles in neuronal damage, neurotransmission, oxidative damage and folate biosynthesis, future work with this technique may enhance our understanding of the pathophysiology of acute ischaemic stroke.

The efficacy of metformin in children with metabolic syndrome and insulin resistance

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Background: The prevalence of obesity in childhood is increasing, including its complications such as metabolic syndrome. There is a high incidence of insulin resistance in obese children. As well as adopting a healthy lifestyle, drugs including metformin, have shown some benefit in improving metabolic syndrome.

Methods: Thirty-two children with metabolic syndrome were randomly selected from clinics. These children underwent BMI assessment before and after treatment, assessment of diet and physical activity, blood-tests to analyse insulin resistance (HOMA), cholesterol, vitamin-D levels, USS-liver, questionnaires to assess energy levels, concentration after treatment with metformin.

Results: Thirty-two children were assessed, 13 were male and 19 female with a mean age of 12.41yrs. BMI was assessed in 21 patients (66%) after treatment with metformin; 13 patients (62%) had a reduction in BMI and 8 patients (38%) an increased BMI after 1-year. HOMA scores improved in 10 patients (50%), worsened in 8 (40%) and remained the same in 2 (10%). 21 patients (84%) reported improvements in energy levels only 1 felt tired whilst on metformin. There was a reduction in cholesterol levels in 11 patients (69%) on metformin. 23 patients had USS-liver at diagnosis of which 10 patients (43%) had fatty infiltration of the liver. 11 patients (55%) were found to have low vitamin-D levels.

Conclusion: Metformin therapy causes a reduction in BMI and insulin levels in children with insulin resistance. Hence metformin can be used for the prevention of type-II diabetes in children with insulin resistance. It should be started at earliest possible obesity stage.

Identifying Biomarkers of Osteolysis After Total Hip Arthroplasty

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Background: Aseptic loosening after THA is the most common cause of implant failure. Positive but weak associations have been identified between some biomarkers and osteolysis, but their predictive value in individual subjects has been poor. The aims of this study were to determine whether the bone markers DKK-1, sclerostin and TRAP5b are elevated in periprosthetic osteolysis.

Method: Fifty subjects that had undergone total hip arthroplasty were separated into two cohorts – 26 with stable hip prostheses and 24 with loose hip prostheses. Serum taken from each patient was tested for each of the three markers using ELISA assay.

Results: Although each marker showed a mean higher in the group with loose prostheses, none of these differences were shown to be significant when set against a grade of significance of $p < 0.05$. The closest result to showing a suitable degree of significance was that of Dkk-1, and the result furthest from showing a suitable degree of significance was that of Sclerostin.

Conclusion: Although this study has failed to prove a significant difference between the cohorts in the 3 serum markers measured, it has succeeded in providing direction towards further research. The different methods of assaying TRAP5b seem to produce different results, and comparison of assay techniques should be undertaken to try to explain this. Of the markers Dkk-1 and Sclerostin it appears that Dkk-1 may hold more hope for application towards the diagnosis of aseptic loosening after total hip arthroplasty.

Survey of sunbed use, attitudes and knowledge in school children aged 15-17 after the under-18s ban

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Sunbed use in childhood is a major risk factor for melanoma. An under-18s sunbed ban was introduced in England in 2011. Impact on use and associated attitudes/knowledge has not been investigated since the introduction of the ban. This cross sectional study aims to estimate the prevalence of under-18s' sunbed use after the ban and identify predictors of use/future use.

All schools in Sandwell, West Midlands were approached. Inclusion criteria were children aged 15-17 available on the day of survey. Anonymous questionnaires were self-completed in class under exam conditions. Data collected include demographics, sunbed use, tanning attitudes, knowledge of sunbed health risks and ban awareness.

Five out of 22 schools participated (22.7%).Of the 437 available students, 390 responded (89.2%). 5.3% (95% CI 3.4% - 8.0%) reported use after the ban, the age standardised prevalence was 7.9% (5.6%-11.0%). 20.5% (16.7% - 24.8%) indicated potential future use. 70.0% (48.1% - 85.5%) used sunbeds in salons, 25.0% (11.2% - 46.9%) used at home. Less than half [48.2% (43.2% - 53.3%)] were aware of the ban. Knowledge of risks was poorer amongst users/future users compared to non-users. Being female, family and friends' sunbed use were independent predictors, these children were 3 to 4 times more likely to have used/intention to use sunbeds.

There is a need for other strategies to reduce underage sunbed use alongside the ban. Campaigns to raise awareness of the associated risks and the ban should target both children and parents to reduce underage use in commercial and domestic settings.

The effect of HSPC1 inhibitors on protein homeostasis and chemoresistance in colorectal cancer cells.

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Worldwide, one million new cases of colorectal cancer (CRC) are reported every year with 500,000 cases of mortality attributed to it. Heat shock proteins (HSPs), in particular HSPA1A, HSPB1 and HSPC1, are major contributors to chemo-resistance, a frequent complication in CRC patients. HSPC1 chaperones client proteins such as HER2 and NF-κB that control cell proliferation, migration and have anti-apoptotic effects. As a result HSPC1 inhibitors are attracting growing attention as novel therapies. This study aimed to explore the effects of HSPC1 inhibitors on client protein expression and HSPA1A/HSPB1 induction and looked at the relationship between HSPA1A/HSPB1 levels and the sensitivity to HSPC1 inhibitors and other CRC drugs.

HSPC1 inhibitor was applied to the CRC cell line HT29 and the level of HSPB1, HSPA1A, HER2, phosphorylated-NF-κB and active-caspase-3 were measured at different time intervals. Gene silencing techniques were also employed to silence HSPA1A and HSPB1 prior to addition of HSPC1 inhibitors or 5-fluorouracil (5-FU).

HSPC1 inhibitor was effective in decreasing the level of HER2 and phosphorylated NF-κB and inducing the levels of HSPB1 and HSPA1A after short-term treatment. Inhibition of HSPA1A or HSPB1 induction had no effect on the response to HSPC1 inhibitor, but did sensitise cells to 5-FU treatment.

In conclusion, HSPC1 client protein degradation begins rapidly following HSPC1 inhibitor treatment and causes apoptosis of CRC cells at nanomolar concentrations. Both HSPA1A and HSPB1 are induced following inhibitor treatment but this induction has no influence on the cellular response to HSPC1 inhibitors. HSPB1 is more important than HSPA1A in the resistance of CRC cells to 5-FU.

Induction of Heme oxygenase-1 Expression Protects Aged Mice from Acute Kidney Injury

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Elderly individuals are more prone to acute kidney injury (AKI). Our previous work demonstrated that pretreatment of 12-month old mice with hemearginate (HA, licensed for human use) strongly upregulated the anti-inflammatory enzyme hemeoxygenase-1 (HO-1) and protected the mice from acute kidney injury (AKI) (Ferenbach *et al.* 2010 *Kidney International*). We now extend this work to 20-month old mice that are more analogous to elderly humans.

Female FVB/nj mice (mean age 20.7 months) received IV HA (30mg/kg) or PBS 24 hours before undergoing a right nephrectomy and renal ischaemia reperfusion injury (IRI) induced by clamping the left renal pedicle (20 minutes). The left kidney was removed at 24hrs. Serum creatinine was measured at baseline and at sacrifice. Fibrillar collagen deposition (picrosirius red staining) and HO -1 immunostaining were quantified by computer image analysis whilst tissue injury was quantified by determining the acute tubular necrosis (ATN) score on H&E stained sections.

Picrosirius red staining demonstrated marked baseline scarring (cortex 13.0%, medulla 6.8%). Administration of HA induced significant expression of HO-1 at baseline (0.2±0.1 vs 15.7±1.5% HO-1 +ve staining; PBS vs HA; $p<0.001$) and after IRI (2.5±1.7 vs 9.5±0.5% HO-1 +ve staining; PBS vs HA; $p<0.01$). HA treated mice exhibited reduced acute renal failure (serum creatinine 65±18.3 vs 38.7±11.4***µmol***/L; PBS vs HA; $p<0.05$) and a reduced ATN score (54.1±1.8 vs 32±3.1% ATN; PBS vs HA; $p<0.001$).

Subchondral Bone Quality in Human Femoral Head Osteoarthritis

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The pathogenesis of osteoarthritis is now understood to involve subchondral bone. Raman spectroscopy has the potential to detect early osteoarthritic changes in subchondral bone. The objective was to investigate the quality of subchondral bone in osteoarthritic femoral heads. In this study, subchondral bone was limited to within 3mm of articular cartilage. It was compared to a site previously considered as subchondral bone (10mm distal to articular cartilage) and the head-neck junction. Several parameters were used as markers for bone quality: mineral-to-matrix ratio, carbonate-to-phosphate ratio, carbonate-to-amide I ratio, mineral crystallinity and volumetric bone mineral density.

Five osteoarthritic femoral heads were compared to five normal cadaveric femoral heads. They were scanned using peripheral quantitative computed tomography and then sectioned coronally. A novel technique, inverse spatially offset Raman spectroscopy, was used to scan across the length of the femoral heads. Cores were subsequently extracted from specific regions and electrophoresis performed to investigate the presence of homotrimeric type I collagen.

Mineralisation in osteoarthritic subchondral bone was 2.4 times greater than controls ($p=0.023$). Within osteoarthritic specimens, the levels of mineralisation increased proximally. The density in osteoarthritic subchondral bone was 89mg/cm3 higher than controls ($p=0.022$) and 494mg/cm3 higher than the osteoarthritic proximal compartment ($p<0.001$). Moreover, the carbonate: amide I ratio was highest in osteoarthritic subchondral bone which may reflect increased turnover. Furthermore, homotrimeric type I collagen was only found in one osteoarthritic specimen.

Raman spectroscopy accurately detects differences between osteoarthritic specimens and controls, further supporting its potential use as a tool for diagnosing bone disorders.

The Role of CD36 in Mediating Podocyte Cell Damage in Proteinuric Renal Disease

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Proteinuria is a potential risk factor for, and mediator of, chronic kidney disease progression. Although the aetiology of proteinuria is multifaceted, podocyte dysfunction has been identified as an important trigger. It has previously been demonstrated that proximal tubular cells endocytose albumin via a receptor-mediated process causing cell injury. Podocytes have also been shown to endocytose albumin using kinetics consistent with a receptor-mediated process. However, the receptor is yet to be identified. The aim of the study was to determine whether the scavenger receptor CD36 plays a role in albumin uptake by podocytes.

Binding and uptake studies were carried out on podocytes exposed to FITC-labelled human serum albumin (FITC-HSA).

Podocyte CD36 expression increased dose dependently on exposure to HSA. No change in CD36 expression was seen in response to fatty acid-free HSA. Endocytosis of FITC-HSA was partially reduced in the presence of a combination of monoclonal and polyclonal anti CD36 antibodies. Immunofluorescence microscopy exhibited partial co-localisation of CD36 and FITC-HSA staining. Western blotting demonstrated that exposure to albumin induced the expression of podocyte injury marker desmin and activated the apoptosis execution enzyme caspase-3, but only if the albumin was fatty acid replete. Nephrin expression was up-regulated dose dependently by albumin, regardless of the presence of fatty acids.

Taken together these data suggest that the endocytic function in podocytes is, at least partially mediated via the CD36 receptor. In addition the adverse consequences of exposure of podocytes to HSA appear to be both dependent and independent of the presence of fatty acids.

Redirecting Viral Immunity to Cancer Using a Novel Immunotherapeutic Agent - Optimisation of the Current Protocol

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Antibody peptide-epitope complex (APEC) is a novel immunotherapy, redirecting viral immunity to cancer, which utilises a monoclonal antibody conjugated to a viral peptide and incorporates a cancer-associated protease-specific cleavage sequence. The monoclonal antibody is a site-specific delivery mechanism for the viral peptide. Cancer-associated proteases are found in abundance at the tumour site and the integrated protease-specific cleavage sequence facilitates release of viral peptide allowing MHC presentation and stimulation of virus-specific T-cells. This acts as a 'safety switch' to prevent non-specific release of highly immunogenic viral peptide and systemic immune activation, making this therapy cancer specific.

Current APEC is conjugated using an unoptimised protocol, which generates functional but unstable APEC. Objectives were to refine this protocol by determining optimum peptide concentration for conjugation and storage of APEC and investigating plasma kinetics with use of peptidomimetics to generate more stable APEC.

Different biotinylated peptide concentrations (0.004mg/ml – 10mg/ml) were assessed using biotin ELISA and flow cytometry. APEC was stored at various temperatures/in the presence of protease inhibitors and biotin loss was measured. APEC and peptidomimetics were incubated in human plasma to determine plasma stability and measured by cytometric bead array or T-cell cytokine response.

Optimal peptide concentration was determined to be 0.5mg/ml. APEC storage at -20°C showed a t½ of 22 days compared to 3 days at +4°C. APEC plasma t½ was ~4 minutes and the use of a N-methylated peptidomimetic extended plasma t½ to 280 minutes from 30 minutes when unmodified.

APEC optimisation in this study moves APEC closer to in vivo studies and becoming a viable cancer immunotherapy.

The association between Gout and Nephrolithiasis: a Systematic Review and Meta-analysis

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Background: Gout is the most common inflammatory arthritis in males in the UK. Nephrolithiasis is also common and can have serious complications. An association between gout and nephrolithiasis has long been recognised. This systematic review aimed to identify and summarise the existing evidence regarding the epidemiologic association between gout and nephrolithiasis in the general population.

Methods: Eligibility criteria for included studies were: participants with gout, outcomes of nephrolithiasis, observational study design and recruitment from the general population/primary care. MEDLINE, EMBASE and CINAHL were searched from inception to present. Reference and citation checking was performed. Two independent reviewers screened the title and abstract of all studies, assessed full-text articles, extracted data and appraised study quality. Meta-analysis was performed on appropriate data.

Results: From 1475 records retrieved, 73 full-text articles were assessed. 12 studies met the eligibility criteria. Lifetime prevalence of nephrolithiasis in gout ranged from 6.1% to 22.7%. Unadjusted odds ratios for the association of nephrolithiasis with gout ranged from 1.36 (95%CI 1.22, 2.04) to 10.16 (2.88, 29.23). Pooling of data from 6 cross-sectional studies produced a lifetime prevalence of nephrolithiasis in gout of 13% (9%, 17%). The pooled odds ratio for the association of nephrolithiasis with gout was 2.81 (2.00, 3.94).

Conclusion: Gout is associated with nephrolithiasis. Individuals with gout have more than twice the odds of experiencing nephrolithiasis compared to individuals without gout. This association deserves wider recognition by clinicians in primary and secondary care and also provides insight into the pathophysiology of nephrolithiasis.

Impact of increased use of pre- operative imaging and laparoscopy on outcomes of Appendicectomy.

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The aim of the study was to analyse the clinical outcomes of appendicectomy in our hospital over a 5 year period, and to assess the utility of radiological investigations and laparoscopy in the management of appendicitis.

A retrospective audit of appendectomies in our hospital over the last five years (01/01/2007 – 31/12/2011) was conducted. Histopathological confirmation of appendicitis was used as the gold standard for diagnosis. Patients undergoing an appendicectomy were stratified by age, gender, and surgical approach (open or laparoscopic) for measuring the association between the use of ultrasound, CT and laparoscopy and the outcome of appendicectomy. The negative appendicectomy rate, perforation rate, and complication rate were used as outcome endpoints.

1055 appendectomies were performed in our hospital over the five year period (965 open and 90 laparoscopic). The negative appendectomy rate was 24.5% (21% for open and 28% for laparoscopic appendectomy) and perforation rate was 14%. The negative appendectomy rate was significantly higher in women of child bearing age (32.8%, p- 0.0028), and lower in patients undergoing CT (12.4%, p- 0.0012) Intra-abdominal abscess (2.3%) and wound infection (1.4%) were the most common complications with the former higher with laparoscopy and the latter in open appendicectomy.

The impact of diagnostic imaging and laparoscopy on negative appendectomy rate varies with age and gender. The rate did not vary significantly with the surgical approach but was significantly reduced in patients undergoing CT scanning.

Intraobserver and interobserver reliability in MRI classification of interspinous ligament degeneration of the lumbar spine

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Background: Posterior spinal ligament pathology is becoming increasingly recognized as a significant cause of low back pain. Despite the growing clinical importance of interspinous ligament degeneration in low back pain patients, formal reliability studies for the magnetic resonance imaging (MRI) evaluation of interspinous ligaments have not been well studied. We seek to test the reliability of the recently proposed MRI classification system by Keorochana *et al* for interspinous ligament degeneration and conducted a comprehensive reliability and reproducibility assessment.

Methodology: Fifty patients who had low back pain with or without leg discomfort (25 males and 25 females) with a mean age of 58.8 years (range 46–80 years) were studied. Intraobserver and interobserver reliability were assessed by kappa statistics. The frequency of disagreement was also identified.

Discussion: The intraobserver agreement was excellent in all readers (kappa range 0.800–0.911). The interobserver agreement was lower as expected, and was substantial to excellent (kappa range 0.701–0.801). Overall complete agreement was obtained in 86.7% of all interspinous ligament levels.

Conclusion: This proposed MRI classification of interspinous ligament degeneration was simple, reliable, and reproducible. Its use as a standardized nomenclature in clinical and radiographic research may be recommended.

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