

Geriatric and Stroke Medicine Bulletin

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Welcome to this bulletin for those interested in the care of older patients. This is a completely experimental first edition and if it survives then new releases should come out at least bimonthly.

The format will mean that it is only distributed as a PDF file and it is designed for reading on screen but it can be printed and read. Web links can be clicked on. Feel free to forward it on to your colleagues in hospital, general practitioners, trainees, junior doctors, medical students. There may well be subjects of interest for nurses and therapists. It will also be available from my website. It is designed to be read over a coffee at work or a glass of something more sustaining at home.

I welcome contributions - there are many interesting topics to be covered. If you would like to contribute please email me with your topic, or I am always happy to suggest one to someone who would like to write a short piece. I am also happy to have interesting cases, important learning points or if you have something you want to say about a particular matter then share it with us.

Debate

Comments from a trainee...

Anon

An ancient Chinese curse, recently borrowed by Terry Pratchett, states "May you live in interesting times". It is hard to know which of the current group of over 600 trainees in Geriatric Medicine (or any other speciality for that matter) upset an ancient Chinaman, but apparently one of us has.

We are a divided group, there are those of us who thankfully avoided the horrors and uncertainty of MMC and are plodding through training equipped with a very heavy red folder containing our curricula and all the paperwork that we could ever need to fill in, and actually needs to only be lifted off the shelf and dusted down once or twice a year. We also train in the now abolished speciality of General (internal) medicine.

Then there are the STs (Specialist Trainees) who have commenced their training in the last 14 months. Equipped with a new title and a sense of disillusionment in the medical powers-that-be, they have endless assessments that need to be completed, but as yet no functioning electronic portfolio and no formally piloted assessment documents. This group will be accredited in the new animal of "acute medicine", for them general simply no-longer exists.

We mustn't forget those that are caught on the cusp, who began as SpRs, but may want to take time to carry out research, or have a family, or a life, who will find themselves in a few years time catapulted into the new system without knowing what will then be expected of them, and how many hoops will need to be jumped through in order to compete with the new tribe.

I have managed to so far avoid mentioning the knowledge based assessment, the three not so little words I have been slightly obsessed with over the past 12 months. This exam is an unavoidable consequence of the new assessment methods, and will be running at great expense to trainees in early March 2009. The test will take place in the centres used to examine driving test theory, it remains to be seen whether geriatricians will find themselves answering questions about road signs and stopping distances, and confused seventeen year olds will wonder how they missed the section on Zimmer frames in their highway codes.

When not filling in assessments, attending compulsory training days, or working nights, trainees have been known to go to a hospital ward, and do some work. There we are dealing with the lack of continuity of care that is an unfortunate result of the increase in shift working that comes with the increasingly strict timetables demanded by the European Working Time Directive.

Despite all of the above issues, when talking to friends and colleagues working at various stages within our speciality there is still the overwhelming sense that once we get through the politics of it all, we really enjoy our jobs. Different things are important to different people, but having the time to do a ward round and sort out a relatively small problem that can never have the less have a big impact on somebody's quality of life makes it all worthwhile. Getting away from the acute setting and being able to do some work in a Community Hospital can help to put everything in perspective and remind us why we wanted to do this in the first place. Things will continue to change, and possibly progress over the coming years; it is going to become increasingly important that we remember why we wanted to be Geriatricians in the first place.

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Learning points

Paradoxically Heparin after 5-10 days of exposure can cause a venous or arterial thrombosis through an immunologically mediated mechanism. The important clue is a marked fall in the platelet count. Heparin must be stopped and alternative measures taken. The BCSH recommend monitoring of platelet counts in all patients on heparin. See guidelines. Warfarin should not be started until the platelet count is normal.

Higher risk individuals

- (1) Females
- (2) Surgical patients
- (3) UFH

Diagnosis - 4T score

- 1) severity of the **T**hrombocytopenia
- 2) the presence or absence of **T**hrombosis
- 3) the **T**iming *vis a vis* heparin exposure
- 4) the presence of **o**ther explanations for the symptoms

You are asked to see Mrs H a 57-year old lady patient on the Orthopaedic ward. She has just had a bilateral knee replacement for severe osteoarthritis. She now has a dense right-sided hemiplegia which has developed overnight. Clinically she meets the criteria for a Left TACS. A CT scan of the head shows a dense clot in the left middle cerebral artery and some loss of grey-white differentiation. She is admitted to the stroke unit. She has been receiving daily prophylactic enoxaparin sodium injections since her operation 6 days ago. She had been slow to mobilise and had suffered an unprovoked DVT seven years earlier. Admitting ECG, chest X-ray and bloods are unremarkable, but there has been a drop in Mrs H's platelet count from $230 \times 10^9/L$ on admission to $63 \times 10^9/L$ done yesterday.

The typical history of heparin-induced thrombocytopenia is of a steep fall in the platelet count (>50%) 5 to 10 days after initial exposure to heparin, or within 24 hours of a re-exposure within usually quoted limit of 100 days of prior exposure. Median platelet counts are about $60 \times 10^9/L$. Rates of thrombosis in people with HIT are reported between 33 and 50%. Most HIT-associated thromboses are actually venous, but risk of arterial thrombosis is also markedly elevated.

Stroke is more common in females, who are also at an increased risk of HIT compared to men. Other patients can have presentations such as adrenal vein thrombosis causing haemorrhage with acute adrenal failure. A small proportion of patients have erythematous skin lesions (sometimes preceding actual thrombocytopenia), and some exhibit a syndrome of inflammatory, haemodynamic and neurological symptoms 5-30 minutes after exposure to heparin.

The risk of HIT is about 1% in anyone requiring heparin for 5 days or longer; it is highest in cardiothoracic surgery patients, followed by orthopaedic and general surgery; medical and obstetric patients are at a lower risk. Some studies have shown a lower rate of HIT in those receiving low-molecular weight heparins such as enoxaparin.

Small benign decreases in the platelet count may occur in anyone exposed to heparin, but these tend to be earlier on in the course of heparin treatment, are self-limiting even after continued heparin treatment, and are sometimes referred to by the obsolete term "HIT type 1". The immune-related severe form, now simply called "heparin-induced thrombocytopenia", was previously known as HIT type 2.

Pathophysiology

Heparin binds to PF4, a platelet antigen of unknown function and elicits an immune response. This leads to the rapid generation (within 5 days) of IgG antibodies, which bind to heparin-PF4 complexes. The Fc fragment of the antibody then links to the platelet FcγIIa receptor. This linkage leads to platelet activation, formation of microvesicles, and generation of platelet-rich "white" thrombi, as well as immune mediated endothelial damage. The thrombi may be arterial or venous. Oddly, despite the presence of an IgG antibody, there seems to be limited immunological memory, and on withdrawal of heparin the antibody typically disappears after a few months.

Diagnosis

Screening for HIT in people on heparin is recommended by the BCSH heparin guideline. In UFH, this means alternate day blood counts between days 4-14, and every 2-4 days in those on LMWH (unless for prophylactic treatment in the obstetric population, in whom the risk is exceedingly low compared to surgical patients).

The diagnosis of HIT is marred by the lack of specificity of the diagnostic assays. It has been estimated that for every 2 patients with a diagnosis of HIT, one has been incorrectly labelled. This leads to major complications in the choice of anticoagulation.

The probability of HIT can be estimated with the 4T score, which predicts the *a priori* risk of HIT by scoring

- 1) the severity of the Thrombocytopenia
- 2) the presence or absence of Thrombosis
- 3) the Timing *vis a vis* heparin exposure
- 4) the presence of **o**ther explanations for the symptoms.

Adequate risk prediction is especially important in settings where there are numerous other possible causes for thrombocytopenia, such as in ITU (where 30-50% of patients may have a low platelet count at some point in their treatment, compared to a 0.3-0.5% risk of HIT).

If there is sufficient suspicion for HIT, diagnostic testing is performed. Initially, an ELISA is performed to assess for the presence of **anti-PF4 antibodies**. This test is highly sensitive, but it is recognised that many people on heparin generate these antibodies without any thrombocytopenia, let alone thrombosis. Therefore, even a positive ELISA needs to be confirmed by a functional assay in a reference laboratory. A common assay incubates the antibody with "washed platelets". If this leads to a measurable release of serotonin, the

confirmatory test is positive.

Treatment

If HIT is likely, **heparin must be discontinued**. The real conundrum is the need for an anticoagulant that prevents the thrombotic complications of HIT while also protecting against the condition that initially required treatment with heparin, all while not cross reacting with heparin. The drugs of choice are direct thrombin inhibitors (e.g. lepirudin, argatroban) or heparin analogues such as danaparoid. For the UK situation, the BCSH guideline (Keeling *et al* 2006) recommends either lepirudin or danaparoid. Lepirudin is monitored by the APTT and may accumulate in renal impairment; in addition it carries a small anaphylaxis risk. Danaparoid is monitored by the anti-Xa activity, an assay that is not widely available.

Warfarin should not be commenced until the platelet counts have recovered to pre-HIT levels, given the risk of skin necrosis which is 100-fold that of other patients receiving warfarin.

Prevention

HIT can be prevented by avoiding heparin where possible (not always realistic or even desirable when Venous thromboembolism avoidance is paramount), or by using LMWH instead of UFH whenever feasible.

Back to the case

Mrs H's 4T score was very high indeed (HIT score 8, the maximum achievable), and was commenced on a lepirudin infusion with regular APTT monitoring while the HIT screen was processed by the haematology laboratory, which turned out to be strongly positive.

Sources

1. Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. *Postgrad Med J* 2007;83(983):575-82. PMID 17823223. DOI 10.1136/pgmj.2007.059188
2. Keeling D, Davidson S, Watson H. The management of heparin-induced thrombocytopenia. *Br J Haematol* 2006;133(3):259-69. PMID 16643427. DOI 10.1111/j.1365-2141.2006.06018.x
3. Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. *Crit Care Med* 2007;35(4):1165-76. PMID 17334253. DOI 10.1097/01.CCM.0000259538.02375.A5
4. Warkentin TE. Think of HIT. *Hematology Am Soc Hematol Educ Program* 2006:408-14. PMID 17124091. DOI 10.1182/asheducation-2006.1.408

EDUCATION

Age-related macular degeneration (AMD)

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AMD is the most common cause of blindness in people aged over 50 years in the western world^{1,2}. There are two types of AMD, referred to as 'dry' (non-exudative) and 'wet' (exudative). Dry AMD is the most common form of the condition, accounting for 90%. It develops very slowly causing gradual loss of central vision. In wet AMD, visual disturbance is often sudden, and can result in profound central visual loss.

Learning points

AMD is a common cause of blindness in the elderly. Dry AMD is commonest and patients are advised to take dietary supplements which slow progression. Wet AMD is less common and early diagnosis and laser treatment and drugs which block VEGF can help reduce the rate of visual loss. New advances have been made in the treatment of wet AMD.

RPE : retinal pigment epithelium

VEGF : vascular endothelial growth factor

CNV : choroidal

neovascular membrane
FFA : Fundus Fluorescein Angiography

OCT : Optical Coherence Tomography

Pathogenesis

In dry AMD, there is atrophy of the retinal pigment epithelium (RPE), and degeneration of photoreceptors leading to slowly progressive deterioration in vision. **Drusen** which is cellular debris that lies between retina and choroid may be seen. In wet AMD, there is **growth of new abnormal blood vessels** (choroidal neovascular membrane, CNV), located beneath the retina. These blood vessels are fragile and cause sudden deterioration of central vision, by either leakage or haemorrhage. There is evidence that angiogenic factors, especially vascular endothelial growth factor (VEGF) play a significant role in the formation of CNV^{3,4}.

Causes

Many studies have attempted to identify genetic or environmental factors as potential risk factors for the development of AMD. However, strong evidence to support these associations is lacking. Various studies have provided informative but controversial data, and besides older age, the best established risk factor for AMD is smoking^{5,6}.

Diagnosis

The diagnosis is made on clinical examination. Baseline investigations include visual acuity measurement, Optical Coherence Tomography (OCT); high quality three-dimensional images and Fundus Fluorescein Angiography (FFA); a series of specialised photographs of the macula. These imaging modalities determine the CNV lesion type, size, and location in relation to the fovea (central part of macula).

Treatment

There is, unfortunately, no treatment currently available for dry AMD, however patients may benefit from supportive measures such as low vision aids. Since smoking is the only proven risk factor for the development of AMD, patients should be advised to stop smoking. They should also be advised to eat balanced diets which may be enhanced with nutritional supplements. Ocular nutritional supplements have been shown (Age-Related Eye Disease Study) to possibly slow the progression of dry AMD⁷.

PDT : verteporfin is a photosensitiser drug given intravenously before laser therapy to improve effectiveness in destroying blood vessels in wet AMD.

In the UK, the supplements that most closely match the ARED study formulation are Ocuvite Preser Vision and Viteyes Original. However, since these products contain beta-carotene, they are contra-indicated in smokers or recent ex-smokers. There are similar formulations available in which beta-carotene has been substituted with lutein, however they lack the evidence base of the original formulation and there have been questions raised about the robustness of the study.

In Wet AMD, laser photocoagulation can be effective for a small group of patients with CNV which is located away from the fovea (extra-foveal CNV). This treatment is limited by the scotoma it causes in the visual field, and has a high recurrence rate.

Photodynamic therapy with verteporfin (PDT) aims to destroy CNV without damaging the overlying retina as it only acts on the new abnormal vessels. This has the advantage over laser treatment since lesions which overlie the fovea (sub-foveal CNV) can also be treated. In September 2003, the National Institute for Clinical Excellence (NICE) published guidelines on PDT, recommending it for the treatment of sub-foveal CNV, with certain FFA characteristics in wet AMD.

Recently there have been major advances in the treatment of wet AMD with the introduction of substances which block VEGF. Two specific agents have been introduced for intraocular injection allowing ophthalmologists to treat all types of sub-foveal CNV lesions, with a wide range of characteristics. Both of these agents are given by intravitreal injection; pegaptanib (Macugen) at intervals of 6 weeks, and ranibizumab (Lucentis) every 4 weeks. These have been shown to be effective in preventing visual loss, and in the case of Lucentis also improving visual acuity in a proportion of patients⁸⁻¹⁰.

Macugen was licensed for use in the United States in December 2004, and has had widespread use since then. It was launched in the United Kingdom in May 2006, however its use in UK clinical practice has been limited as services are yet to be commissioned by PCTs. Lucentis was licensed in the United States in 2006 and in the UK in Feb 2007. Both Macugen and Lucentis have been undergoing NICE appraisal, during which time, these treatments have been administered either via PCT-approval or in private medical practice. This has led to the 'off-label' use of a cheaper third agent; bevacizumab (Avastin), which has biological similarity to Lucentis (from pilot studies) when given intravitreally. Avastin is licensed for the treatment of colorectal or breast cancer, but not for intraocular administration.

On 27 August 2008, NICE recommended that patients with wet AMD may receive treatment with Lucentis. Macugen, however has yet not had the approval, which has raised concerns amongst ophthalmologists for patients who are allergic to Lucentis, or those who are unable to attend hospital appointments monthly.

Combination therapy with PDT and anti-VEGF may prove to be even more effective than either therapy on its own. Trials of such combinations are currently on going.

References

1. Klein R, Klein B, Linton RL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 1992; 99: 933-43.
2. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1995; 102: 1450-60.
3. Kvanta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age related macular degeneration express vascular endothelial growth factor. *Invest Ophthalmol Vis Sci* 1996; 37:1929-34.
4. Lopez PF, Sippy BD, Lambert HM et al. Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1996; 37 :855-868.
5. Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. (1996). A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA*; 27,147-51.
6. Delcourt C, Diaz JL, Ponton-Sanchez A, Papoz L. Smoking and age-related macular degeneration. The POLA Study. *Pathologies Oculaires Liees a l'Age*. (1998). *Arch Ophthalmol* 116:1031-5
7. Age-Related Eye Disease Study Research Group. A randomised, placebo-controlled, clinical trial of high dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss : AREDS report no. 8. *Arch Ophthalmol* 2001; 119 : 1417-36.
8. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularisation Clinical Trial Group. *N Engl J Med* 2004; 351:2805-16.
9. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS et al for the MARINA Study Group. Ranibizumab for Neovascular Age-Related Macular Degeneration. *N Engl J Med* 2006; 355:1419-31.
10. VISION Clinical Trial Group (D'Amico DJ et al). Pegaptanib sodium for neovascular age related macular degeneration: two year safety results of the two year prospective, multicentre, controlled clinical trials. *Ophthalmology* 2006; 113: 992-1001.

Jobs

Do you have any jobs to advertise then please let me know
<http://careers.bmj.com/careers/welcome.html>

Diary

I would also like to keep a diary of important courses and meetings so just email me if you would like a mention.

Useful Links

British Geriatric Society <http://www.bgs.org.uk/>

There has been a great deal of work on stroke both from the Royal College of Physicians and the AHA and many useful documents have been published in the past few months. So here are a number of useful stroke links

- NICE - The diagnosis and acute management of stroke and transient ischaemic attacks - <http://www.nice.org.uk/Guidance/CG68>
- RCP - National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) <http://www.rcplondon.ac.uk/pubs/contents/9c4488ac-d8f1-43d8-b9da-b801441bcdfb.pdf>
- RCP - National clinical guideline for stroke 3rd edition <http://www.rcplondon.ac.uk/pubs/contents/6ad05aab-8400-494c-8cf4-9772d1d5301b.pdf>
- American Heart association Guidelines for the Early Management of Adults With Ischemic Stroke <http://stroke.ahajournals.org/cgi/reprint/38/5/1655>
- British association of Stroke Physicians <http://www.basp.ac.uk/>

Book reviews

**Essential Geriatrics -
Henry Woodford,**
Radcliffe Publishing pp
309

The author, a Consultant Geriatrician in Cumbria, has done a superb job in covering most of the big topics in Geriatric medicine. As expected it deals with those particular problems that affect the elderly patient and complements a standard medical textbook. I particularly like the author's own illustrative attempts, they are somewhat more interesting than the typical over illustrated diagrams in most textbooks which somehow end up distracting from the point they wished to show. Overall this is an excellent book and one that which all working with older patients should seriously consider purchasing.

Last but not least this issue's question is ...

Why does one get a
meniscus on the CXR in a
patient with a pleural
effusion ?

Sadly there is no prize
except that of the joy of
learning something you
might not have known !

Clue...it has nothing
whatsoever to do with
surface tension



Feedback

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