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# British Journal of Medical Practitioners

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## Dabigatran: A look before we leap

Naseer A Masoodi and Bilal Ahmad

Warfarin is the most commonly used oral anticoagulant and has established efficacy for more than 50 years for the prevention of thromboembolic events, but its use is limited by fear of bleeding, drug-drug and drug-food interactions, and routine monitoring of international normalized ratio (INR). In patients with atrial fibrillation (AF), warfarin prevents 64% of strokes in research studies but the real-world effectiveness drops to 35% because of various factors leading to its suboptimal use.<sup>1</sup> In October 2010 the United States (US) Food and Drug Administration (FDA) approved Pradaxa capsules (dabigatran etexilate) as the first new agent to prevent stroke and systemic emboli in patients with non-valvular AF. In this article we will discuss some of the evidence for and against the use of dabigatran.

In the RE-LY study<sup>2</sup> (Randomized Evaluation of Long-term Anticoagulant Therapy), high-dose dabigatran (150mg twice a day) was found to be superior to warfarin for the prevention of stroke and systemic emboli, required no routine INR monitoring, and had few food and drug interactions. James Freeman and colleagues,<sup>3</sup> using data from the RE-LY trial, found that high-dose dabigatran (150mg twice a day) was the most efficacious and cost-effective strategy compared with adjusted-dose warfarin among adults older than 65 with AF.

Dabigatran has been shown to specifically and reversibly inhibit thrombin, the key enzyme in the coagulation cascade. Studies in healthy volunteers<sup>4</sup> and in patients undergoing orthopaedic surgery have indicated that dabigatran has a predictable pharmacokinetic/pharmacodynamic profile, allowing for a fixed-dose regimen. Peak plasma concentrations of dabigatran are reached approximately two hours after oral administration in healthy volunteers, with no unexpected accumulation of drug concentrations upon multiple dosing. Excretion is predominantly via the renal route as unchanged drug. Dabigatran is not metabolized by cytochrome P450 isoenzymes. Though use of dabigatran for non-valvular AF and venous thromboembolism (VTE) is gaining practice,<sup>5</sup> it remains far from being the standard of care.

What are the concerns with use of dabigatran? In the RE-LY study the INR control was relatively poor (64% TTR (time in the therapeutic range)) but, probably more importantly, the

relationship between events and individual's INR control was not reported. The use of centre's time in therapeutic range (cTTR) in the RE-LY study as a surrogate for INR control may not truly reflect TTRs for individual patients. Also in RE-LY study, randomization was stratified for centre and by the centre-based analyses, and the quality of oral anticoagulant services was the basis for the comparisons in this report. A subgroup analysis<sup>6</sup> concluded that relative effectiveness of dabigatran versus warfarin was mainly seen at centres with poorer INR control. For example, Swedish centres had good TTR and the relative effectiveness and safety of dabigatran was virtually the same as with warfarin; thus, it is only the price difference that counts. It also highlights how local standards of care affect the benefits of use of new treatment alternatives and hence further limits the generalizability of any 'overall average' cost-effectiveness of dabigatran, raising the question that if an intervention does not do more, why should a payer pay more for it? There are several other factors that could impact on the cost-effectiveness<sup>7</sup> of dabigatran such as patient medication adherence, dosing frequency, and the potential effect of new efficient methods of warfarin management improving INR control by patient self-testing.

The other shortcomings of dabigatran include lack of antidotes when patients do bleed and lack of any alert to physicians that patients are not compliant with dabigatran (INR serves this purpose for warfarin). Additionally, in the RE-LY trial, dabigatran was used twice daily thus raising compliance issues compared to once daily warfarin (the rates of discontinuation of dabigatran were higher at 15% and 21% at one and two years, respectively); 11.3% reported dyspepsia (twice the rate of warfarin group); high rate of gastrointestinal bleed compared with warfarin; patients in the dabigatran cohort were at slightly higher risk of myocardial infarction (not sure how it will translate in real world practice); and contraindication of dabigatran in severe renal dysfunction raises some more questions about its use and cost effectiveness. In addition, the RE-LY trial excluded patients who had: contraindications to anticoagulation, severe heart-valve disorder, stroke within 14 days or severe stroke within six months before screening, a condition that increased risk of haemorrhage, creatinine clearance of less than 30ml per minute, active liver disease, and pregnancy. Clinicians will need to use their judgement to

weigh and balance the risk for bleeding with this new agent in a setting of an acute stroke versus the risk of having another ischaemic stroke in someone with AF if not given anti-coagulation therapy immediately. Safety and efficacy at extremes of body weight is not well established with current FDA approved doses of dabigatran either.

In summary dabigatran is a very exciting new agent with significant advantages over warfarin. However, in view of dabigatran's higher non-adherence rate and greater risk of non-haemorrhagic side effects, patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran.<sup>1</sup> Until more studies and post-marketing data become widely available, we should advocate tight INR control for which there is a wealth of evidence for benefits, and promote strategies to improve the management of therapy with warfarin.

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**Competing Interests**

None Declared

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**REFERENCES**

1. Gage BF. Can we rely on RE-LY? *N Engl J Med.* 2009; 361:1200-1202.
2. Connolly SJ, Ezekowitz MD, Yusuf S et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361:1139-1151.
3. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, Wang PJ, Turakhia MP. *Ann Intern Med.* 2011 Jan 4;154(1):1-11.
4. Stangier J, Rathgen K et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol.* 2007 September; 64(3):292-303.
5. Clayville LR, Anderson KV et al. New options in anticoagulation for the prevention of venous thromboembolism and stroke. *P T.* 2011 February; 36(2):86-88, 93-99.
6. Wallentin L, Yusuf S, Ezekowitz MD et al; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet.* 2010; 376:975-83.
7. Masoodi NA. Compared with warfarin, high-dose dabigatran might be cost-effective for preventing stroke in older patients with nonvalvular AF (Comment). *ACP Journal Club.* 2011 Jun 21; 154:JC6-12.

## Sedation by Surgeons: Is patient safety being compromised by non-anaesthetists?

Priyan R Landham, Umer Butt, Aabid Sanaullah, Hester C Taekema and Ahmed Shawky Eid

**Introduction:** Sedation is frequently administered by non-anaesthetic doctors in the emergency department whilst minor procedures are carried out. Guidelines and protocols exist but are non-anaesthetic doctors familiar with them?

**Methods:** A questionnaire survey of 53 orthopaedic surgeons (registrars) in Bristol and Cardiff was carried out to ascertain their current clinical practice, knowledge, and training with regards to sedation.

**Results:** Sedation had been administered by all the orthopaedic doctors surveyed at some stage in their careers to facilitate fracture or joint reduction or to apply traction in settings outside the operating room. Forty-five percent of respondents had read the sedation protocol for their hospital but fewer respondents ensured monitoring data forms were completed during and after the procedure (21% and 23% respectively). Morphine and other opioids were the most commonly used sedative medication. The pharmacology section of the questionnaire revealed a reasonable knowledge base for most trainees with a mean score of 4.29 out of 7. Whilst the majority of respondents had undergone advanced life support training (89%), only 30% of respondents had undergone formal training regarding sedation techniques.

**Conclusion:** Sedation for minor procedures is widely performed by orthopaedic doctors. There is the potential for significant morbidity and mortality, so doctors need to be aware of and follow sedation guidelines. Adequate training needs to be incorporated into postgraduate training speciality programmes to ensure safe sedation practices.

### Introduction

Sedation is frequently administered outside of the operating theatre by non-anaesthetic doctors to facilitate minor procedures. This can be in both primary care including dental surgeries as well as in hospital departments such as radiology, endoscopy and the emergency department. Clinical practice including medication and monitoring equipment available and the personnel involved, varies not only between hospitals and regions but also between departments.

In the emergency department sedation is often performed in a busy clinical setting by junior doctors. This enables minor procedures to be carried out with subsequent discharge home reducing admission rates and the requirement for general anaesthesia. Other advantages include less workload pressure on the anaesthetic team and a significant improvement in the patient experience. Sedation is not without risk and significant morbidity and mortality is still associated with its use, particularly in the elderly and in combination with other medication<sup>1,2</sup>. Guidelines and protocols do exist to ensure safe practice but often it is only anaesthetic doctors who are aware of them<sup>3-7</sup>. A recent study by Fanning highlighted discrepancies in practice, skills and knowledge of doctors of various specialities and grades who administered sedation<sup>8</sup>. Anecdotal reports from orthopaedic colleagues suggested the variability in competence of doctors with clear implications for patient safety. We therefore sought to ascertain the current clinical practice, knowledge and prior training in sedation techniques of specialist registrars in orthopaedic and trauma surgery in our region.

### Materials and Methods

A questionnaire based survey of 53 specialist registrars in orthopaedic and trauma surgery in the neighbouring Severn and South Wales regions was carried out. The questionnaire was modified from that developed by Fanning<sup>8</sup> and circulated for completion at regional teaching sessions in Swansea and Bristol (Appendix 1). Each respondent had 15 minutes to complete the questionnaire based on their own experience, practice and knowledge. Respondents were not allowed to confer and full confidentiality was assured. The questionnaire was split into several sections that ascertained the respondents' clinical practice including the procedures that sedation was used for, prior training, awareness of protocols and safety issues. Knowledge of the basic pharmacology of commonly used sedative agents was also tested. The final section asked respondents whether they had ever encountered any adverse events, the nature of the adverse event and whether assistance was required from the anaesthetic department.

### Results

Orthopaedic specialist registrars (post basic surgical training) who were in higher surgical training completed 53 questionnaires. Sedation was performed in the emergency department by all respondents for manipulating fractures, reducing dislocated joints and for applying traction. Twenty-four respondents (45%) had read the sedation protocol for their hospital/emergency department. Thirteen respondents (25%) completed pre-sedation assessment forms, whilst only eleven (21%) completed the during-procedure monitoring data forms

and twelve (23%) filled the after-procedure forms (Figure 1). Twenty-eight (53%) respondents ensured that either they or an assistant provided the patient with discharge advice.

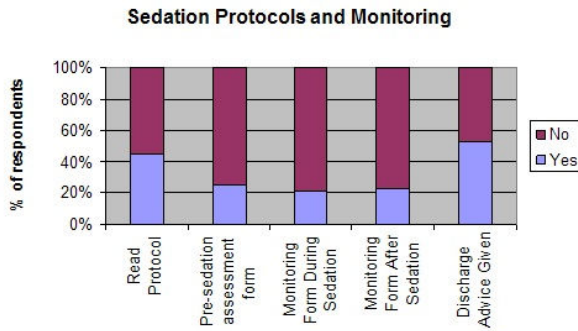


Figure 1 The percentage of respondents who had read the departmental protocol, completed monitoring forms and given advice prior to discharge.

Table 1: Sedative agents used.

Medication/Sedative Agent	No of Respondents
Diazepam	31
Pethidine	1
Midazolam	35
Propofol	15
Fentanyl	3
Morphine	44
Opiates with BDZs	12
Local anaesthesia with sedation	17

Almost all (98%) respondents administered sedation in the presence of an assistant. Forty-seven (89%) checked their medication with another healthcare professional. All fifty-three respondents supplied patients with concurrent oxygen whilst fifty-two ensured that resuscitation equipment was available nearby. In terms of specific training, forty-seven (89%) registrars had undergone Advanced Life Support training (ALS) but this qualification was only valid (within three years) for thirty-six (68%). Sixteen registrars (30%) stated they had undergone formal training or teaching regarding sedation (Figure 2). With regards to monitoring of patients, thirty-six (68%) respondents used pulse oximetry, fourteen (26%) used electrocardiogram (ECG) monitoring and twenty-eight (53%) measured blood pressure.

Morphine and other opioids were the most commonly used sedative medication (44 responses), followed by midazolam (35 responses), diazepam (31 responses) and propofol (15 responses). Twelve respondents combined opiates and benzodiazepines, whilst seventeen combined local anaesthesia with sedation (Table 1).

Have you received training in administering sedation?

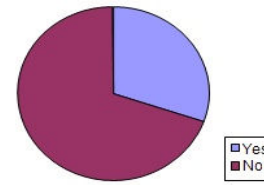


Figure 2 The proportion of respondents who had received training in administering sedation

Two-thirds of respondents (35 out of 53, 66%) administered sedation in boluses rather than calculating the correct dose per kilogram. The pharmacology questions devised by Fanning<sup>8</sup> tested knowledge of metabolic pathways, duration of action and side effects. Overall, each question was answered correctly by over 50% of respondents (Figure 3). The mean score was 4.29 out of 7.

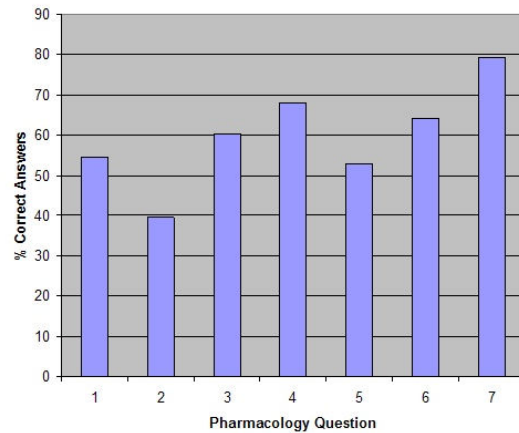


Figure 3 The percentage of correct answers for each of the seven pharmacology questions.

Eighty percent of surveyed orthopaedic doctors (43 respondents) reported an adverse event after administering sedation. Twenty-nine respondents had at some stage contacted the anaesthetic department for assistance in managing a patient following sedation (Table 2).

Table 2: Adverse Events reported.

Adverse Effects	No of Respondents
Hypoxia	20
Respiratory Depression	13
Loss of consciousness	7
Hypotension	14
Prolonged Sedation	13
Nausea and Vomiting	14



## Discussion

Non-anaesthetic doctors are permitted and often required to administer sedation to perform procedures in settings outside of the operating theatre. There are various published guidelines that detail the level of care and monitoring that should be provided when sedation is given<sup>3-7</sup>. It has been recommended that the same standards of monitoring apply to procedures under sedation or local anaesthesia as to procedures under general anaesthesia, and are irrespective of the location of the procedure<sup>3</sup>.

The report by an intercollegiate working party led by the Royal College of Anaesthetists summarised the key aspects of administering sedation based on existing guidelines<sup>6</sup>. Patients should be first assessed before the procedure by attendant staff, risk factors noted and further examination or investigations performed as necessary. Drug administration technique should be "one defined by a relevant specialty organisation"<sup>6</sup> and doses adjusted to individual patient requirements. Combinations of drugs should be "employed with particular caution" especially sedatives and opioids. The opioids should be administered first and given time to be maximally effective before any sedative is given. The patient should be monitored during the procedure by a suitably trained individual recording pulse oximetry, blood pressure and electrocardiography. High flow oxygen should also be available. Doctors administering sedation should be able to control an airway using basic manoeuvres or airway adjuncts.

There is significant morbidity and mortality associated with sedation<sup>1,2</sup>. It is difficult to know the true incidence of cardio-respiratory complications after sedation, as this is often related to the procedure and patient factors. An audit of 14,000 endoscopic procedures reported a 30-day mortality of 1 in 2000<sup>9</sup> and there are several anecdotal reports of death following sedation<sup>10,11</sup>.

It is apparent that not all doctors are aware of or follow sedation guidelines. In the study by Fanning<sup>8</sup>, 42% of respondents completed a pre-procedure assessment form and 70% completed monitoring data sheets. In this study, whilst 45% of respondents had read departmental protocols, only 25% completed a dedicated pre-assessment of the patient and an equally low number recorded monitoring data forms during (21%) and after the procedure (25%). These low numbers are of potential concern. Time and resource constraints may play a part, particularly in a busy emergency department. Also, as junior doctors frequently rotate between hospitals, they may not be aware of departmental policies in each unit. It is understandably impractical to perform a procedure and concurrently complete a data monitoring form. This role should be delegated to an assistant.

Knowledge of basic pharmacology amongst respondents seemed reasonable and indeed better scores were achieved than in Fanning's original paper. It would appear that a large number

of respondents (n=29) have contacted anaesthetic colleagues for help following adverse events. This may simply reflect an acknowledgement of limited anaesthetic capabilities amongst respondents and a pre-emptive call for assistance rather than an anaesthetic "bail out" after cardio-respiratory compromise.

Whilst the questionnaire used is neither a formal assessment tool of clinical competence nor an accurate log of experience, it serves to highlight the potential limitations of current training. A clear issue is the low number of respondents who claim to have received formal teaching or training with regards to sedation. This may be due to the fact that little or no postgraduate training is provided in hospital specialities that require sedation. This is an area that needs to be addressed. The issues raised by this study are not new. In fact, a similar survey by Hewitt and Hartley in 1994 had similar findings and suggested that "sedation techniques should be included in induction teaching for A&E and orthopaedic juniors" and that all doctors administering sedation should have the "opportunity of resuscitation refresher courses"<sup>12</sup>.

## Conclusion

Sedation is widely administered by non-anaesthetic doctors including orthopaedic surgeons in order to perform basic procedures outside of the operating theatres, mainly in the Accident and Emergency department. Whilst this study only involves 53 doctors in one speciality across two regions, it does give an insight into the self-reported clinical practice, knowledge and experience of a group of surgical doctors who are often required to administer sedation. Significantly, the majority of doctors surveyed reported they had not received any formal training. It is also apparent that departmental guidelines are not always known or followed. Due to the inherent risks of sedation, it is important that doctors are aware of and follow available guidelines. It is crucial that adequate training should be given to non-anaesthetic doctors to ensure they have the knowledge and skills to safely administer sedation. Otherwise a medical doctor, perhaps a registrar level from the Accident and Emergency department, should be present for patient assessment and management of airway compromise or any arising complication.

### Competing Interests

None declared

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**APPENDIX: QUESTIONNAIRE****Procedures**

What procedure do you use sedation for?

**Protocols and Practice**

1. Have you read the sedation protocol available in your hospital/department?
2. Do you complete a pre-sedation assessment form prior to administering sedation?
3. Do you or an assistant complete a monitoring data form:
  - a) during the procedure?
  - b) after the procedure?
4. Do you or an assistant advise the patient on discharge care?

**Safety and Training**

1. What monitoring do you use during sedation?
2. Do you have an assistant during sedation? (Nurse/doctor/healthcare professional)
3. Do you check your drugs with someone?
4. Do you give your patient oxygen?
5. Do you have resuscitation equipment available?
6. Have you completed Adult Life Support (ALS) training?
7. Is your Adult Life Support (ALS) still valid?
8. Have you received formal teaching prior to using sedation?

**Medications** (Please circle medications you use)

Diazepam/Pethidine/Midazolam/Propofol/Fentanyl/Morphine  
Opiates in conjunction with benzodiazepines  
Local anaesthesia in conjunction with sedation

**Pharmacology**

1. When administering medications, do you tend to administer the medication in boluses or as dose per kilogram?
2. Midazolam affects neuromuscular transmission:  
Yes or No
3. Diazepam has greater amnesic effects than midazolam:  
Yes or No
4. Fentanyl-induced respiratory depression is dose-dependent:  
Yes or No
5. Morphine does not possess active metabolites:  
Yes or No
6. Pethidine is metabolised mainly in the kidney:  
Yes or No
7. Opiates increase biliary pressure:  
Yes or No
8. Midazolam has a longer duration of action than diazepam:  
Yes or No

**Adverse effects**

Has a patient of yours experienced an adverse event? (Please Circle)

- \* Hypoxia
- \* Respiratory depression
- \* Loss of consciousness
- \* Hypotension
- \* Prolonged sedation
- \* Nausea/vomiting
- \* Cardiovascular collapse/arrest

If your patient suffered an adverse effect, did you contact the anaesthetic department?

Yes or No

**REFERENCES**

1. Cravero JP, Blike GT, Beach M, Gallagher SM, Hertzog JH, Havidich JE, Gelman B. Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. *Pediatrics* 2006 Sep;118(3):1087-96.
2. Cote CJ, Notterman DA, Karl HW, Weinburg JA, McCloskey C. Adverse sedation events in pediatrics: a critical incident analysis of contributing factors. *Pediatrics* 2000;105:805-14.
3. Association of Anaesthetists of Great Britain and Ireland. Recommendations for Standards of Monitoring during Anaesthesia and Recovery. Guidelines of the Association of Anaesthetists of Great Britain and Ireland, December. London: AAGBI, 2000.
4. Pitetti RD, Singh S, Pierce MC. Safe and efficacious use of procedural sedation and analgesia by non-anaesthesiologists in a pediatric emergency department. *Archives of Pediatric and Adolescent Medicine* 2003;157:1090-6.
5. Holzman RS, Cullen DJ, Eichhorn JH, Philip JH. Guidelines for sedation by non-anaesthesiologists during diagnostic and therapeutic procedures. The Risk Management committee of the Department of Anesthesia of Harvard Medical School. *Journal of Clinical Anesthesia* 1994;6:265-76.
6. <http://www.rcoa.ac.uk/docs/safesedationpractice.pdf> [accessed December 2009]
7. Commission on the Provision of Surgical Services. The Royal College of Surgeons of England. Guidelines for Sedation by Non-anaesthetists. 1993
8. Fanning RM. Monitoring during sedation given by non-anaesthetic doctors. *Anaesthesia*, 2008; 63: 370-374.
9. Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A. A prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing and sedation methods. *Gut* 1995;36:462-7. (12 from working party)
10. Kovac C. Airline passenger dies after being sedated by doctor. *BMJ* 1999;318:12.
11. <http://www.topix.com/forum/county/cook-il/THDSMC6MO19B32TMC> [accessed December 2009]
12. Hewitt SM, Hartley RH. Manipulation under sedation in the accident and emergency department. *Journal of Accident and Emergency Medicine* 1994;11(3):186-8.

## The Association of NCF1 Gene with the Severity of Malaria

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### Abstract

The phagocyte oxidase 47 (P47Phox) is produced by the NCF1 gene which is located on chromosome 7. The P47 Phox forms an important component of the NADPH oxidase complex enzyme which leads to the production of reactive oxygen species (ROS). The NCF1 gene exists in two versions, one is a wild type gene with GTGT at the start of exon 2. The other is a pseudogene and it has its GT deletion at the start of exon2 which leads to passive production of ROS. The role of ROS in malaria was studied through the restriction enzyme *Geobacillus stearothermophilus* GR75 (BsrGI) found in the NCF1 gene. This enzyme digests only the pseudogene and has no impact on the wild type gene. The comparison of 88 malarial patients with 100 healthy individuals proves that there was no association of NCF1 gene with malaria because the P value was greater than 0.05.

**Background:** Malaria is a mosquito-borne infectious disease which is caused by a eukaryotic protist of the genus *Plasmodium*. The most fatal form of the disease is caused by *Plasmodium falciparum*. The neutrophil cytosolic factor 1 (NCF1), also known as p47 phox, is an important subunit of NADPH oxidase which plays a role in the production of ROS. The forming of ROS is a pivotal component of innate immunity against parasitic and bacterial infection.

**Aim:** The aim of study was to find out that whether the NCF1 gene and ROS had a role in malaria.

**Method:** Samples from 88 malarial patients and 100 healthy individuals were processed with the restriction enzyme BsrGI.

**Conclusion:** It was found that the NCF1 gene and ROS have no association with malaria.

### Introduction

Malaria is a major worldwide scourge, infecting and killing several million individuals each year<sup>1</sup>. Malaria is common in mostly tropical and subtropical areas such as The Americas, Asia and Africa<sup>2, 3</sup>.

The NADPH oxidase complex is responsible for the reduction of oxygen in cells, yielding a superoxide anion ( $O_2^{\cdot-}$ ) that is subsequently converted into other ROS; including hydrogen peroxide ( $H_2O_2$ ) and the hydroxyl radical ( $OH^{\cdot}$ )<sup>4</sup>.

The Sequence analysis showed that the NCF1 wild type gene is 15,236 bp long, contains 11 exons and has an intron/exon structure identical to the highly homologous pseudogene<sup>5</sup>. The pseudogene which is highly homologous to the wild type gene is located on the same region of the chromosome, which is 7q11.23 of chromosome 7<sup>6</sup>. Comparative sequence analysis between the wild type gene and pseudogene demonstrates greater than 98% homology but the pseudogene has a GT deletion ( $\Delta GT$ ) at the start of exon 2<sup>7</sup>. The genomic pattern of wild type NCF1 gene and its pseudogene may influence the production of reactive oxygen species (ROS) in parasitic and bacterial infections and also in autoimmune diseases.

During malarial infection, the ROS production can contribute to rapid parasite clearance in mild malaria<sup>8</sup> but in severe malaria the high capacity production of ROS was associated with anaemia. This means that ROS has a possible role in both parasite clearance and anaemia during *P.falciparum* infection<sup>9</sup>. Genetic variation in components of the leukocyte NADPH

oxidase may, therefore, influence disease susceptibility to, and disease duration of parasitic infection and autoimmune disease<sup>10</sup>.

### Study Design

#### Inclusion and exclusion criteria

Patients who had fever with malarial parasites detected microscopically from blood smears and had no evidence of other illnesses were selected. Patients were excluded if they developed other illnesses within three days of admission or if there was any other present infection.

Relatives of patients in the hospital and in the laboratory and members of the community without malaria or any other febrile illness were included after clinical evaluation. These formed the control group of healthy individuals.

#### Patients and healthy individuals

To determine the association of NCF1 gene in malaria, the blood samples were collected from malarial patients and healthy individuals in storage tubes coated with EDTA. Malaria was diagnosed on the basis of clinical observation and positive smear test containing various types of plasmodium.

#### Materials and Methods

The restriction fragment length polymorphism (RFLP) method was performed to determine the prevalence of NCF1 gene GT deletion ( $\Delta GT$ ) among patients with malaria and among

healthy individuals in a Pakistani population. In order to determine whether there was an association between NCF1 gene GT deletion ( $\Delta$ GT) at the start of exon 2 with susceptibility to malaria, 88 malarial patients and 100 healthy individuals were genotyped for the GT deletion by restriction enzyme analysis.

Genetic Analysis

Genomic DNA of patients and of the healthy control subjects was extracted from venous blood samples using the nucleospin blood extraction kit (NucleoSpin<sup>®</sup> Blood, Germany) according to the manufacturer’s protocol. The NCF1 gene was analyzed by the restriction fragment length polymorphism (RFLP) method. The exon 2 was amplified using both forward and reverse primer as shown in Table 1. The reaction mixture (50  $\mu$ l) for PCR was prepared in 0.2 ml tubes (Axygen<sup>®</sup>, California, USA) by adding the following: 1.2  $\mu$ l of sample DNA (50 ng/ $\mu$ l), 5  $\mu$ l (10X) from the PCR buffer (Fermentas, Burlington, Canada), 4  $\mu$ l of 25mM magnesium chloride (MgCl<sub>2</sub>) (MBI Fermentas, Burlington, Canada), 3  $\mu$ l of 2 mM deoxyribonucleotide triphosphates (dNTPs) mixture (MBI Fermentas, Burlington, Canada), 2.6 $\mu$ l of each forward primer (10 pm/ $\mu$ l), 2.6  $\mu$ l of the reverse primers (10 pm/ $\mu$ l) and 1.2 $\mu$ l Taq DNA polymerase (MBI Fermentas, Burlington, Canada) in 30.40  $\mu$ l nuclease free water with cycling conditions 95 °C for 5 min, followed by 35 cycles at 95 °C for 1 min, 60.6 °C for 1 min, 72 °C for 1 min and finally a 10 min extension at 72 °C.

The amplified products were then treated with the restriction enzyme BsrGI (*Geobacillus stearothermophilus* GR75) (Fermentas life science). For a 20  $\mu$ l mixture we took 10  $\mu$ l of PCR product, 2  $\mu$ l 10X buffer tango, 1  $\mu$ l BsrGI enzyme and 7  $\mu$ l of nuclease free water to make the mixture volume up to 20  $\mu$ l and checked the result on 2% agarose gel.

Table 1: sequence of primers and product size

Deletion Exon	primers	sequence	Product size
	DNCF2F	5'- GCTTCCTCCAGTGGGTAGTG-	
	DNCF2R	5- GCAAGACCCTGGGTGACAGA-3'	
GTGT			358 bp
GT			356 bp

**Statistical Analysis**

Statistical analysis was performed using the Study Result Software Version 1.0.4 (CreoStat HB Frolunda, Sweden). The association of both types of genes in malaria patients and healthy individuals were compared using the  $\chi^2$  or Fischer’s exact test. Similarly to elucidate whether there was an association between the age and gender of both patients and

healthy controls, analysis was done using the T-test and chi-square test by the online Graphpade software.

**Results**

Characteristics of patients

The characteristics of patients and healthy individuals are mentioned in Table 2 and table 3.

Table 2: Total number of patients and healthy individuals with their respective mean ages

Characteristic	Patients	Mean age	Control	Mean age	P value	± SD
Total number of subjects	88	22	100	26	0.43761	0.8627
Adults > 22 year	60		60			
Children <22 year	28		40			

Table 3: Total number of Patients and healthy individuals enlisted with respective mean age.

Characteristic	Patients	Mean age for patients	Control	Mean age for controls
No of males	75	24	80	26
No of females	13	20	20	27
Total	88	22	100	26

A chi-square test was performed to test the null hypothesis regarding whether there was an association between gender and the number of subjects in the control group and patient groups. No statistically significant association was found,  $\chi^2 (1, N = 188) = 0.559, p = 0.4545$ ". Similarly, a chi-square test was performed to test whether there was any association between the gender and ages of subjects in the control group and in the patient group. Again no statistically significant association was found,  $\chi^2 (1, N = 188) = 0.299, p = 0.5848$ ".

PCR amplification of exon 2 of NCF1 gene

The exon 2 was amplified by polymerase chain reaction to obtain 358 base pair long regions in the case of the wild type gene and 356 base pair long regions in the case of the pseudogene. The products were treated with a restriction enzyme, *Geobacillus stearothermophilus*, GR75 (BsrGI) which digests only the wild type gene (GTGT), which meant two bands of 265 bp and 93 bp were obtained respectively. Whereas with the pseudogene ( $\Delta$ GT) there was no digestion and the original band of 356 bp was obtained. When the individuals had both the wild type gene (GTGT) and the

pseudogene ( $\Delta$ GT) three bands of 265 bp, 93 bp and 356 bp were obtained, two of the wild type gene and one of the pseudogene respectively, which is shown in figure 1.

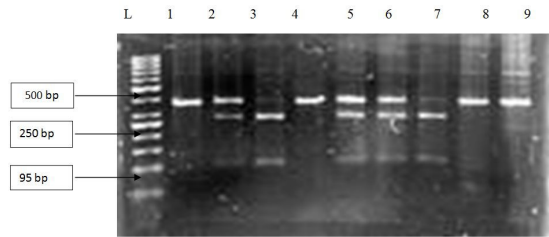


Figure 1: Agarose gel (2%) showing genotypes of eight patients with malaria. The GT deletions ( $\Delta$ GT) were checked using the RFLP method, using the restriction enzyme BsrGI. The lane L contains 50 base pair markers, while lane 1 contains a negative sample and 3 and 7 contain amplified wild type gene (GTGT) products. Lane 2, 5 and 6 contain amplified wild type gene and pseudogene ( $\Delta$ GT) products and lane 4, 8 and 9 contain amplified pseudogene products respectively. The result shows that the 2<sup>nd</sup>, 5<sup>th</sup> and 6<sup>th</sup> patients have both the wild type gene and pseudogene (GT/GTGT). The 3<sup>rd</sup> and 7<sup>th</sup> patients have the wild type gene (GTGT) and THE 4<sup>th</sup>, 8<sup>th</sup> and 9<sup>th</sup> patients have the pseudogene ( $\Delta$ GT).

#### Genotypic Frequencies of wild type gene and pseudogene in Malaria Patients

It was found that in the Pakistani population, the frequency of the wild type gene in malarial patients (37.5%) was no higher than in healthy individuals (45%) with  $P = 0.30427$ . The combination of wild type gene and pseudogene (GTGT/  $\Delta$ GT) was equally prevalent in malarial patients (39.8%) as it was in healthy individuals (40%) with  $P = 0.99999$ , while the pseudogene ( $\Delta$ GT) was also slightly different among healthy individuals (15%) as compared to malarial patients (22.7%) with  $P = 0.19263$  which is shown in table 4. There was no significant association found because the P values was greater than 0.05.

Table 4: Show the association of NCF1 gene with malaria

NCF1 gene	Control (n = 100)	Frequency (%)	Patients (n = 88)	Frequency (%)	P value
GTGT	45	45	33	37.5	0.30427
GT	15	15	20	22.7	0.19263
GTGT/GT	40	40	35	39.8	0.99999

#### Discussion

In this study the association of a wild type gene and a pseudogene with malarial infection, which affects the hepatic, haematological and respiratory systems was investigated.

There was no association found between the wild type gene and pseudogene and the severity of malaria. The innate immune mechanisms that have been proposed to kill malaria parasites are those mediated by ROS and RNS, especially NO and ONOO<sup>-</sup>, both generated early during infection prior to the activation of adaptive immune mechanisms and later as components of the effector arm of the adaptive immune response<sup>11, 12</sup>. The parasite-killing role for these molecules has often been conflicting, especially when looking at in vitro and in vivo studies<sup>13</sup>. It was confirmed that neither RNS nor ROS are essential for the elimination of blood stage malaria parasites<sup>14</sup>. It was also shown in other studies that on occasion the generation of ROS via NADPH oxidase does kill blood stage malaria parasites, which is a controversial finding. A possible explanation of the discrepancies between Brad et al. and those of Sanni et al. is that these *Plasmodium* parasites differ in their susceptibility to the action of ROS, with *P. yoelii* and *P. chabaudi* being more resistant than *P. berghei*. ROS might be incapable of killing blood stage malarial parasites for several reasons:

(i) The in vivo ability to kill malaria parasites may be masked by the antibody response of the infected host, and (ii) the killing mechanisms mediated by these molecules may function in a redundant fashion<sup>15</sup>. The present data does not confer the association of the wild type gene and pseudogene with the severity of malaria but there is a need for further study involving a larger population. However within a group of children with severe malaria during the acute disease, a weak association of the wild type gene /pseudogene ( $\Delta$ GT/GTGT) ratio with ROS production in whole blood was found. It has been suggested that the wild type gene/ pseudogene ( $\Delta$ GT/GTGT) ratio influences the expression levels of ROS<sup>16</sup>. However, no influence of the wild type gene /pseudogene ( $\Delta$ GT/GTGT) ratio on *Plasmodium falciparum* malarial infection was detected, although it was previously shown that ROS production plays a role in parasite clearance as well as in the pathology of the disease<sup>17, 9</sup>. As for parasitic diseases, in humans there has been only one study conducted so far which examined the putative genetic associations of the wild type gene and pseudogene ( $\Delta$ GT/GTGT) ratio with malaria<sup>18</sup>.

#### Competing Interests

None declared

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## REFERENCES

1. Volkman SK, Barry AE, Lyons EJ et al. Recent origin of *Plasmodium falciparum* from a single progenitor. *Science* 2001; 293:482–484.
  2. Singh B, Kim Sung L, Matusop A. A large focus of naturally acquired *Plasmodium knowlesi* infections in human beings. *Lancet* 200; 363 (9414): 1017–24.
  3. Fong YL, Cadigan FC, Coatney GR. A presumptive case of naturally occurring *Plasmodium knowlesi* malaria in man in Malaysia. *Trans. R. Soc. Trop. Med. Hyg* 1971; 65 (6): 839–40.
  4. Babior, B.M. NADPH oxidase: an update. *Blood* 1999; 93 (5): 1464–1476.
  5. Gorlach A, Lee P, Roesler J, et al. The p47-phox pseudogene carries the most common mutation causing p47-phox deficient chronic granulomatous disease. *J Clin Invest* 1997; 100(8):1907–1918.
  6. Francke U, Hsieh C-L, Foellmer B, et al. Genes for two autosomal recessive forms of chronic granulomatous disease assigned to 1q25 (NCF2) and 7q11.23 (NCF1). *Am J Hum Genet* 1990; 47:483–492
  7. Chanock SJ, Roesler J, Zhan S, et al. Genomic structure of the human p47-phox (NCF1) gene. *Blood Cells Mol Dis* 2000; 26:37– 46.
  8. Greve B, Lehman LG, Lell B, et al. High oxygen radical production is associated with fast parasite clearance in children with *Plasmodium falciparum* malaria. *J Infect Dis* 1999; 179:1584-1586.
  9. Greve B, Kremsner PG, Lell B, et al. Malarial anaemia in African children associated with high oxygen radical production. *Lancet* 2000; 355(3):40-41.
  10. Uhlemann AC, Szlezak NA, Vonthein R, et al. DNA phasing by TA dinucleotide microsatellite length determines in vitro and in vivo expression of the gp91phox subunit of NADPH oxidase and mediates protection against severe malaria. *J Infect Dis* 2004;189 (12):2227-2234.
  11. Clark RA, Malech HL, Gallin JI, et al. Genetic variants of chronic granulomatous disease: prevalence of deficiencies of two cytosolic components of the NADPH-oxidase system. *N Engl J Med* 1989; 321;160:647-52.
  12. Taylor-Robinson A. W, Phillips R. S, Severn A, et al. The role of TH1 and TH2 cells in a rodent malaria infection. *Science* 1993; 260:1931–1934.
  13. Mohan, K., and Stevenson M. M. Acquired immunity to asexual blood stages. In I. W. Sherman (ed.), *Malaria: parasite biology, pathogenesis, and protection*. American Society for Microbiology, Washington, D.C 1998; p. 467–493
  14. Brad M, Gillman, Batchelder J, et al. Suppression of *Plasmodium chabaudi* Parasitemia Is Independent of the Action of Reactive Oxygen Intermediates and/or Nitric Oxide 2004;72(11); p. 6359–6366
  15. Weidanz W. P, Kemp J. R, Batchelder J. M, et al. Plasticity of immune responses suppressing parasitemia during acute *Plasmodium chabaudi* malaria. *J. Immunol* 1999; 162:7383–7388.
  16. Heyworth PG, Cross AR, Curnutte JT. Chronic granulomatous disease. *Curr Opin Immunol* 2003; 15:578-584.
  17. Rosen GM, Pou S, Ramos CL, et al. Free radicals and phagocytic cells. *FASEB J* 1995; 9 (2):200-209.
  18. Bernhard G, Peter H, Reinhard V, et al. NCF1 gene and pseudogene pattern: association with parasitic infection and autoimmunity. *Malaria Journal* 2008; 251(7);1475-2875.
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## Response Predictors in ECT: A discussion about Seizure Threshold

Madhavan Seshadri and Nadeem Z Mazi-Kotwal

### Abstract

Electroconvulsive Therapy (ECT) has been in use since 1938 and remains one of the most important and controversial treatments. The National Institute of Clinical Excellence in UK specifically recommends considering ECT as an option in treatment of severe depression (when life threatening and a rapid response is needed or when other treatments have failed), moderate depression (not responding to multiple treatments), catatonia and a prolonged and severe manic episode. For ECT to have a therapeutic response, it is now recognised that a generalised tonic-clonic seizure is essential. The degree by which the stimulus intensity exceeds the seizure threshold is an important determinant of both therapeutic effectiveness and cognitive side effects. This article attempts to discuss the significance of estimating the seizure threshold and the practical ways of lowering it, to reduce the side effects during the course of the treatment.

**Keywords :** ECT, Electroconvulsive Therapy, Seizure Threshold

**Abbreviations:** ECT: Electroconvulsive Therapy

### Introduction

The use of convulsive therapy for psychiatric conditions evolved after its first use by Meduna using camphor in 1934, and by 1938, Cerletti and Bini had documented the use of electricity to induce convulsions and therapeutic benefit. The technique has been extensively modified by the addition of muscle relaxants and general anaesthesia. Electroconvulsive Therapy is now an important and effective treatment option for certain severe neuropsychiatric disorders.

Most developments and changes in the practice of ECT have been driven to reduce the adverse effects and not by the need to make it more efficacious. The aim is to induce a generalised tonic-clonic seizure with a sufficient dose to maximise efficacy but not too high to reduce cognitive side effects. The newer brief-pulse, constant-current, square-wave machines are more efficient in inducing seizure than the older sine-wave, constant-voltage machines.

Between January and March 2002, there were nearly 12800 ECT administrations in England to 2300 individuals<sup>1</sup>. The National Institute of Clinical Excellence currently recommends that ECT is only used to achieve rapid and short term improvement of severe symptoms after an adequate trial of other treatment options have proved inefficient and/or when the condition is life threatening as in people with severe depression, catatonia or prolonged/severe manic episode<sup>2</sup>. The newer guidelines on depression suggest that ECT be considered as a treatment option in moderate depression when it has failed to respond to multiple treatments<sup>15</sup>. It has been noted from the observation of the users' experiences that the cognitive

impairment often outweighed their perception of any benefit after ECT treatment.

It has been recognised that the induction of a generalised tonic-clonic seizure is necessary to achieve a therapeutic response and a number of studies demonstrate superiority of ECT over Sham ECT. It is also noted that administration of an electrical stimulus that fails to induce a seizure and immediate termination of a seizure after induction does not result in clinical improvement. Stimulus which just about produces a generalised tonic-clonic seizure may not ensure therapeutic potency, but the degree to which the stimulus intensity exceeds the Seizure Threshold is an important determinant of the therapeutic effectiveness. Unfortunately, this also corresponds to the cognitive side effects<sup>3</sup>.

### Seizure Threshold

Seizure Threshold is empirically defined as the minimal electrical dose that induces generalised tonic clonic seizure activity. Boylan et al found that greater than 40% of individuals had an initial seizure threshold of less than 50mC with unilateral electrode placement<sup>4</sup> and Scott and Dykes and Sakheim concluded that for bilateral ECT, this was around 7%<sup>5,9</sup>.

Standard fixed doses continue to be used in UK, and this can result in a dose which is several times the seizure threshold, contributing to acute and long term cognitive side effects without any additional benefits of clinical efficacy. It is also associated with a greater risk of missed or partial seizures that have no therapeutic effect.

There is a great deal of variability between seizure thresholds in different individuals. Many factors influence it and Box 1 summarises them. Seizure threshold is generally higher in older men than younger women. Electrolyte imbalances, particularly, hyponatremia and hypocalcaemia can lower the seizure threshold. It is important for the clinician to consider these before starting the course of ECT.

**Box 1: Factors influencing Seizure Threshold**

Individual characteristics

Increases with age

Higher in men

Increases with increase in skull density

Higher for bilateral electrode placement

Electrolyte imbalances

Seizure Threshold increases during course of ECT

Medication increasing Seizure Threshold

Anticonvulsants, Benzodiazepines, Hypnotics, Anti-arrhythmics

Medication decreasing Seizure Threshold

Antidepressants, Antipsychotic, Lithium, Theophylline

Anaesthetic Induction agent

Increased: Propofol & Barbiturates

Decreased/minimal effect: Methohexital, Etomidate, Ketamine

Machine characteristics

Brief-pulse, constant-current, square-wave output better

Initiation of a course of Electroconvulsive Therapy treatment should routinely involve the estimation of the seizure threshold by gradual dose titration (Stimulus dosing) and then treatment by using the supra threshold doses. Once seizure threshold is determined a dose of 1.5 to 2 times the seizure threshold for bilateral ECT and at least 2.5 to 3 times the seizure threshold for unilateral ECT may provide the best balance of clinical efficacy and cognitive side effects<sup>3</sup>. This is supposed to be a better practice compared to the fixed dose method used to initiate the ECT treatment.<sup>6</sup>

**Missed Seizure**

An adequate electrical dose will manifest as generalised tonic, followed by clonic activity of skeletal muscle, accompanied by a typical seizure pattern on EEG. The absence of both is deemed a missed seizure<sup>7</sup>. Pippard's audit of ECT practice showed that in nearly 22% of ECT treatments, there was either no seizure or a brief seizure.

**Box 2: Causes for Missed Seizure**

Low stimulus intensity

Excess impedance

Premature stimulus termination

Excess Anaesthetic Agent

Increase of seizure threshold by ECT

Other factors increasing seizure threshold

The causes of Missed Seizures are summarised in Box 2. Missed seizures may be due to faulty technique leading to insufficient stimulus intensity, excess impedance or premature stimulus termination. Individual patient factors such as electrolyte imbalances, particularly dehydration and hypercarbia can lead to missed seizures. A common reason for raised seizure threshold is the administration of high dose of anaesthetic

induction agent<sup>5</sup>. Propofol, the most commonly used agent for ECT increases seizure threshold and also decreases the seizure duration. Use of alternatives like Methohexital, Etomidate or Ketamine may be successful as they either have minimal or no effect on seizure threshold and may increase the seizure duration.

During the course of treatment seizure threshold usually rises and this may lead to missed seizures. In addition to delaying the improvement, missed seizures cause more irritability and restlessness<sup>10</sup>. By measuring the seizure duration during the course of ECT missed seizure could be anticipated and appropriate steps can be taken. Some of the effects of a missed seizure are listed in Box 3.

**Box 3: Consequences of Missed Seizure**

Anxiety

Headache

Confusion

Lethargy

Tiredness

A missed seizure should prompt monitoring and correction of electrolyte imbalance if any. Seizure activity during the ECT procedure is affected by medication as well. Administration of seizure threshold increasing drugs should be reviewed and where possible stopped or reduced. If the treatment is for depression, consider using tricyclic drugs which lower the seizure threshold and augment ECT.

The maximum dose deliverable by the ECT machines is restricted in some countries and this may be inadequate due to very high seizure threshold in a few individuals. The US Food and Drug Administration restrict the maximum output of ECT machines to 576 millicoulombs compared to the Royal College of Psychiatrists which has recommended a maximum output charge of 1200 millicoulombs<sup>8</sup>. While higher electric doses may be able to induce generalised seizure activity, the cognitive side effects are also increased<sup>11</sup>. Therefore attempts must be made to decrease the seizure threshold to minimise these side effects.

**Seizure Threshold Lowering Techniques**

The aim of ECT treatment is to induce a generalised seizure activity; failure to do so makes the treatment session ineffective and of no therapeutic benefit. If a patient does not have generalised tonic-clonic seizure after a stimulus it is important to wait for at least 20 seconds after a non-seizure and at least 45 seconds after a partial/focal seizure prior to restimulating. Using appropriate techniques to avoid like low stimulus intensity, inappropriate application of electrodes, premature stimulus termination, etc are important<sup>6</sup>.

Charter and Simpson established the use of hyperventilation immediately before the application of the electrical stimulus and it has been shown to enhance seizure duration<sup>12</sup>. Sleep deprivation safely reduces the seizure threshold and also



increases the seizure duration<sup>13</sup>. Caffeine prolongs the seizure duration, but has no effect on the seizure threshold<sup>14</sup>.

### Conclusions

ECT remains the most maligned and misunderstood of psychiatric treatments. Whilst it has no doubt, successfully saved many lives and provided relief from the abyss of depression, proving its efficacy, the thrust of recent developments have been towards minimising the side effects. Adequate training and supervision of trainee psychiatrists will be essential to raise the standards of ECT administration techniques and skills.

Being aware of the significance of seizure threshold and ways to lower it, as an alternative to electric dose increase may address to some extent, the concerns about cognitive difficulties.

#### Competing Interests

None declared

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### REFERENCES

1. England. Department of Health. Electro Convulsive Therapy: Survey covering the period from January 2002 to March 2002, p1: 2003
2. Guidance on the use of Electroconvulsive therapy (ECT): National Institute for Health and Clinical Excellence; 2003 Apr. p5: Technology appraisal 59.
3. Sackeim H A., Prudic J., et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of ECT. *NEJM*. 1993; 328: 839-846.
4. Boylan L S, Haskett R F, et al. Determinants of seizure threshold in ECT, benzodiazepine use, anaesthetic dosage, and other factors. *Journal of ECT*. 2000;16:3-18.
5. Sackeim H A, Devanand D P, Prudic J. Stimulus intensity, seizure threshold and seizure duration: impact on the efficacy and safety of ECT. *Psychiatric Clinics of North America*, 1991;14: 803-843.
6. Scott A I F Editor, *The ECT Handbook*, second edition; The third Report of the Royal College of Psychiatrists' Special Committee on ECT. CR128, 2004.
7. Pippard J. Audit of electroconvulsive treatment in two National Health Service regions. *British Journal of Psychiatry*. 1992;160: 621-637.
8. Lisanby Sarah H.; Devanand D P ; Nobler Mitchell S.; Prudic Joan; Mullen Linda; Sackeim Harold A. Exceptionally High Seizure threshold: ECT device limitations. *Convulsive Therapy*, 1996; 12, 156-164.
9. Scott A I F & Dykes S. Initial seizure threshold in the clinical practice of bilateral electroconvulsive therapy in Edinburgh, Scotland. *Journal of ECT*, 1999; 15: 118-124
10. Scott A I F & Boddy H. The effect of repeated bilateral electroconvulsive therapy on seizure threshold. *Journal of ECT*. 2000;16: 244-251.
11. Weiner R D, Rogers H J, Davidson J R, et al (1986) Effects of stimulus parameters on cognitive side effects. *Annals of the New York Academy of Sciences*. 1986: 462, 315-325.
12. Chater S N, & Simpson K H., Effect of passive hyperventilation on seizure duration in patients undergoing ECT. *British Journal of Anaesthesia*. 1988: 60: 70-73.
13. Gilabert E; Rojo E, Vallejo J. Augmentation of Electroconvulsive Therapy Seizures with Sleep Deprivation. *Journal of ECT*. 2004; 20: 242-247
14. McCall W V, Reid S, Rosenquist P, Kiesow-Webb N. A reappraisal of the role of caffeine in ECT. *American Journal of Psychiatry*. 1993; 150: 1543-1545.
15. Depression: The Management and Treatment of Depression in Adults: National Institute of Clinical Excellence, Clinical Guideline 90 (CG90), May 2010

## Oesophageal dysfunction and disease in obesity

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### Abstract

Patients with morbid obesity suffer a wide range of symptoms that relate to their oesophagus and stomach. It is rather paradoxical that patients who are overweight suffer the symptoms of difficulty in swallowing, pain during eating or pain after eating, because the symptoms of difficulty eating do not translate into weight reduction. There are a range of underlying causes that include gastro-oesophageal reflux disease, dysmotility in the oesophagus, peptic ulceration and the nature and pattern of dietary intake. In addition the surgical treatments used for morbid obesity cause similar symptoms from gastric bands leading to dysphagia or reflux from being too tight or from erosion into the stomach, from balloons being displaced and bypass complications. Serious oesophageal conditions occur more frequently in patients with obesity such as Barrett's oesophagus and Adenocarcinoma of the oesophagus. This article reviews the literature to highlight the range of potential problems from oesophageal symptoms and disease and how they can be managed in the context of morbid obesity.

### Keywords

Obesity, Reflux, GORD, Bariatric, Balloon, Gastric band, Gastric Bypass, Dysphagia, Sleeve gastrectomy, Vertical gastric banding

### Introduction

Patients with morbid obesity suffer a wide range of symptoms that relate to their oesophagus and stomach. It is rather paradoxical that patients who are overweight suffer the symptoms of difficulty in swallowing, pain during eating or pain after eating because the symptoms of eating difficulty do not translate into weight reduction. There are a range of underlying causes that include gastro-oesophageal reflux disease, dysmotility in the oesophagus, peptic ulceration and the nature and pattern of dietary intake. The pathophysiology of gastro-oesophageal reflux disease and of dysphagia will be considered. The detrimental effects of the treatments of balloons, gastric bands and gastric bypass will be described and options for management discussed. The serious complications of adenocarcinoma and its premalignant precursor, Barrett's oesophagus will be reviewed.

### Gastro-oesophageal reflux disease (GORD)

GORD is highly prevalent in obese people with increasing BMI a risk factor for developing the disease. The relation between GORD and obesity has been studied for decades and there have been conflicting results. A person with BMI of  $\geq 30$  kg/m<sup>2</sup> is 3 times more likely to suffer from heartburn and acid regurgitation<sup>1</sup>.

Though the mechanism of this is poorly understood, a number of epidemiological studies have proven this association. Since recently, more evidence has emerged in favour of a positive association<sup>2</sup>. In 2000, Lagergren et al, based on a population based interview study on 820 Swedish, concluded that GOR symptoms occurred independent of BMI<sup>3</sup>. His claim was

supported by two previous studies, one of which used oesophageal pH measure and other assessed the impact of weight loss on symptom relief<sup>4,5</sup>. A contrary view has emerged since this, with large number of western studies showing a positive association<sup>1,2,6-12</sup>. This, however, has not been the case with Asian and Afro-Caribbean population. In a large population study with various ethnicities, a strongly positive association was found between BMI and GOR symptoms in white population. This was not the case in Asian and black population<sup>13</sup>, a view re-iterated by another study from Iran<sup>14</sup>. The overall incidence of GORD is high in western world between 10% and 20%, compared to 5% in Asia<sup>6</sup>.

The mechanism of GORD in obesity is very poorly understood. Various theories have been postulated and the evidence for each is discussed below, including the theory that the pathophysiology of reflux in the morbidly obesity could differ from others and might require a different therapeutic approach<sup>9</sup>

### Increased intra-abdominal pressure as a cause of reflux

Increasing intra-abdominal pressure has been hypothesised to be the cause for reflux symptoms. Increasing BMI has been shown to increase intra-gastric pressure and pressure study in a prospective cohort has shown 10% increase in intra-gastric pressure with rise in each unit of BMI<sup>15</sup>. A pH and manometry study in general population with GORD showed a higher pressure gradients across the Oesophago-gastric junction than that in controls both before and during transient lower oesophageal sphincter relaxation. This phenomenon is thought to be caused by increased intra-gastric pressure, supporting the above theory<sup>16</sup>.

### Lower oesophageal sphincter dysfunction as a cause

Kuper et al showed a dysfunction of LOS and altered oesophageal motility even in asymptomatic patients with morbid obesity using pH and manometry study (BMI >40 kg/m<sup>2</sup>)<sup>17</sup> and Wu et al showed an abnormal post-prandial LOS with prolonged transient lower oesophageal relaxation<sup>18</sup>. These findings were re-iterated by ayazi et al, showing obese patients to be more than twice as likely to have a mechanically defective LOS<sup>20</sup>. However, another study back in 1987 had shown a similar LOS pressure in normal weight and obese patients, though the gastro-oesophageal pressure gradient to LOS pressure ratio was high in obese<sup>21</sup>.

### Diet

The amount or composition of dietary intake and its relation to GORD has been studied. There is some evidence that volume, fat content and a high-caloric diet increases the oesophageal acid exposure time, giving rise to symptoms<sup>22-24</sup>. This would suggest an improvement of symptoms with reduction of these in the diet. More studies have shown an improvement in reflux symptoms with improved diet<sup>25-29</sup>. But, there is no convincing evidence to implicate the role of diet in reflux symptoms of obese patients.

### Hiatus hernia

The incidence of hiatus hernia is over 50% in morbid obesity<sup>30</sup>. Hiatus has been shown to be predicted by intra-gastric pressure, gastro-oesophageal pressure gradient and BMI. BMI has in turn been shown to predict the former two. This confirms a positive association between BMI and presence of hiatus hernia<sup>31</sup>. High BMI is more likely to have oesophago-gastric junction disruption, leading to hiatal hernia and an augmented gastro-oesophageal pressure gradient, providing a perfect scenario for reflux to occur<sup>32</sup>. The incidence of defective LES was twice as much in obese patients with hiatus hernia, compared to obese without it<sup>20</sup>. Hiatus hernia thus plays a role in the obese patients and the subsequent development of GORD<sup>33</sup>.

### Poor mobility and mental state

There is no evidence to support the theory of reflux symptoms secondary to poor mobility and depression in the morbidly obese patients.

### Treatment of GORD in obesity

#### Medical therapy

Medical therapy with a PPI remains the first line of treatment of GORD symptoms in obesity as in patients with a normal BMI. No guidelines are available for dose adjustments in the obese patients<sup>34</sup>. They continue to receive the standard therapy, adjusted to the severity of disease and symptoms.

#### Endoluminal therapy

Endoluminal therapy was introduced recently as treatment alternative for GORD and has shown promising results. This looked a safe option for use in obese patients. However, published results have shown high rate of post-operative PPI requirement in the obese patients<sup>35</sup>. Further evidence has to emerge before this option can be recommended for use in the obese patients.

#### Balloon

Intra-gastric balloon therapy has been an established temporary procedure for weight loss. GORD symptoms in obese tends to improve with weight loss, but as studies have shown, a balloon insertion tended to worsen symptoms<sup>36,37</sup>. Balloon is hence not considered an option for treatment of obesity with patients with reflux symptoms.

#### Gastric band

Gastric banding provides a sufficient anti-reflux barrier in most of the obese patients with GORD. Abnormal manometric findings like increased LES (lower oesophageal sphincter) residual pressure and peristaltic wave duration are frequently encountered after banding. The clinical significances of these manometric abnormalities are not clear<sup>38</sup>. The oesophageal stasis caused by the band could explain the reflux in patients during longer follow up. Though, the reflux from the distal stomach is prevented by the gastric band, formation of a proximal pouch predisposes to stasis and reflux. This is more common in patients with preoperatively defective oesophageal motility. The studies suggesting a good GORD symptom control following banding had shorter follow up, explaining the results<sup>39,40</sup>. Hence it could be concluded that gastric banding may aggravate GORD symptoms and cause oesophageal dilatation, especially in patients with pre-operative motility defects. Routine pre-operative testing should be done and alternative bariatric surgical procedures such as Roux-en-Y gastric bypass considered in these patients<sup>41-43</sup>.

#### Sleeve Gastrectomy (Vertical gastric banding)

Gastrectomy reduces weight, but not gastro-oesophageal acid reflux. Although this procedure has been shown to have anti-reflux properties<sup>44</sup>, it has fallen to disrepute in terms of relieving the reflux symptoms, especially with the superior results of RYGB<sup>45-48</sup>. A number of these cases requiring revision, due to reflux symptoms, have been reported<sup>49-51</sup>.

#### Gastric Bypass Vs Anti-reflux surgery

Though laparoscopic fundoplication is the standard operation for GORD, gastric bypass has been shown to improve the reflux symptoms in the morbidly obese, apart from reducing their weight and obesity related co-morbid conditions such as diabetes mellitus, hypertension etc. Patterson et al. showed an equivalent symptomatic improvement and objective DeMeester score improvement with Laparoscopic Nissen fundoplication

and laparoscopic gastric bypass. The LES (lower oesophageal sphincter) pressure was also noted to improve, following bypass<sup>52</sup>. This was in light of an earlier report of 31% recurrence rate of reflux symptoms following laparoscopic Nissen's in obese patients<sup>53</sup>. Hence, morbidly obese patients with GORD should be offered laparoscopic gastric bypass as a surgical option<sup>27, 30, 54-59</sup>.

The improvement in GORD symptoms after gastric bypass is related to the way that the operation staples off the distal 90% or more of the stomach body and antrum, removing any possibility that acid generated in this part of the stomach can reach the oesophagus. The parietal cell mass within the small gastric pouch that is left attached to the oesophagus, the complete elimination of duodeno-gastric reflux owing to a long Roux limb, and decrease in intra-abdominal pressure with weight loss all contribute to an almost total reflux control in all patients. The overall complications secondary to this procedure were lower than in laparoscopic fundoplication<sup>54</sup>. It is also the procedure of choice for previous other weight-loss surgery, when reflux symptoms develop<sup>49-51</sup>. Thus, a bariatric team prior to surgical intervention should review obese patients with GORD symptoms.

#### Dysphagia in obesity

Dysphagia in obesity is often related to the interventions used to treat obesity, though it can be primary in nature.

Various modalities of interventions available in obesity have been discussed above. Intra-gastric balloon therapy can be complicated by its displacement into the distal stomach, precipitating dysphagia and outlet obstruction. Gastric bands can be overfilled, causing this problem, and a slipped band or a band eroding through the stomach wall can also lead to dysphagia<sup>60-64</sup>. There has been no report of gastric bypass resulting in dysphagia, in the literature.

It is our understanding that patients with obesity may present with primary oesophageal dysmotility. Although there is little published literature on this issue, it is our hypothesis that fatty infiltration of the oesophageal wall and myenteric plexus may result in a poor amplitude peristaltic contraction.

#### Other oesophageal conditions associated with obesity

##### Barrett's Oesophagus

This is characterised by the replacement of the normal squamous epithelium of the lower oesophagus by a specialised metaplastic columnar epithelium. Barrett's oesophagus is a known risk factor for oesophageal adenocarcinoma, with a 30 to 125 times increased risk compared to general population<sup>65</sup>. Risk factors leading to Barrett's have been poorly understood, though GORD is widely believed to be the main risk factor<sup>66-68</sup>. Since several studies have found an association between obesity and GORD<sup>1, 2, 6-12</sup>, and obesity as a risk factor for

Barrett's have gained momentum in the recent year. Abdominal obesity or waist circumference has been shown to be more associated with Barrett's than BMI<sup>69</sup>.

A recent systematic review showed a statistically significant relation between increasing BMI and Barrett's<sup>70</sup>. However, two older systematic reviews had found a rather weak relation between these two, showing a need for further well designed studies<sup>71,72</sup>. To mention a few studies, Jacobson et al showed a positive relation between BMI and Barrett's in women, independent of GORD, though the waist circumference was not found to have any association<sup>73</sup> and Stein et al., found a positive relation between BMI and Barrett's in war veterans<sup>74</sup>. Abdominal obesity or circumference appears to be more influential in the incidence of Barrett's oesophagus in another study<sup>75</sup>. There is however, little evidence to suggest an increased progression of Barrett's to neoplasia in obesity<sup>69</sup>.

Obesity is a modifiable risk factor and if proven to be a risk for Barrett's and subsequent neoplasia, resources can be directed at modifying this, as there is evidence to suggest the regression Barrett's with weight loss<sup>69</sup>. Barrett's have been shown to regress with weight loss following gastric bypass and hence this has been recommended as bariatric procedure of choice in the morbidly obese with Barrett's<sup>76-79</sup>. A precise endoscopic evaluation before bariatric surgery with continuing postsurgical surveillance in patients with known Barrett's oesophagitis, and early evaluation in patients who develop new symptoms of GERD after bariatric surgery is suggested<sup>80, 81</sup>.

##### Adenocarcinoma of oesophagus

The incidence of oesophageal adenocarcinoma has increased about 400% during the past three decades, the most rapid rate of increase of any cancer in the United States<sup>82-84</sup>. The association between high BMI and oesophageal adenocarcinoma is strong and well established, though the mechanism of this is still unclear. The risk is higher with increasing BMI, especially in men<sup>85-94</sup>. Obesity has also been shown to play a role in adenocarcinomas with a family history<sup>95</sup>. The incidence of adenocarcinoma of the cardia of stomach has not been so strongly related to BMI<sup>96, 97</sup>. Squamous cell carcinoma of oesophagus has not shown any association to obesity either<sup>85, 93, 94, 98, 99</sup>. Few studies have negated the association of obesity with oesophageal adenocarcinoma, but many were due to the fact that they included oesophageal and proximal stomach together<sup>96</sup>. The majority of these cancers arise from a background of premalignant Barrett's oesophagus, though less than 10% of the patients with oesophageal adenocarcinoma were known to have Barrett's oesophagus previously. Presently there is no evidence that strongly supports any specific strategy to screen a subgroup of the population at risk for Barrett's oesophagus and adenocarcinoma of the oesophagus<sup>100</sup>.

A number of studies have also looked at the mechanism or pathway of this metaplasia-dysplasia-adenocarcinoma sequence. Visceral adiposity rather than BMI is thought to have a greater role in chronic inflammation and subsequent neoplasia. It has a clear association with Barrett's as above. Increasing abdominal girth increases the risk of adenocarcinoma and it has been shown for Barrett's<sup>98</sup>. Visceral fat is hypothesised as a major producer of interleukin-6, adiponectin, leptin and other adipokines that may be associated with the development of various gastro-intestinal cancers<sup>101-103</sup>. More specifically, insulin-like growth factor has been implicated in the pathogenesis of adenocarcinoma in the obese<sup>104</sup>. Oesophago-gastric tumours after bariatric surgery, has been reported, though rare. This condition, when occurs, requires the close collaboration of the bariatric team to achieve a successful oncological result, due to the altered anatomy like the blood supply to the gastric pouch and excluded stomach<sup>105</sup>.

### Conclusion

Obesity is associated with oesophageal disease, benign and malignant, and both the effects of obesity and the effects of its treatment can aggravate oesophageal symptoms. The management of reflux and of dysphagia in obese patients requires a broad understanding of these issues.

#### Competing Interests

None declared

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### REFERENCES

- Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, et al. Relationship between body mass and gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. *Int J Epidemiol* 2003;32(4):645-50.
- Fischella PM, Patti MG. Gastroesophageal reflux disease and morbid obesity: is there a relation? *World J Surg* 2009;33(10):2034-8.
- Lagergren J, Bergstrom R, Nyren O. No relation between body mass and gastro-oesophageal reflux symptoms in a Swedish population based study. *Gut* 2000;47(1):26-9.
- Kjellin A, Ramel S, Rossner S, Thor K. Gastroesophageal reflux in obese patients is not reduced by weight reduction. *Scand J Gastroenterol* 1996;31(11):1047-51.
- Lundell L, Ruth M, Sandberg N, Bove-Nielsen M. Does massive obesity promote abnormal gastroesophageal reflux? *Dig Dis Sci* 1995;40(8):1632-5.
- Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54(5):710-7.
- Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA, Jr. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006;354(22):2340-8.
- Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, Stolte M, Lind T, et al. Association of body mass index with heartburn, regurgitation and esophagitis: results of the Progression of Gastroesophageal Reflux Disease study. *J Gastroenterol Hepatol* 2007;22(11):1728-31.
- Herbella FA, Sweet MP, Tedesco P, Nipomnick I, Patti MG. Gastroesophageal reflux disease and obesity. Pathophysiology and implications for treatment. *J Gastrointest Surg* 2007;11(3):286-90.

- El-Serag H. The association between obesity and GERD: a review of the epidemiological evidence. *Dig Dis Sci* 2008;53(9):2307-12.
- Breckan RK, Paulssen EJ, Asfeldt AM, Mortensen L, Straume B, Florholmen J. The impact of body mass index and Helicobacter pylori infection on gastro-oesophageal reflux symptoms: a population-based study in Northern Norway. *Scand J Gastroenterol* 2009;44(9):1060-6.
- Schneider JM, Brucher BL, Kuper M, Saemann K, Konigsrainer A, Schneider JH. Multichannel intraluminal impedance measurement of gastroesophageal reflux in patients with different stages of morbid obesity. *Obes Surg* 2009;19(11):1522-9.
- Corley DA, Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut* 2007;56(6):756-62.
- Solhpour A, Pourhoseingholi MA, Soltani F, Zarghi A, Habibi M, Ghafarnejad F, et al. Gastro-oesophageal reflux symptoms and body mass index: no relation among the Iranian population. *Indian J Gastroenterol* 2008;27(4):153-5.
- El-Serag HB, Tran T, Richardson P, Ergun G. Anthropometric correlates of intragastric pressure. *Scand J Gastroenterol* 2006;41(8):887-91.
- Frankhuisen R, Van Herwaarden MA, Scheffer R, Hebbard GS, Goosens HG, Samsom M. Increased intragastric pressure gradients are involved in the occurrence of acid reflux in gastroesophageal reflux disease. *Scand J Gastroenterol* 2009;44(5):545-50.
- Kuper MA, Kramer KM, Kischniak A, Zdichavsky M, Schneider JH, Stuker D, et al. Dysfunction of the lower esophageal sphincter and dysmotility of the tubular esophagus in morbidly obese patients. *Obes Surg* 2009;19(8):1143-9.
- Wu JC, Mui LM, Cheung CM, Chan Y, Sung JJ. Obesity is associated with increased transient lower esophageal sphincter relaxation. *Gastroenterology* 2007;132(3):883-9.
- Schneider JH, Kuper M, Konigsrainer A, Brucher B. Transient lower esophageal sphincter relaxation in morbid obesity. *Obes Surg* 2009;19(5):595-600.
- Ayazi S, Hagen JA, Chan LS, DeMeester SR, Lin MW, Ayazi A, et al. Obesity and gastroesophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. *J Gastrointest Surg* 2009;13(8):1440-7.
- Mercer CD, Wren SF, DaCosta LR, Beck IT. Lower esophageal sphincter pressure and gastroesophageal pressure gradients in excessively obese patients. *J Med* 1987;18(3-4):135-46.
- Colombo P, Mangano M, Bianchi PA, Penagini R. Effect of calories and fat on postprandial gastro-oesophageal reflux. *Scand J Gastroenterol* 2002;37(1):3-5.
- Fox M, Barr C, Nolan S, Lomer M, Anggiansah A, Wong T. The effects of dietary fat and calorie density on esophageal acid exposure and reflux symptoms. *Clin Gastroenterol Hepatol* 2007;5(4):439-44.
- Iwakiri K, Kobayashi M, Kotoyori M, Yamada H, Sugiura T, Nakagawa Y. Relationship between postprandial esophageal acid exposure and meal volume and fat content. *Dig Dis Sci* 1996;41(5):926-30.
- El-Serag HB, Graham DY, Satia JA, Rabeneck L. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. *Am J Gastroenterol* 2005;100(6):1243-50.
- Austin GL, Thiny MT, Westman EC, Yancy WS, Jr., Shaheen NJ. A very low-carbohydrate diet improves gastroesophageal reflux and its symptoms. *Dig Dis Sci* 2006;51(8):1307-12.
- De Groot NL, Burgerhart JS, Van De Meeberg PC, de Vries DR, Smout AJ, Siersema PD. Systematic review: the effects of conservative and surgical treatment for obesity on gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2009;30(11-12):1091-102.
- Fass R. The pathophysiological mechanisms of GERD in the obese patient. *Dig Dis Sci* 2008;53(9):2300-6.
- Weiss H, Labeck B, Klocker J, Nehoda H, Mittermair R, Aigner F, et al. Effects of adjustable gastric banding on altered gut neuropeptide levels in morbidly obese patients. *Obes Surg* 2001;11(6):735-9.
- Suter M, Dorta G, Giusti V, Calmes JM. Gastro-oesophageal reflux and esophageal motility disorders in morbidly obese patients. *Obes Surg* 2004;14(7):959-66.
- de Vries DR, van Herwaarden MA, Smout AJ, Samsom M. Gastroesophageal pressure gradients in gastroesophageal reflux disease: relations with hiatal hernia, body mass index, and esophageal acid exposure. *Am J Gastroenterol* 2008;103(6):1349-54.
- Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ. Obesity: a challenge to esophago-gastric junction integrity. *Gastroenterology* 2006;130(3):639-49.

33. Stene-Larsen G, Weberg R, Froyshov Larsen I, Bjortuft O, Hoel B, Berstad A. Relationship of overweight to hiatus hernia and reflux oesophagitis. *Scand J Gastroenterol* 1988;23(4):427-32.
34. Anand G, Katz PO. Gastroesophageal reflux disease and obesity. *Rev Gastroenterol Disord* 2008;8(4):233-9.
35. White B, Jeansonne LO, Cook M, Chavarriaga LF, Goldenberg EA, Davis SS, et al. Use of endoluminal antireflux therapies for obese patients with GERD. *Obes Surg* 2009;19(6):783-7.
36. Mathus-Vliegen EM, van Weeren M, van Eerten PV. Los function and obesity: the impact of untreated obesity, weight loss, and chronic gastric balloon distension. *Digestion* 2003;68(2-3):161-8.
37. Rossi A, Bersani G, Ricci G, Petrini C, DeFabritiis G, Alvisi V. Intra-gastric balloon insertion increases the frequency of erosive esophagitis in obese patients. *Obes Surg* 2007;17(10):1346-9.
38. Gamagaris Z, Patterson C, Schaye V, Francois F, Traube M, Fielding CJ, et al. Lap-band impact on the function of the esophagus. *Obes Surg* 2008;18(10):1268-72.
39. Korenkov M, Kohler L, Yucel N, Grass G, Sauerland S, Lempa M, et al. Esophageal motility and reflux symptoms before and after bariatric surgery. *Obes Surg* 2002;12(1):72-6.
40. Ovrebo KK, Hatlebakk JG, Viste A, Bassoe HH, Svanes K. Gastroesophageal reflux in morbidly obese patients treated with gastric banding or vertical banded gastroplasty. *Ann Surg* 1998;228(1):51-8.
41. Tolonen P, Victorzon M, Niemi R, Makela J. Does gastric banding for morbid obesity reduce or increase gastroesophageal reflux? *Obes Surg* 2006;16(11):1469-74.
42. Klaus A, Gruber I, Wetscher G, Nehoda H, Aigner F, Peer R, et al. Prevalent esophageal body motility disorders underlie aggravation of GERD symptoms in morbidly obese patients following adjustable gastric banding. *Arch Surg* 2006;141(3):247-51.
43. Suter M, Dorta G, Giusti V, Calmes JM. Gastric banding interferes with esophageal motility and gastroesophageal reflux. *Arch Surg* 2005;140(7):639-43.
44. Deitel M, Khanna RK, Hagen J, Ilves R. Vertical banded gastroplasty as an antireflux procedure. *Am J Surg* 1988;155(3):512-6.
45. Di Francesco V, Baggio E, Mastromauro M, Zoico E, Stefanelli N, Zamboni M, et al. Obesity and gastro-esophageal acid reflux: physiopathological mechanisms and role of gastric bariatric surgery. *Obes Surg* 2004;14(8):1095-102.
46. Naslund E, Granstrom L, Melcher A, Stockeld D, Backman L. Gastro-oesophageal reflux before and after vertical banded gastroplasty in the treatment of obesity. *Eur J Surg* 1996;162(4):303-6.
47. Ortega J, Escudero MD, Mora F, Sala C, Flor B, Martinez-Valls J, et al. Outcome of esophageal function and 24-hour esophageal pH monitoring after vertical banded gastroplasty and Roux-en-Y gastric bypass. *Obes Surg* 2004;14(8):1086-94.
48. Braghetto I, Lanzarini E, Korn O, Valladares H, Molina JC, Henriquez A. Manometric changes of the lower esophageal sphincter after sleeve gastrectomy in obese patients. *Obes Surg*;20(3):357-62.
49. Balsiger BM, Murr MM, Mai J, Sarr MG. Gastroesophageal reflux after intact vertical banded gastroplasty: correction by conversion to Roux-en-Y gastric bypass. *J Gastrointest Surg* 2000;4(3):276-81.
50. Sugerman HJ, Kellum JM, Jr., DeMaria EJ, Reines HD. Conversion of failed or complicated vertical banded gastroplasty to gastric bypass in morbid obesity. *Am J Surg* 1996;171(2):263-9.
51. Iannelli A, Addeo P, Dahman M, Buratti MS, Ben Amor I, Piche T, et al. Laparoscopic conversion of vertical banded gastroplasty with an antireflux wrap into Roux-en-Y gastric bypass. *Obes Surg* 2007;17(7):901-4.
52. Patterson EJ, Davis DG, Khajanchee Y, Swanstrom LL. Comparison of objective outcomes following laparoscopic Nissen fundoplication versus laparoscopic gastric bypass in the morbidly obese with heartburn. *Surg Endosc* 2003;17(10):1561-5.
53. Perez AR, Moncure AC, Rattner DW. Obesity adversely affects the outcome of antireflux operations. *Surg Endosc* 2001;15(9):986-9.
54. Varela JE, Hinojosa MW, Nguyen NT. Laparoscopic fundoplication compared with laparoscopic gastric bypass in morbidly obese patients with gastroesophageal reflux disease. *Surg Obes Relat Dis* 2009;5(2):139-43.
55. Mejia-Rivas MA, Herrera-Lopez A, Hernandez-Calleros J, Herrera MF, Valdovinos MA. Gastroesophageal reflux disease in morbid obesity: the effect of Roux-en-Y gastric bypass. *Obes Surg* 2008;18(10):1217-24.
56. Tai CM, Lee YC, Wu MS, Chang CY, Lee CT, Huang CK, et al. The effect of Roux-en-Y gastric bypass on gastroesophageal reflux disease in morbidly obese Chinese patients. *Obes Surg* 2009;19(5):565-70.
57. Merrouche M, Sabate JM, Jouet P, Harnois F, Scaringi S, Coffin B, et al. Gastro-esophageal reflux and esophageal motility disorders in morbidly obese patients before and after bariatric surgery. *Obes Surg* 2007;17(7):894-900.
58. Clements RH, Gonzalez QH, Foster A, Richards WO, McDowell J, Bondora A, et al. Gastrointestinal symptoms are more intense in morbidly obese patients and are improved with laparoscopic Roux-en-Y gastric bypass. *Obes Surg* 2003;13(4):610-4.
59. Frezza EE, Ikramuddin S, Gourash W, Rakitt T, Kingston A, Luketich J, et al. Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. *Surg Endosc* 2002;16(7):1027-31.
60. Bernante P, Francini Pesenti F, Toniato A, Zangrandi F, Pomerri F, Pelizzo MR. Obstructive symptoms associated with the 9.75-cm Lap-Band in the first 24 hours using the pars flaccida approach. *Obes Surg* 2005;15(3):357-60.
61. Lucchese M, Alessio F, Valeri A, Cantelli G, Venneri F, Borrelli D. Adjustable silicone gastric banding: complications in a personal series. *Obes Surg* 1998;8(2):207-9.
62. Patel SM, Shapiro K, Abdo Z, Ferzli GS. Obstructive symptoms associated with the Lap-Band in the first 24 hours. *Surg Endosc* 2004;18(1):51-5.
63. Pinski I, Dukhno O, Levy I, Ovnat A. Gastric outlet obstruction caused by total band erosion. *Obes Surg* 2004;14(9):1277-9.
64. Srikanth MS, Oh KH, Keskey T, Rumbaut R, Fox SR, Fox ER, et al. Critical extreme anterior slippage (paragastric Richter's hernia) of the stomach after laparoscopic adjustable gastric banding: early recognition and prevention of gastric strangulation. *Obes Surg* 2005;15(2):207-15; discussion 215.
65. Wild CP, Hardie LJ. Reflux, Barrett's oesophagus and adenocarcinoma: burning questions. *Nat Rev Cancer* 2003;3(9):676-84.
66. Cameron AJ. Epidemiology of Barrett's esophagus and adenocarcinoma. *Dis Esophagus* 2002;15(2):106-8.
67. Conio M, Filiberti R, Bianchi S, Ferraris R, Marchi S, Ravelli P, et al. Risk factors for Barrett's esophagus: a case-control study. *Int J Cancer* 2002;97(2):225-9.
68. Eloubeidi MA, Provenzale D. Clinical and demographic predictors of Barrett's esophagus among patients with gastroesophageal reflux disease: a multivariable analysis in veterans. *J Clin Gastroenterol* 2001;33(4):306-9.
69. Murray L, Romero Y. Role of obesity in Barrett's esophagus and cancer. *Surg Oncol Clin N Am* 2009;18(3):439-52.
70. Kamat P, Wen S, Morris J, Anandasabapathy S. Exploring the association between elevated body mass index and Barrett's esophagus: a systematic review and meta-analysis. *Ann Thorac Surg* 2009;87(2):655-62.
71. Seidel D, Muangpaisan W, Hiro H, Mathew A, Lyrazopoulos G. The association between body mass index and Barrett's esophagus: a systematic review. *Dis Esophagus* 2009;22(7):564-70.
72. Cook MB, Greenwood DC, Hardie LJ, Wild CP, Forman D. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. *Am J Gastroenterol* 2008;103(2):292-300.
73. Jacobson BC, Chan AT, Giovannucci EL, Fuchs CS. Body mass index and Barrett's oesophagus in women. *Gut* 2009;58(11):1460-6.
74. Stein DJ, El-Serag HB, Kuczyński J, Kramer JR, Sampliner RE. The association of body mass index with Barrett's oesophagus. *Aliment Pharmacol Ther* 2005;22(10):1005-10.
75. Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. *Gastroenterology* 2007;133(2):403-11.
76. Csendes A, Burgos AM, Smok G, Burdiles P, Henriquez A. Effect of gastric bypass on Barrett's esophagus and intestinal metaplasia of the cardia in patients with morbid obesity. *J Gastrointest Surg* 2006;10(2):259-64.
77. Houghton SG, Romero Y, Sarr MG. Effect of Roux-en-Y gastric bypass in obese patients with Barrett's esophagus: attempts to eliminate duodenogastric reflux. *Surg Obes Relat Dis* 2008;4(1):1-4; discussion 4-5.
78. Cobey F, Oelschlager B. Complete regression of Barrett's esophagus after Roux-en-Y gastric bypass. *Obes Surg* 2005;15(5):710-2.
79. Chang CG, Perez E. Case reports--resolution of Barrett's disease and esophageal epithelial atypia after gastric bypass and LAP-BAND. *Obes Surg* 2009;19(11):1597-8.
80. Melstrom LG, Bentrem DJ, Salvino MJ, Blum MG, Talamonti MS, Pritanic KJ. Adenocarcinoma of the gastroesophageal junction after bariatric surgery. *Am J Surg* 2008;196(1):135-8.
81. Varela JE. Barrett's esophagus: a late complication of laparoscopic adjustable gastric banding. *Obes Surg*;20(2):244-6.
82. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF, Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991;265(10):1287-9.

83. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. *Semin Oncol* 1999;26(5 Suppl 15):2-8.
84. Kubo A, Corley DA. Marked regional variation in adenocarcinomas of the esophagus and the gastric cardia in the United States. *Cancer* 2002;95(10):2096-102.
85. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999;130(11):883-90.
86. Veugclers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. *Dis Esophagus* 2006;19(5):321-8.
87. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;143(3):199-211.
88. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* 2008;57(2):173-80.
89. Abnet CC, Freedman ND, Hollenbeck AR, Fraumeni JF, Jr., Leitzmann M, Schatzkin A. A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma. *Eur J Cancer* 2008;44(3):465-71.
90. Merry AH, Schouten LJ, Goldbohm RA, van den Brandt PA. Body mass index, height and risk of adenocarcinoma of the esophagus and gastric cardia: a prospective cohort study. *Gut* 2007;56(11):1503-11.
91. Brown LM, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, Greenberg RS, et al. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995;87(2):104-9.
92. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Control* 2005;16(3):285-94.
93. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1995;4(2):85-92.
94. Ryan AM, Rowley SP, Fitzgerald AP, Ravi N, Reynolds JV. Adenocarcinoma of the oesophagus and gastric cardia: male preponderance in association with obesity. *Eur J Cancer* 2006;42(8):1151-8.
95. Chak A, Falk G, Grady WM, Kinnard M, Elston R, Mittal S, et al. Assessment of familiarity, obesity, and other risk factors for early age of cancer diagnosis in adenocarcinomas of the esophagus and gastroesophageal junction. *Am J Gastroenterol* 2009;104(8):1913-21.
96. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;15(5):872-8.
97. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;340(11):825-31.
98. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev* 2008;17(2):352-8.
99. Chow WH, Blot WJ, Vaughan TL, Risch HA, Gammon MD, Stanford JL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;90(2):150-5.
100. Pera M, Manterola C, Vidal O, Grande L. Epidemiology of esophageal adenocarcinoma. *J Surg Oncol* 2005;92(3):151-9.
101. Abrams JA. Obesity and Barrett's oesophagus: more than just reflux. *Gut* 2009;58(11):1437-8.
102. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. *J Clin Endocrinol Metab* 2008;93(11 Suppl 1):S64-73.
103. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. *Arch Physiol Biochem* 2008;114(1):71-83.
104. MacDonald K, Porter GA, Guernsey DL, Zhao R, Casson AG. A polymorphic variant of the insulin-like growth factor type I receptor gene modifies risk of obesity for esophageal adenocarcinoma. *Cancer Epidemiol* 2009;33(1):37-40.
105. Kuruba R, Jawad M, Karl RC, Murr MM. Technique of resection of esophageal adenocarcinoma after Roux-en-Y gastric bypass and literature review of esophagogastric tumors after bariatric procedures. *Surg Obes Relat Dis* 2009;5(5):576-81.

## An unusual case of Lactic Acidosis

Muhammad Badar Ganaie and Rodney Hughes

**KEYWORDS:** Lactic Acidosis, Metabolic Acidosis, Severe Asthma, Salbutamol, Albuterol

### Introduction

Lactic acidosis is an important cause of metabolic acidosis in hospitalised patients. This usually occurs either due to over production or under utilisation of lactate<sup>1</sup>. Most cases of lactic acidosis are due to marked tissue hypoperfusion or hypoxia in systemic shock.

Asymptomatic lactic acidosis has been reported previously during acute severe asthma and attributed to fatiguing respiratory muscles, hypoxaemia and liver ischaemia. It has also been linked to  $\beta_2$  agonist therapy in asthma, although lactic acidosis causing increasing dyspnoea in the asthmatic patient has only been recorded rarely.

### Case presentation

We present a case of lactic acidosis in a patient with acute severe asthma who did not have any overt signs of sepsis or tissue hypoperfusion.

Mr IL was a 49 years old male who was known to have moderate asthma. He had multiple previous admissions to hospital with exacerbation of asthma but had never required an intensive care admission and had never been intubated. His other comorbidities included atrial fibrillation, ischaemic heart disease and depression.

His usual medications included salbutamol, budesonide and salmeterol inhalers, aspirin, atorvastatin and digoxin. He was a mechanic by trade with no obvious occupational sensitisation. He had no pets at home. He was a smoker with a 20 pack year history. Recent lung function tests showed an FEV1/FVC of 0.68 with a post bronchodilator FEV1 of 4.17 L (95% predicted).

He was admitted with a 1 week history of worsening shortness of breath, dry cough and wheeze. His baseline blood tests including full blood count, C reactive protein, liver and renal function were normal. Chest radiograph was unremarkable.

Arterial blood gas showed no evidence of hypoxia or acidosis. He was treated as acute severe asthma with back to back nebulisers, intravenous hydrocortisone and magnesium sulphate resulting in gradual improvement in bronchospasm and peak expiratory flow rate.

Despite optimal treatment, his breathing started to deteriorate. Arterial blood gas at this time showed lactic acidosis with normal oxygenation (Table 1). There was no clinical or biochemical evidence of haemodynamic compromise or sepsis. A presumptive diagnosis of lactic acidosis secondary to salbutamol was made. The nebulisers were withheld and he was transferred to high dependency unit for closer monitoring. The acidosis completely resolved in the following 12 hours on stopping salbutamol and the patient made an uneventful recovery.

### Discussion

Lactate is a product of anaerobic glucose metabolism and is generated from pyruvate. Normal plasma lactate concentration is 0.5-2 meq/L. Most cases of lactic acidosis are due to marked tissue hypoperfusion or hypoxia in systemic shock<sup>2</sup>.

Lactic acidosis can occur in acute severe asthma due to inadequate oxygen delivery to the respiratory muscles to meet an elevated oxygen demand<sup>3</sup> or due to fatiguing respiratory muscles<sup>4</sup>. A less recognised cause of lactic acidosis is treatment with salbutamol. The mechanism of this complication is poorly understood.

Salbutamol is the most commonly used short acting  $\beta$  agonist. Stimulation of  $\beta$  adrenergic receptors leads to a variety of metabolic effects including increase in glycogenolysis, gluconeogenesis and lipolysis<sup>5</sup> thus contributing to lactic acidosis.

Table 2 shows an assortment of previously published case reports and case series of lactic acidosis in the context of acute asthma.



**Table 1: Serial Arterial Blood Gases (On admission, 4 hours later and on stopping salbutamol)**

	00:22	04:06	07:42 Salbutamol withheld	10:50	11:35	12:24	14:29	17:33	23:32
FiO <sub>2</sub>	100%	60%	60%	60%	60%	40%	40%	35%	28%
pH (7.35-7.45)	7.36	7.28	7.26	7.32	7.34	7.37	7.37	7.39	7.41
pCO <sub>2</sub> (4.5-6.0 kPa)	4.87	4.74	4.15	3.31	3.98	3.9	4.7	5.08	5.49
pO <sub>2</sub> (11-14 kPa)	27	19.2	16.5	19	18	14.1	12.5	13	11.8
HCO <sub>3</sub> (22-28 mmol/L)	22	16.3	13.6	12.4	15.6	16.6	19.9	22	25.6
BE (2- -2)	-2	-9.1	-12	-12	-9	-7.6	-4.4	-1.5	1.4
Lactate (0.5-2 mEq/L)	1.8	7.6	9.7	9.3	7.6	6.8	3.6	1.4	1.1

**Table 2: Details of etiology and consequences of lactic acidosis in previously published case reports**

Reference	n	Suggested etiology of lactic acidosis	Effect of lactic acidosis
Roncoroni et al, 1976 [6]	25	Uncertain: increased respiratory muscle production, decreased muscle or liver metabolism	None observed
Appel et al, 1983 [7]	12	Increased respiratory muscle production, decreased muscle or liver metabolism	8 out of 12 developed respiratory acidosis, 6 required invasive ventilation
Braden et al, 1985 [8]	1	2 agonist, steroid and theophylline therapy	None
O'Connell & Iber, 1990 [9]	3	Uncertain: intravenous 2 agonist versus severe asthma	None
Mountain et al, 1990 [10]	27	Hypoxia and increased respiratory muscle production	None
Maury et al, 1997 [11]	1	2 agonist therapy	Inappropriate intensification of 2 agonist therapy
Prakash and Mehta, 2001 [2]	2	2 agonist therapy	Contributed to hypercapnic respiratory failure
Manthous, 2001 [12]	3	2 agonist therapy	None
Stratakos et al, 2002 [3]	5	2 agonist therapy	None
Creagh-Brown and Ball, 2008 [13]	1	β <sub>2</sub> agonist therapy	Patient required invasive ventilation
Veenith and Pearce, 2008 [14]	1	β <sub>2</sub> agonist therapy	None
Saxena and Marais, 2010 [15]	1	2 agonist therapy	None

## Discussion

Lactate is a product of anaerobic glucose metabolism and is generated from pyruvate. Normal plasma lactate concentration is 0.5-2 meq/L. Most cases of lactic acidosis are due to marked tissue hypoperfusion or hypoxia in systemic shock<sup>2</sup>.

Lactic acidosis can occur in acute severe asthma due to inadequate oxygen delivery to the respiratory muscles to meet an elevated oxygen demand<sup>3</sup> or due to fatiguing respiratory muscles<sup>4</sup>. A less recognised cause of lactic acidosis is treatment with salbutamol. The mechanism of this complication is poorly understood.

Salbutamol is the most commonly used short acting β<sub>2</sub> agonist. Stimulation of β<sub>2</sub> adrenergic receptors leads to a variety of metabolic effects including increase in glycogenolysis,

gluconeogenesis and lipolysis<sup>5</sup> thus contributing to lactic acidosis.

Table 2 shows an assortment of previously published case reports and case series of lactic acidosis in the context of acute asthma.

## Conclusion

In this case, the patient developed lactic acidosis secondary to treatment with salbutamol nebulisers. The acidosis resolved spontaneously without any specific treatment.

Lactic acidosis secondary to β<sub>2</sub> agonist administration may be a common scenario which can be easily misinterpreted and confuse the clinical picture. Acidosis itself results in hyperventilation which could be mistaken for failure to treat the

response. This may in turn lead to inappropriate intensification of treatment.

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#### Competing Interests

None declared

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#### REFERENCES

1. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest* 2000; 117:260–267
  2. Prakash S, Mehta S: Lactic acidosis in asthma: Report of two cases and review of the literature. *Canadian Respiratory Journal*. 2002, 9(3):203–208
  3. Stratakos G, Kalomenidis J, Routsis C, Papis S, Roussos C. Transient lactic acidosis as a side effect of inhaled salbutamol. *Chest*. 2002 Jul;122(1):385–6
  4. Mountain RD, Heffner JE, Brackett NC Jr, Sahn SA. Acid-base disturbances in acute asthma. *Chest*. 1990 Sep;98(3):651–5
  5. Haffner CA, Kendall MJ. Metabolic effects of  $\beta_2$  agonists. *J Clin Pharm Ther* 1992; 17:155–164
  6. Roncoroni AJ, Adrougué HJ, De Obrutsky CW, Marchisio ML, Herrera MR. Metabolic acidosis in status asthmaticus. *Respiration*. 1976;33(2):85–94
  7. Appel D, Rubenstein R, Schrager K, Williams MH., Jr. Lactic acidosis in severe asthma. *Am J Med*. 1983 Oct;75(4):580–584
  8. Braden GL, Johnston SS, Germain MJ, Fitzgibbons JP, Dawson JA. Lactic acidosis associated with the therapy of acute bronchospasm. *N Engl J Med*. 1985 Oct 3;313(14):890–1
  9. O'Connell MB, Iber C. Continuous intravenous terbutaline infusions for adult patients with status asthmaticus. *Ann Allergy*. 1990 Feb;64(2 Pt 2):213–8
  10. Mountain RD, Heffner JE, Brackett NC, Jr, Sahn SA. Acid-base disturbances in acute asthma. *Chest*. 1990 Sep;98(3):651–655
  11. Maury E, Ioos V, Lepecq B, Guidet B, Offenstadt G. A paradoxical effect of bronchodilators. *Chest*. 1997 Jun;111(6):1766–1767
  12. Manthous CA. Lactic acidosis in status asthmaticus : three cases and review of the literature. *Chest*. 2001 May;119(5):1599–1602
  13. Creagh-Brown BC, Ball J. An under-recognized complication of treatment of acute severe asthma. *Am J Emerg Med*. 2008 May;26(4):514.e1–3
  14. Veenith TV, Pearce A. A case of lactic acidosis complicating assessment and management of asthma. *Int Arch Med*. 2008 Apr 15;1(1):3
  15. R Saxena, G Marais. Salbutamol: beware of the paradox! *BMJ Case Reports* 2010; doi:10.1136/bcr.01.2010.2665
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## Tumefactive Multiple sclerosis

Potjana Jitawatanarat , Bhatraphol Tingpej and Paul Deringer

### Introduction

Tumefactive multiple sclerosis (MS) is a rare variant of MS. This form of MS can masquerade as neoplasm or infectious etiology. Understanding of the disease is limited to case report but it is associated with high morbidity and mortality.

### Case report

A 44 year old man presented with a 2-month history of progressive right upper extremity weakness, confusion and visual change. Physical exam revealed weakness, hyperreflexia on the right side and right homonymous hemianopia. MRI of the brain showed multiple ring-enhancing lesions located in both cerebral hemispheres. CSF analysis disclosed elevated protein with positive oligoclonal bands and myelin basic protein. Stains and cultures for bacteria and mycobacteria were negative. Serologies including HIV, Toxoplasmosis, and Lyme were all negative. Patient was treated with high-dose IV corticosteroid and clinically improved. One month later, he presented with increasing confusion, aphasia and progressive weakness. Repeat MRI of the brain revealed worsening multiple ring-enhancing lesions with surrounding vasogenic edema in most lesions. High-dose corticosteroid was promptly started. There was also concern about infection, especially brain abscess; hence, intravenous ceftriaxone, vancomycin, and metronidazole were empirically given. Due to uncertainty of diagnosis, first brain biopsy at right frontal lobe lesion yielded non-specific gliosis. Repeat MRI brain showed increasing number of ring-enhancing lesions in both cerebral hemispheres. As a result, a second brain biopsy was performed, which showed an active demyelinating process consistent with multiple sclerosis. Patient experienced severe disability and was discharged to long-term facility with slowly tapered schedule of corticosteroid. He was readmitted several times and eventually family decided hospice care.

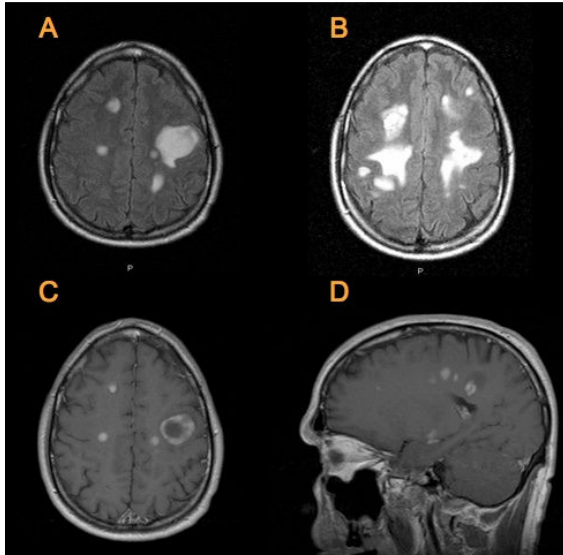
### Discussion

Multiple sclerosis is diagnosed by demonstrating clinical and/or radiographic evidence of dissemination of disease in time and space<sup>1</sup>. Tumefactive MS is a term used when the clinical

presentation and/or MRI findings are indistinguishable from a brain tumor<sup>2</sup>. Not all case of tumefactive MS are fulminant. Marburg variant MS is an acute rare variant of MS which has a rapidly progressive course with frequent, severe relapses leading to death or severe disability within weeks to months<sup>3</sup>. The tumefactive demyelinating lesions are defined as large (>2 cm.) white matter lesions with little mass-like effect or vasogenic edema, and post-gadolinium magnetic resonance imaging (MRI) typically showing an incomplete ring enhancement<sup>2,4</sup>. The clinical and imaging characteristics of these demyelinating lesions may mimic primary and secondary brain tumors, brain abscess, tuberculoma, and other inflammatory disorders e.g. sarcoidosis, primary sjogren's syndrome<sup>5</sup>. As a result, tumefactive MS is frequently misdiagnosed. There are some MRI characteristics that are more suggestive of tumefactive demyelinating lesions than of other etiologies. These include incomplete ring enhancement, mixed T2-weighted iso- and hyperintensity of enhanced regions, absence of a mass effect and absence of cortical involvement<sup>2,6</sup>. Differential diagnosis of rapidly progressive neurological deficit with ring-enhancing lesions include brain abscess, primary brain neoplasm or brain metastasis, acute disseminated encephalomyelitis (ADEM) and tumefactive multiple sclerosis. Careful clinical history, CSF study, serial MRI evaluation and follow-up are usually sufficient to make a diagnosis. Some cases pose considerable diagnostic difficulty owing to clinical and radiographical resemblance to brain tumor, for which biopsy may be warranted. Pathologically, the lesions are characterized by massive macrophage infiltration, acute axonal injury, and necrosis. No specific histological features distinguished specimens derived from patients developing classic multiple sclerosis from those who had tumefactive form<sup>7</sup>. A limited number of cases of Marburg's variant MS have been reported in the literature whereby most patients died within a period of weeks to months. Only two cases survived after one year<sup>7,8</sup>. There is no current standard treatment for this condition. Plasma exchange and Mitoxantrone are reportedly showed some promising options<sup>9,10</sup>.

Our patient presented somewhat like a stroke with visual field defect and right hemiparesis which is unusual in MS, but MRI

and CSF exam yielded a diagnosis of probable MS. Because of his abrupt clinical deterioration and impressive worsening of his MRI, concern was raised about possibility of infection or neoplasm. Hence, he received two brain biopsies, the second of which showed active demyelination, confirming the diagnosis of severe tumefactive multiple sclerosis and can be consider as a Marburg variant multiple sclerosis.



**Figure A:** FLAIR imaging at first presentation showed lesion in both hemisphere. **Figure B:** FLAIR imaging at one month later showed progression of multiple lesion in both hemisphere. **Figure C:** T1 Post contrast imaging showed intense ring enhancement pattern in almost all lesions with mild edema and minimal mass effect. **Figure D:** Showed lesion view as sagittal section.

### Conclusion

Marburg variant multiple sclerosis carries a high morbidity and mortality. This disease notoriously mimics other conditions leading to delay diagnosis and treatment. Absence of definitive diagnosis test apart from brain biopsy makes diagnosis, prognosis and treatment decisions difficult.

### Competing Interests

None declared

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### REFERENCES

1. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of multiple sclerosis. *Ann Neurol*.2001; 50: 121–7.
2. Dagher AP, Smirniotopoulos J. Tumefactive demyelinating lesions. *Neuroradiology*. 1996; 38: 560–5.
3. Canellas AR, Gols AR, Izquierdo JR, et al. Idiopathic inflammatory-demyelinating disease of central nervous system. *Neuroradiology*.2007; 49:393-409.
4. Lucchinetti CF, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. *Brain*.2008; 131:1759-75.
5. Sanahuja J, Ordonez-Palau S, Beque R, Brieva L, Boquet D. Primary Sjogren syndrome with tumefactive central nervous system involvement. *Am J Neuroradiol*.2008 Nov; 29(10):1878-79.
6. Kim DS, et al. Distinguishing tumefactive demyelinating lesions from glioma or central nervous system lymphoma: Added value of unenhanced CT compared with conventional contrast-enhanced MR imaging. *Radiology*. 2009; 251:467-75.
7. Turatti M, Gajofatto A, Rossi F, et al. Long survival and clinical stability in Marburg variant multiple sclerosis. *Neurol Sci*. 2010; 31(6):807-11.
8. Giubilei F, Sarrantonio A, Teisei P, et al. Four-year follow-up of a case of acute multiple sclerosis of the Marburg type. *Ital J Neurol Sci*.1997; 18:163-166.
9. Jeffery DR, Lefkowitz DS, Crittenden JP. Treatment of Marburg variant multiple sclerosis with mitoxanthrone. *J Neuroimaging*. 2004; 14:58-62
10. Rodriguez M, Karnes WE, Bartleson JD, Pineda AA Plasmapheresis in acute episodes of fulminant CNS inflammatory demyelination. *Neurology*.1993; 43 (6):1100-4.

## Malignant Hypertension Masquerading as Thrombotic Thrombocytopenic Purpura

Zohaib Bawany , Zeeshan Tariq , Thomas Sodeman and Anand Mutgi

### Abstract

Hypertension is common, but with early detection and treatment, it is rare to see malignant hypertension. Malignant hypertension is a medical emergency with an incidence of 1% in hypertensive patients. We report on a patient who presented with signs suggestive of Thrombotic Thrombocytopenic Purpura and severe hypertension, which resolved with the treatment of hypertension.

### Keywords

Malignant Hypertension, Thrombotic Thrombocytopenic Purpura (TTP)

### Introduction

Hypertension is common but, with early detection and treatment, it is rare to see malignant hypertension. We report a patient who presented with signs suggestive of thrombotic thrombocytopenic purpura and severe hypertension, which resolved with the treatment of hypertension.

### Case Report

A 34 year old African American male presented to the emergency department (ED) having experienced nausea, vomiting and diarrhoea for two days. He denied haematochezia, melena or sick contacts at home. He complained of blurred vision without photophobia, headache and mild chest discomfort. His past medical history was unremarkable. The patient did not have any significant family history. Smoking history was significant for a pack of cigarettes daily for seven years. He reported occasional alcohol intake, and denied use of recreational drugs. On presentation, this patient's blood pressure was 201/151 mmHg, with a mean of 168 mmHg. Pulse 103 beats per minute, respirations 20 per minute and temperature 98.4F. Physical examination was otherwise unremarkable, including absence of focal neurological deficits.

Blood tests showed: Haemoglobin 12.6 g/dl, White cell count 13.9 g/dl, Platelets 67000, Sodium 136, Potassium 3.4, BUN 24, Creatinine 2.56 and LDH 556. Chest x-ray showed cardiomegaly. A non-contrast computed tomography scan of the brain did not show any sign of stroke (haemorrhage). Urinalysis was positive for proteins 4+, a large amount of blood, 0-2 white blood cells/high power field (HPF) and 0-2 red blood cells/HPF.

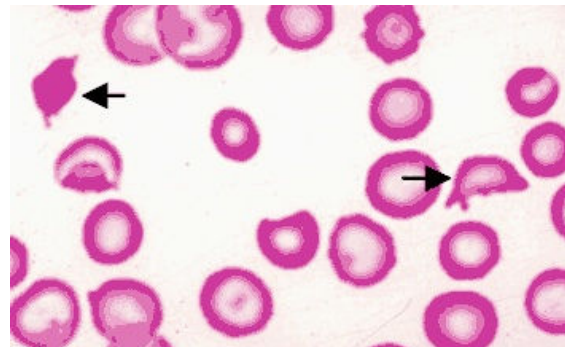


Figure 1

The patient's initial treatment whilst in the ER consisted of a Labetalol drip. His mean arterial pressure decreased to approximately 115 mmHg during the first hour, and his chest pain and headache improved with the control of elevated mean arterial pressure. Furthermore, over the next 24 - 48 hours, the patient's blood pressure was brought down to 138/86 mmHg and his blurred vision improved significantly. Subsequently, intravenous medications were switched to an oral regimen. Blood peripheral smear from the day of admission was significant for the schistocytes (Figure 1) suggesting ongoing haemolysis. Renal ultrasound was unremarkable. His cardiac ultrasound revealed an enlarged left ventricle, however no valvular abnormality was seen. Serum calcium and thyroid stimulating hormone levels were normal, as were urine catecholamines and vanillylmandelic acid level. On two week follow up in the outpatient clinic, the patient's platelet count and creatinine had returned back to baseline and peripheral

smear did not reveal any schistocytes as the blood pressure came under better control. [Table 1]

Table 1

Variable	On day 1	Day 3	Day 5	Day 6	Follow-up in 2 weeks
Haemoglobin	12.6	9.3	9.3	10.3	11.4
Platelets	67,000	65,000	90,000	125,000	204,000
Retic. count	3.9	--	--	4.3	--
Creatinine	3.06	2.86	2.69	2.4	2.3
BUN	29	27	28	27	27
LDH	556	370	333	240	--
Troponin	0.10	0.08	0.06	0.05	--
Peripheral Smear	Schistocytes	--	--	--	No Schistocytes

## Discussion

Malignant hypertension is a medical emergency with an incidence of 1% in hypertensive patients<sup>1</sup> and is more common in the African American population<sup>2</sup>. Depending on the clinical presentation, it must be differentiated from thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), glomerulonephritis and vasculitis.

Suspicion for TTP was initially high in this patient because of haemolysis, thrombocytopenia, central nervous system (CNS) manifestations and renal insufficiency. However, TTP did not explain the presence of elevated blood pressure<sup>3,4</sup> nor the improvement in symptoms and signs with the management of this, which clearly supports our diagnosis. Rapidly progressive glomerulonephritis did not explain the CNS symptoms, and a normal prothrombin time and activated partial thromboplastin time ruled against disseminated intravascular coagulation<sup>5</sup>. The patient did not have a history of preceding diarrhoea<sup>6</sup>, which could possibly direct towards haemolytic uraemic syndrome (HUS)<sup>4</sup>. There was no history of prosthetic valves, nor clinical evidence of vasculitis. The patient's symptoms of severe hypertension, haemolysis, thrombocytopenia and renal failure

were consistent with malignant hypertension, and treating the hypertension<sup>7</sup> gradually resolved the thrombocytopenia, haemolysis and renal failure<sup>8</sup>.

## Conclusion

This case report highlights that malignant hypertension is a medical emergency which can present with features resembling a wide variety of diseases, including TTP and HUS. Using appropriate management to control the elevation in blood pressure can help reveal the underlying diagnosis.

## Competing Interests

None declared

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## REFERENCES

1. Kitiyakara C, Guzman NJ. Malignant hypertension and hypertensive emergencies. *J Am Soc Nephrol* 1998;9:133-42.
2. Khanna A, McCullough PA. Malignant hypertension presenting as hemolysis, thrombocytopenia, and renal failure. *Rev Cardiovasc Med* 2003;4:255-9.
3. Patel A, Patel H. Thrombotic thrombocytopenic purpura: the masquerader. *South Med J* 2009;102:504-9.
4. Shibagaki Y, Fujita T. Thrombotic microangiopathy in malignant hypertension and hemolytic uremic syndrome (HUS)/ thrombotic thrombocytopenic purpura (TTP): can we differentiate one from the other? *Hypertens Res* 2005;28:89-95.
5. Kitchens CS. Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). *Hematology Am Soc Hematol Educ Program* 2009:240-6.
6. Hertig A, Ridel C, Rondeau E. [Hemolytic uremic syndrome in adults]. *Nephrol Ther* 2010;6:258-71.
7. Varon J, Marik PE. The diagnosis and management of hypertensive crises. *Chest* 2000;118:214-27.
8. Gassanov N, Pollok M, Er F. Acute renal failure associated with malignant hypertension. *Dtsch Med Wochenschr* 2009;134:2224-7

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## MRSA infection of a Primary TKA following an infected IV cannula site complicated by Stevens-Johnson Syndrome- A Case Report

SKM Annamalai, SS Raju and VG Langkamer

### Abstract

We present here a 63 year old lady who had a primary total knee arthroplasty( TKA) for osteoarthritis of knee. She developed methicillin resistant staphylococcus aureus( MRSA )infection of the primary prosthesis following an intravenous(IV) cannula site infection with MRSA bacteraemia. This was complicated by Stevens-Johnson syndrome following vancomycin therapy for the infection, which was confirmed by clinical features including typical skin rashes and skin biopsy. She was treated with alternative antibiotics and was referred to a specialist orthopaedic unit where she had a two- stage revision. In retrospect, the infection could have been avoided if the IV cannula was not left in for so long. She also unfortunately had an adverse reaction to the vancomycin which complicated the situation, making management difficult. A team consisting of orthopaedic surgeons, microbiologists, dermatologists and physiotherapists was essential for successful management of this difficult and complicated situation.

### Abbreviations

MRSA (methicillin resistant staphylococcus aureus), IV( intravenous), TKA (total knee arthroplasty), DM( diabetes mellitus)

### Introduction

Infection of a prosthetic total knee joint is a serious complication<sup>1</sup> and should be diagnosed promptly<sup>2</sup> and treated aggressively. We present an interesting case of MRSA infection of a primary total knee replacement following an IV cannula infection leading to bacteraemia and subsequent infection of the knee prosthesis, complicated by stevens- Johnson syndrome .

There were many challenging issue which are outlined including diagnosis and management.

### Case Report

A 63-year- old lady had an elective total knee arthroplasty for severe osteoarthritis of the knee. She had a background history of well-controlled type 2 diabetes mellitus and was on warfarin for a previous pulmanory embolism. As per the hospital protocol her warfarin was stopped before surgery until her INR was <1.5 and she was heparinised with a view of

warfarinizing after the surgery. She had an uneventful knee arthroplasty, but unfortunately one of her IV cannula site became cellulitic. She was empirically started on oral flucloxacillin after taking blood cultures and sending the cannula tip for microscopic culture and sensitivity (which is routinely done has hospital protocol for infected cannula sites).

Surprisingly the tip grew MRSA and also had MRSA bacteraemia. She became systemically unwell and septic, and was treated aggressively with parentral vancomycin for MRSA bacteraemia. She had a transeophageal echocardiogram to rule out cardiac vegetation. She gradually improved but developed

typical papular rashes over her palm, dorsum of hand, extensor surface of arm and forearm and trunk and buccal mucosa (Fig 1 and 2).



Fig 1: Rash over the dorsum hands



Fig 2: Rash over the extensor aspects of forearm

She had a severe allergic reaction to vancomycin and the skin biopsy of the lesion confirmed that she had developed Stevens-Johnson syndrome. An alternative antibiotic was started following discussion with the specialist bone infection unit. She gradually improved over the next few weeks without any problem in her prosthetic replaced knee. At about 6 weeks post-operatively she developed severe pain and hot swelling of her replaced knee with decrease range of motion. Her inflammatory markers were markedly raised and the knee aspirate confirmed MRSA infection of the total knee replacement. She was referred to a specialist bone infection unit due to the complexity of the case, where she successfully underwent two-stage revision.

## Discussion

Infection of a Knee replacement is a serious complication that requires significant hospital-based recourse for successful management<sup>3</sup>. The rate of infection of a primary knee replacement varies from 0.5- 12%<sup>1</sup>. Rheumatoid arthritis, previous surgery, diabetes mellitus are all associated with an increased risk of infection<sup>4</sup>. Although there is no absolute diagnostic test for peri-prosthetic infection<sup>2</sup>, a high index of clinical suspicion is essential. There has been a case report on MRSA cervical epidural abscess following IV cannulation<sup>5</sup>, but to the best of our knowledge there has been no previous report of MRSA- infected knee arthroplasty following complications of IV cannulation. Stevens-Johnson syndrome involves rare but severe cutaneous adverse reactions related to a variety of medications including antibiotics<sup>6</sup>. Parenteral vancomycin is the first line treatment for MRSA bacteraemia. It is recognised that vancomycin is indicated in inducing Stevens-Johnson syndrome, mortality being 30-100%<sup>7</sup>. It is vital that Stevens-Johnson syndrome is recognised early so that offending agents are stopped and supportive treatment commenced. Early dermatological consultation, skin biopsy and direct immunofluorescence<sup>7</sup> are essential to confirm diagnosis so that effective treatment can be instituted. The diagnosis and

management of this serious complication is complex and requires considerable recourse allocation by the patient, the hospital, the infectious disease specialist, and the orthopaedic surgeon<sup>1,5</sup>.

## Competing Interests

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## REFERENCES

1. Blom AW, Brown J, Taylor AH, Pattison G, Whitehouse S, Bannister GC. Infection after total knee arthroplasty. *J Bone Joint surgery Br* 2004 Jul;86(5):688-91.
2. Elie Ghanem et al. Cell Count and Differential of the Aspirated fluid in the Diagnosis of the Infection at the Site of Total Knee Arthroplasty. *J Bone Joint Surg Am.* 2008;09: 1637-43.
3. Buechel F F, Femino FP, D'Alessio J. Primary Exchange Revision Arthroplasty for Infected Total Knee Arthroplasty: A Long-Term study *The American journal Of Orthopaedics* .2004;April.190-98.
4. Bengtson S, Knutson K. The infected Knee arthroplasty. A 6 year follow-up of 357 cases. *Acta Orthop Scand* 1991 Aug;62(4):310-11.
5. Burgess CM, Wolverson AS, Dale MT. Cervical epidural abscess: a rare complication of intravenous cannulation. *Anaesthesia*. 2005 Jun;60(6):605-8.
6. Mockenhaupt-Maja et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. *The Euro SCAR- study: J-Invest- Dermatol*, Jan2008, vol128, no. 1, p 35-44.
7. Jones DH, Todd M, Craig TJ. Early diagnosis is key in vancomycin-induced linear IgA bullous dermatosis and stevens- Johnson syndrome. *J Am Osteopath Assoc.* 2004 Apr;104(94):157-63



## Paediatric Gastro-Oesophageal Reflux Disease

Harween Dogra , Bhavini Lad and Dinesh Sirisena

### Definition

Gastro-oesophageal reflux (GOR) is the passage of gastric contents into the oesophagus. In most infants with GOR the outcome is benign & self-limiting. <sup>(1)</sup>

### Incidence/Prevalence

Peak incidence of GOR is around 4 months of age, and it resolves spontaneously by 1-2 years of age in most patients. <sup>(2)</sup>

Regurgitation (possetting or spitting up) is the most common presentation in infants with GOR. Regurgitation of at least one episode a day is seen in:

- 50% of infants 0-3 months
- 67% of infants at 4 months
- 5% at 10 to 12 months of age <sup>(3)</sup>

It is important to note that in infants (younger than 1 year of age) who are otherwise well and symptomatic, regurgitation may be considered entirely normal. <sup>(4)</sup>

### Causes/Risks

GOR occurs due to the transient, inappropriate relaxation of the lower oesophageal sphincter, which allows the stomach contents to pass into the oesophagus.

GOR can be physiological or pathological:

- Physiological GOR – when the infant has normal weight gain and experiences no complications and is generally well.
- Pathological GOR – also known as gastro-oesophageal reflux disease (GORD) is when reflux is associated with other symptoms like failure to thrive or weight loss, feeding or sleeping problems, chronic respiratory disorders, oesophagitis, haematemesis etc <sup>(3)</sup>

Several anatomical and physiological conditions make infants (younger than 1 year of age) more prone to GORD than older children and adults:

- Short, narrow oesophagus
- Delayed gastric emptying
- Shorter, lower oesophageal sphincter that is slightly above, rather than below, the diaphragm
- Liquid diet and high calorie requirements, putting a strain on gastric capacity

- Larger ratio of gastric volume to oesophageal volume<sup>(4)</sup>

Most children have no specific risk factors for GORD. Children with the following conditions are at increased risk for developing GORD and for progressing to severe GORD:

- Severe neurological impairment
- Prematurity
- Cystic fibrosis
- Gastro-oesophageal abnormalities (even after surgical repair), e.g. Oesophageal atresia, diaphragmatic hernia, pyloric stenosis
- Bronchopulmonary dysplasia (preterm infants with lung disease)
- Hiatus hernia
- Oesophageal sphincter disorders
- Raised intra-abdominal pressure<sup>(5)</sup>

### Symptoms

GORD in infants and children can present with a variety of symptoms many of which can be relatively non-specific. Equally, other pathologies may lead to the development of reflux. Those in the early years tend to be based on observations by parents, while older, more vocal children express symptoms more akin to adult presentations.

As such, the history/symptoms will be broadly divided into those expected for infants (<1yr), young children (1-5yrs) and older children (>5yrs).

### Infants <sup>(6-10)</sup>

- 1) Excessive possetting/regurgitation
  - a) Possetting is a normal phenomenon in infants
  - b) Frequent episodes, together with vomiting may indicate underlying GORD
  - c) Projectile vomiting may indicate an obstructive pathology
- 2) Difficult/rapid cessation of feeds
  - a) There may be difficulty initiating feeds and latching
  - b) Early cessation may be precipitated with the onset of reflux
- 3) Failure to thrive
  - a) No weight loss can be expected
  - b) Weight loss crossing centiles on the growth chart must be addressed urgently
- 4) Sleep disturbance
  - a) Particularly after an evening feed

- b) This is often associated with irritability and inconsolable crying
- 5) Irritability and inconsolable crying
  - a) One of the commonest presentations to the GP
  - b) This may occur during feeds or shortly afterwards
- 6) Apnoeic episodes
  - a) A witnessed pausing in respiratory effort
  - b) Occurring at night, it can mimic obstructive sleep apnoea
  - c) This may indicate a more serious underlying pathology and requires urgent assessment
  - d) It is likely to be more prevalent in this age group

#### Young Children<sup>(6-10)</sup>

- 1) Regurgitation/vomiting
  - a) Beating/rubbing the chest may be an early sign of this pathology
  - b) Reflux symptoms can be typical of those in adults
- 2) Failure to thrive
- 3) Refusing food
  - a) Similar to the infant, however, the younger child can be more vocal in their refusal
- 4) Abdominal/chest pain
  - a) With increasing age, children may demonstrate gastric irritation with abdominal pain
  - b) Acid reflux producing oesophagitis may present as chest discomfort
  - c) Both are similar to symptoms adults experience
- 5) Irritability
- 6) Persistent/nocturnal cough/wheezing
  - a) There may be a dry, non productive cough
  - b) Secondary to pharyngeal irritation
  - c) There may be no co-morbidities or underlying pathologies
  - d) Symptoms can be mistaken for asthma by parents

#### Older Children<sup>(9)</sup>

- 1) Dyspepsia/vomiting
  - a) These symptoms in older children are thought to have a similar reliability in diagnosis as in adults
- 2) Dysphagia/odynophagia
  - a) As children become more articulate they may be able to describe these symptoms in relation to meals
  - b) Particularly with chronic GORD and the development of a Barrett's Oesophagus
- 3) Abdominal/chest pains
- 4) Persistent/nocturnal coughing/wheezing

#### Other Symptoms

Symptoms which can be identified but which may be considered less life-threatening include:

- 1) Dental erosions
- 2) Hiccups
- 3) Halitosis

Those deserving urgent investigation and intervention include:

- 1) Forceful/Bilious vomiting

- 2) Suggesting a possible obstructive pathology
- 3) This requires urgent surgical referral
- 4) Force of vomiting may not always indicate the severity of the problem
- 5) Upper gastrointestinal bleeding/hematemesis
- 6) This may be a consequence of increased pressure from vomiting
- 7) Similar to a Mallory-Weiss pathology
- 8) An urgent review by local Paediatric Gastroenterologists is warranted
- 9) Profuse diarrhoea or constipation
- 10) Failure to thrive/weight loss
- 11) Lethargy
- 12) Apnoeic episodes

#### **Physical Signs**

As with the previous section, physical signs will be considered for each age range as above: infants (<1yr), young children (1-5yrs) and older children (>5yrs).

#### Infants<sup>(9)</sup>

- 1) Irritability when lying flat
  - a) Particularly following feeds
  - b) Especially when supine
- 2) Weight loss
  - a) Regular monitoring with repeat measurements
  - b) A single weight cannot imply loss
  - c) This is usually a late sign
- 3) Arching of the back
  - a) Secondary to oesophageal irritation
  - b) Can be associated with increased tone and crying
- 4) Dehydration
  - a) Loss of fluid through vomiting
  - b) Look for
- 5) Dry mouth
- 6) Sunken fontanelle
- 7) Prolonged capillary refill time
- 8) Reduced skin turgor
- 9) Reduced urine output
- 10) Crying without tears
- 11) Apnoeas
  - a) Periods of reduced respiratory effort
  - b) Noted by parents as pauses in breathing

#### Young Children<sup>(9)</sup>

- 1) Weight loss
- 2) Dehydration
- 3) Anaemia
  - a) Associated with chronic symptoms and gradual loss of iron
  - b) Look for Pallor/pale conjunctivae, Glossitis, Angular stomatitis, Pica
- 4) Dysphagia/choking with food
  - a) Particularly with prolonged GOR and development of stricturing
- 5) Difficulty in breathing/wheezing/lower respiratory tract infection (LRTI)

- a) Similar to asthma on examination
- b) Signs of LRTI on auscultation
- c) Possibly stridor

**Older Children** <sup>(9)</sup>

- 1) Weight loss
- 2) Dehydration
- 3) Anaemia
- 4) Dysphagia/Choking with food
- 5) Difficulty in breathing/Wheezing/LRTI
- 6) Persistent sinusitis

Signs requiring urgent intervention include <sup>(9)</sup>:

- 1) Hematochezia
  - a) Unaltered blood in stool
  - b) Stools take on a red appearance
- 2) Onset of vomiting after 6 months of life
- 3) Fever
  - a) Uncommon with GOR
  - b) Indicating an infective pathology
- 4) Hepatosplenomegaly
  - a) An underlying condition other than GOR is likely
  - b) Important pathologies must not be missed
- 5) Bulging fontanelle
  - a) Indicating increased intracranial pressure and an alternative pathology underlying the reflux
- 6) Macro/microcephaly
  - a) Suggestive of hydrocephalus or a congenital malformation
- 7) Seizures
  - a) Related to a number of other problems
  - b) Metabolic pathologies should figure highly in any differential diagnosis
- 8) Abdominal distension with reduced bowel sounds
  - a) Tinkling bowel sounds and an pain may suggest bowel obstruction

**Differential diagnoses**

Common differential diagnoses have been noted in Table 1, however, this is by no means a definitive list of conditions or presentations. It should be taken as an indication to the diverse presentations that can mimic or precipitate GOR (adapted from <sup>(9)</sup> and <sup>(10)</sup>).

Condition	History/Symptoms	Signs
Pyloric Stenosis	Sudden onset vomiting Constantly hungry baby Usually males First 4-6 weeks of life	Non-bilious projectile vomiting Visible peristalsis Positive test feed
Malrotation	Sudden onset pain in volvulus Reduced bowel movement Vomiting	Bilious vomiting Abdominal distension Pulling up legs with pain onset
Cow's Milk Allergy	Vomiting and Diarrhoea Eczema Relationship to feeds Failure to thrive	Urticaria Watery stool Weight loss crossing centiles

Constipation	Infrequent stools Straining Blood in nappy	Palpable stool on examination Irritable baby
Urinary Tract Infections	Vomiting Fever (can be without focus) Poor feeding	Lethargy Reduced urinary output Abdominal pain
Viral Gastroenteritis	Vomiting Diarrhoea Fever Lethargy	Dehydration Viral Rash
Hypocalcemia	Poor feeding Lethargy Tetany Seizures	Seizures Apnoeas Tremor Abdominal distension
Hydrocephalus	Vomiting Lethargy Confusion Visual changes	Increased head size Gait change Altered consciousness
Meningitis	Fever Lethargy Vomiting Confusion	Neck stiffness Photophobia Rash (late onset)
Drugs/Toxins	Vomiting Lethargy Ingestion history	Dependant upon drug ingested

Table 1

**Investigations and management of infants (<1 yr old)**

Complicated cases of GORD (not gaining weight/faltering growth or non-GI symptoms e.g. cough), should be referred to a Paediatrician while investigating for causes and instituting simple management.

Simple investigations to do in primary care:

- 1) Abdominal examination for hernias/pyloric stenosis (test feed)
- 2) Urine dip to rule out UTI
- 3) Blood tests for electrolyte abnormalities, coeliac screen (if weaned)

Referral to a Paediatrician will result in imaging investigations such as Abdominal x-ray and upper GI contrast study to rule out malrotation/hiatus hernia/achalasia in older children, sometimes GORD can be seen on contrast studies. The Paediatrician may go on to arrange a pH/impedance study, upper GI endoscopy or allergy testing.

Management

- 1) Calculate feed requirements, parents may be over feeding, e.g. approximate fluid requirement 100-120ml/kg/day every 3-6hrs (depending on age and whether weaned on to solids)
- 2) In thriving infants there is no evidence that pharmacological therapy will make a significant difference to symptoms.
- 3) Therefore the mainstay of management is reassurance. Simple pharmacological intervention can be tried with feed thickener (in formula fed babies) or Alginates e.g. Gaviscon (can be mixed with water for breast fed babies)

- 4) If there are continued concerns refer to Paediatrician for on going investigations and management.
- 5) Recent evidence shows that some infants may have cow's milk protein intolerance<sup>(9)</sup>. Therefore for breast fed babies the mother could try cutting out dairy from her diet (important to have supervision from dietician re: nutritional requirements while breast feeding). Formula fed babies can have a 2 week trial of hydrolysed/amino acid based formula e.g. Progestimil, Nutramigen, Neocate.
- 6) Reviews from ESPGHAN<sup>(9)</sup> and DTB<sup>(11)</sup> recommend H2RA (H2 receptor antagonists eg. Ranitidine) may help, though there is little evidence – these could be commenced while waiting for an appointment with the Paediatrician.
- 7) (Currently there is no role for Domperidone. The next medication a Paediatrician may try is Omeprazole ± omission of cow's milk protein)<sup>(11)</sup>

#### Investigation and management of older children (>18mths)

As before, complicated cases of GORD (not gaining weight/faltering growth or non-GI symptoms e.g. cough), should be referred to a Paediatrician while investigating for causes and instituting simple management.

#### Investigations

- 1) Urine dip, if there are symptoms of vomiting
- 2) Stool H. Pylori antigen test
- 3) Bloods tests inc. inflammatory markers, H. Pylori antigen, celiac screen

#### Management

- 1) If main symptom heartburn with no evidence of H. Pylori:
- 2) Reassurance and lifestyle changes (weight loss, dietary changes, timing of meals), up to 4 week trial of PPI (Proton pump inhibitor e.g. lansoprazole, omeprazole).
- 3) If symptoms improve then continue PPI for up to 6 months, then wean off over 4 weeks (evidence that if stopped suddenly patients may get rebound symptoms)<sup>(10)</sup>.
- 4) If PPI doesn't help or symptoms recur after stopping the PPI, then refer to a Paediatrician.
- 5) The Paediatrician may investigate with more blood tests e.g. Autoimmune screen, allergy testing, imaging, pH/impedance study, endoscopy.

#### REFERENCES

1. Pritchard DS, Baber N, Stephenson T. Should domperidone be used for the treatment of gastro-oesophageal reflux in children? Systematic review of randomized controlled trials in children aged 1 month to 11 years old. *Br J Clin Pharmacol.* 2005; 59(6): 725-9.
2. Nelson SP, Chen EH, Syniar GM, Christoffel K. Prevalence of symptoms of gastro-esophageal reflux during infancy: a paediatric practice-based survey. *Arch Pediatr Adolesc Med.* 1997; 151: 569-72.
3. Salvatore S, Vanderplas, Y. Gastroesophageal reflux & cow milk allergy: Is there a link? *Pediatrics.* 2002; 110(5): 972-984.
4. Henry, SM. Discerning differences: gastroesophageal reflux & gastroesophageal reflux disease in infants. *Advances in Neonatal Care.* 2004; (4)4: 235-247.
5. www.gpnotebook.co.uk. [http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20100221174705261069&linked=7]. Accessed 14/1/2011.
6. Bentley D et al. *Pediatric Gastroenterology and Clinical Nutrition.* London: REMEDICA. 2002.
7. Taeusch D et al. *Pediatric Gastroenterology and Clinical Nutrition.* Philadelphia: ELSEVIER. 2005.
8. Fanaroff A and Martin R. *Neonatal-perinatal medicine: diseases of the fetus and infant, Volume 1. 7th ed.* Massachusetts: MOSBY. 2001.
9. Vandenas Y et al. (2009) *Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society For Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society For Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN).* *Journal of Pediatric Gastroenterology and Nutrition.* 2009; 49: 498-547.
10. Jung A. Gastroesophageal Reflux in Infants and Children. *Am Fam Physician.* 2001; 64 1853-60.
11. Managing gastro-oesophageal reflux in infants, *Drugs and Therapeutics Bulletin, BMJ* 2010; 341:c4420

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## Why I want to be a Doctor

Asif Rajah

“The more we care for the happiness of others, the greater our own sense of well being becomes.” *The Medicine of Altruism: Dalai Lama*

### Introduction

The fundamental mission of any medical school is to select those individuals who possess the qualities and personality traits best suited to becoming a good doctor. The first part of this article takes a critical look at how United Kingdom (UK) medical schools select doctors, which can vary considerably, and asks whether it can be improved. The qualities needed to be a good doctor are discussed and asks whether work experience illustrates at least some of these personal qualities and should therefore be an essential prerequisite for applying to medical school. Such experience helps the student to make an informed career choice and exploring it at interview can reflect student motivation to study medicine. My experience in Ghana gave me the opportunity to find out at first hand if I had what it takes to become a doctor. The trip was totally inspirational. It made me realise that medicine is much more than being master of all sciences. In Ghana I saw many of the qualities one needs to be a doctor, how this contrasts with the current selection criteria in the UK, and made me wonder whether the UK system offers our society the best practice available.

### Critique of UK medical school selection

Applying to medical school has become increasingly competitive. Selection into medical schools is not an exact science but one assumes that best available evidence is being used. The present system almost certainly turns away students who would make good doctors and accepts some who are mediocre or poor or even drop out of medicine altogether. The selection criteria for entry into medicine have to be accurate. However, no system is fool proof and the number of drop-outs in UK training stands at 6.8 – 12%.<sup>1,2,3</sup> I believe that better selection criteria would reduce the drop-out rate and save personal distress among those who made an unwise choice. This makes economic sense. There is widespread agreement that we should select medical students on wider criteria than scores of academic success,<sup>4, 5</sup> though in practice many medical schools have valued academic scores at the expense of other considerations.<sup>6,7</sup> A Levels alone should not be sufficient to gain a place at medical school. True communication calls for some

shared life experiences and empathy with others. I believe that students who are totally absorbed in their studies to the exclusion of almost everything else are less likely to make good doctors. In one study, a ten-year follow-up after entry into medical school showed no correlation between academic score at entry and drop-out rate, but significant correlation between low interview scores and later drop-out.<sup>8</sup> Reasons for drop-out were a variety of personal reasons including lack of motivation for study or for medicine. In a medical school that carefully evaluates applicants, empathy and motivation to be doctors were found to be particularly important in predicting both clinical and academic success.<sup>9</sup>

Another major study, looking at the dropping out from medical schools in the UK over a ten year period (1990-2000),<sup>10</sup> showed that drop-out rates increased during this period and concluded that the probability of dropping out of medical school is 20% lower for students with a parent who is a doctor. The authors comment that this may be the result of greater commitment or better preparation and insight before starting the course. Ethnic background of students was recorded only between 1998-2000. The study found that Indian females were around 1.9% less likely to drop out compared with white females, whereas Indian males were no different from white males. Other ethnic groups were less likely to drop-out by around 0.8%. A concerning fact in this paper was the degree to which drop-out rates varied between different medical schools. No study to date has been done to find the reasons for these differences. Surely potential applicants need to be aware of these results. The differences could be accounted for by variable selection processes among the medical schools.<sup>11</sup> Some medical schools shortlist for interview only on predicted academic performance or the number of A\* GCSEs or decide by the UK Clinical Aptitude Test (UKCAT) / BioMedical Admissions Test (BMAT) scores. Some use information presented in the candidate's personal statement and referee's report while others ignore this because of concern over bias. In some cases candidates fill in a supplementary questionnaire. Interviews vary in terms of length, panel composition, structure, content, and scoring methods. Some schools do not interview.

The commonest reasons cited in many papers for dropping out of medical school were because it is not for them, they found it boring, they did not like patients, the work environment was

not what they want to spend their time on, or they did not like responsibility.<sup>12</sup> Essentially they had realised too late that Medicine was not for them. They had failed to find out what they were letting themselves in for before applying and the medical school had failed to pick this up. There is a strong argument for pooling resources so that applicants get one good assessment instead of four poor ones.

Concern for people	Committed to self-learning
Sense of responsibility	Emotionally stable
Professionalism	Good judgement and perception
Good communication skills	Good listener
Highly motivated	An enquiring mind
Honesty	Well organised
Integrity	Patience
Ability to handle pressure	Mental strength
Confident	Resilience
Determination	Respect for other people
Perseverance	Respect for confidentiality
Decisiveness	Tolerance
Conscientious	Hard working
Team player	An open mind
Leadership qualities	A rational approach to problems
Humility	Critical reasoning
Flexible and adaptable to change	Separate important points from detail
Logical thinking	Recognise limits of professional competence

A levels, used for medical selection, do not indicate any personality attributes of the candidate and are affected by socio-economic bias. The UKCAT was introduced to level the playing fields. This test doesn't examine acquired knowledge and candidates can't be coached to pass, so in theory it should provide a fairer assessment of aptitude than A level grades. It was also thought that the various components of the UKCAT, namely verbal reasoning, quantitative reasoning, abstract reasoning, and decision making, could help to pick the students who have the personality attributes to make good doctors. Unfortunately, a recent paper suggests that the UKCAT does not provide any more assessment of aptitude than A levels.<sup>13</sup> However, an inherent favourable bias towards students from well-off backgrounds or from grammar and independent schools was also found. Moreover the test does not compensate for talented candidates whose education has been affected by attending a poor school. Another paper looked at the predictive validity of the UKCAT.<sup>14</sup> This showed that UKCAT scores did not predict Year 1 performance at two medical schools. Although early prediction is not the primary aim of the UKCAT, there is some cause for concern that the test failed to

show even the small-to-moderate predictive power demonstrated by similar admission tools.

There is no doubt that potential doctors must have enough intellectual capacity to do the job but they must also possess other important traits (Table 1).

What patients rate highly among the qualities of a good doctor are high levels of empathy and interpersonal skills.<sup>15</sup> Personality traits such as conscientiousness have been positively associated with pre-clinical performance.<sup>16</sup>

The criteria being used more and more by admission tutors include the candidate's insight into medicine including as evidenced from work experience.<sup>17</sup> Surprisingly, very little has been written on work experience and the value placed on it varies considerably between medical schools. Many would regard this experience as a prerequisite for entry into medical school. It enables a student to experience at first hand what he/she is letting him/herself in for. Some find the experience fascinating and challenging while others may find it is not for them. Work experience should not be seen as a hurdle to climb, but part of the decision-making process in determining whether medicine really is for you. I fear that another contributing factor to the increase in drop-out rates from medical schools is the increasing difficulty in obtaining work experience. Gone are the days when students could join theatre staff and watch an exciting operation or shadow doctors in Accident and Emergency (A&E). Useful work experience is so important and it is becoming harder and harder to get, but is still possible. Therefore considerable desire, commitment and motivation by the student are required to obtain it. The work does not need to be medically related, but work experience in any care setting is essential. These placements can be used to illustrate at least some of the personal qualities that are sought after in a good doctor including: appreciation of the communication skills required of a doctor; a thorough awareness of the realities of medicine and the National Health Service (NHS); an understanding of teamwork; an ability to balance commitments; and observation of the caring and compassionate nature of the doctors. Furthermore, as demonstrated in general practice,<sup>18</sup> personal experiences can have a highly positive influence on an individual's attitude to a particular speciality. Encouraging school students to experience general practice would therefore not only increase their awareness of the life to which they are about to commit, but could aid recruitment to general practice as a speciality.

### My Ghana Experience

I decided that, as part of my work experience, I would go to Ghana with a charity organisation (Motec UK Life). The reason was not to impress medical admissions tutors, but to discover if I had what it takes to become a doctor. I realised how comfortably we live in our small bubble, with little appreciation of what goes on in the rest of the world. Ghana is a third world

country, which not only has great poverty and malnutrition but also has many deadly diseases such as Acquired Immunodeficiency Syndrome (AIDS)/Human Immunodeficiency Virus (HIV), malaria, hepatitis, typhoid and sickle cell disease. My trip was demanding as I was stripped of my luxuries and removed from my comfort zone, but it helped me to understand the real values in life through helping the most needy and vulnerable people. I felt the suffering and the pain they went through, day in and day out, but knew that making even the slightest difference to their lives motivated me and enabled me to persevere through my time there.

One of the hospitals we stayed was Nkawkaw, which was in the middle of a shantytown with houses made of metal sheets. Yet, despite the presence of great poverty and disease, I did not find a single person who was not extremely kind and welcoming and always smiling. It made me think of the contrasting situation back home in the UK where people were relatively well off, and yet so unhappy. I spoke to as many people as possible, not realising that I was developing my people- and communication-skills. I played football with the children and made them smile. I was able to visit the AIDS/HIV clinic and gained a first-hand account of how this devastating disease was controlled and dealt with in a third-world country. The pain, grief and suffering were immense and difficult to comprehend unless one was actually there witnessing it. AIDS here hurts everyone, but children are always the most vulnerable. The children were born with HIV from their mothers, or infected through breast milk, or in the past infected by unsafe medical treatments. They were often orphaned and destitute, having to build their own homes, grow their own food, and care for younger brothers and sisters. That is the cruel reality.

Equally heartbreaking was seeing so many people in the HIV clinic who could not afford the anti-retroviral drug that would improve the quality and duration of life. This feeling of helplessness motivated me even further to pursue a career in medicine in order to help people at their most vulnerable. On this trip I was greatly impressed by the dedication, commitment and professionalism shown by the doctors in difficult situations. I saw doctors working with little supervision and little equipment, and yet they seemed confident, well organised, and adapted themselves well to the conditions. Their enthusiasm and compassion never waned despite working long hours.

I saw many types of operation being performed including joint replacements, hernia repairs and caesarean sections. On one particular day, I observed the team performing many knee and hip joint replacements. The deformities of the joints were much more severe than seen in the UK. I enjoyed and appreciated the skills of the orthopaedic surgeons in carrying out these operations, which were being done under spinal anaesthesia, and so I was able to talk to the patients and comfort them. Throughout the day, after seeing many operations, I did not flinch or feel queasy at the sight, and this further encouraged me to believe that I could handle a career in medicine. On

watching the caesarean sections, the excitement of bringing new life into the world was overwhelming. Seeing another baby being born with severe hydrocephalus marred this. No treatment facilities for this condition were available for hundreds of miles and the baby was too ill to be transferred such a large distance. I witnessed the doctors conveying the heartbreaking news to the family with compassion. It became clear to me that there are negative aspects to this career. There is a great deal of emotion and stress to cope with in such circumstances but I believe that, given training, I would be mentally stronger to take control of these situations.

I was always allowed to follow the doctors on their ward rounds, and was encouraged to ask questions and make comments, so that I often felt that I was being treated as a medical student, which was strange in some ways but also very gratifying. On this trip I was involved in teaching and in helping to set up a workshop, which lasted for a whole day for doctors from all over Ghana. This involved lectures as well as demonstrating the latest surgical and theatre equipment. I was impressed by the teamwork and organisation shown by the group. The communication skills of the group had to be of the highest quality in order to get the message across. I found that teaching about the devastating effects of HIV, in a local school in Ghana, was particularly challenging as some of the students before me were sufferers and so I found it difficult to look them in the eye, knowing that although they were being taught the safety precautions, many did not have much of a future. This reinforced my feeling of helplessness but, although this situation was heartbreaking, I remained enthusiastic for the children, to keep their morale high in order to prepare them for their inevitable future.

## Conclusion

My trip was totally inspirational. It made me realise that medicine is much more than being a master of all sciences. In Ghana I observed in doctors the real passion and drive needed for medicine as well as many other essential qualities I believed doctors needed. This contrasts with the current selection criteria in the UK; sadly we are missing out on too many good doctors because of our obsession with grades rather than looking for real qualities that are going to make a difference to our patients. I discovered that seeing the immense suffering, and the close bond of doctors and patients in an entirely different social and economic context, helped me to evaluate and shape my own emotions and personal values. My motivation in wanting to become a doctor has increased tremendously since this trip. My trip to Ghana also inspired me to create a medical journal in my school as a fund-raising initiative. I brought together a group of fellow students to write articles about common teenage problems (teenage drinking, anorexia, obsessive compulsive disorder (OCD), stress, smoking, sexually transmitted diseases (STDs)) as well as articles on euthanasia and assisted suicide, stem cell research and the NHS. I wrote about my personal experiences in Ghana in addition to editing and publishing the

school journal. All the funds raised from the school medical journal will be going to the HIV victims in Ghana.

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#### Competing Interests

None declared

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#### REFERENCES

- Parkhouse J. Intake, output, and drop out in United Kingdom medical schools. *Br Med J.* 1996; 312: 885.
  - McManus IC. Drop out rate from medical schools seems reasonable. *Br Med J.* 1996; 313(7050): 173.
  - Wallace M, Berlin A. 'Dropouts' from London medical schools: A comparison with the rest of the United Kingdom. *Health Trends.* 29: 106-8.
  - Bligh J. More medical students for England. *Med Ed.* 2001; 35: 712-713.
  - McManus IC, Smithers E, Partidge P et al. A levels and intelligence as predictors of medical careers in UK doctors: 20 year prospective study. *Br Med J.* 2003; 327: 139-142.
  - Collins JP, White GR, Kennedy JA. Entry to medical school: an audit of traditional selection requirements. *Med Ed.* 1995; 22-6.
  - Whitehouse C. Pre-medicine and selection of medical students. *Med Ed.* 1997; 31(suppl. 1): 3-12.
  - Powis D, Neame RLB, Bristow T, Murphy LB. The objective structured interview for medical student selection. *Br Med J.* 1988; 296: 765.
  - Powis D, Waring TC, Bristow T, O'Connell DL. The structured interview as a tool for predicting premature withdrawal from medical school. *Australian and New Zealand Journal of Medicine.* 1992; 22: 669-698.
  - Arulampalam W, Naylor RA, Smith JP. Dropping out of medical school in the UK: explaining changes over 10 years. *Med Ed.* 41 (No. 4): 385-394.
  - Parry J, Mathers J, Stevens A, Parsons A, Lilford R, Spurgeon P. Admission process for five-year medical courses at English Schools: Review. *Br Med J.* 2006; 332(7548) 1005-8.
  - Powis D. Selecting medical students. *Med Ed.* 1994; 28: 443-469.
  - James D, Yates J, Nicholson S. Comparison of A level and UKCAT performance in students applying to UK medical and Dental schools in 2006: cohort study. *Br Med J.* Feb 2010; 16:1.
  - Lynch B, Mackenzie R, Dowell J, Cleland J, Prescott G. Does the UKCAT predict Year 1 performance in medical school? *Med Ed.* 2009; 43(12): 1203-
  - Greengross S. What patients want from their doctors? In: Allen I, Brown P, Hughes P, Eds. *Choosing Tomorrow's Doctors.* London: Policy Studies Institute, 1997: 12-19.
  - Ferguson E, James D, O'Hehir F, Sanders A. Pilot study of the roles of
  - Personality, references and personal statements in relation to performance
  - Over the five years of a medical degree. *Br Med J.* 2003; 326:429-431.
  - Park J, Philipp R, Hughes A. Do we value work experience before medical School. *British Journal of General Practice.* 2005 March 1; 55(512): 242-243.
  - Henderson E, Berlin A, Fuller J. Attitude of medical students towards general practice and general practitioner. *British Journal of General Practice.* 2002; 52: 359-363.
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## Perineal Necrotising Fasciitis

Stephen O'Neill, Syed Imran Hussain Andrabi and Michael Whiteside

We present a case of a 48-year-old lady with a history of bony metastatic breast carcinoma who presented with abdominal pain, diarrhoea and bleeding per rectum. She had recently finished a course of chemotherapy 2 weeks ago.

On examination, she was febrile with a temperature of 38.4°C. Her blood pressure was 84/54mmHg and pulse rate was 130/min. She had lower abdominal tenderness with bowel sounds present and a small perineal haematoma. Per rectal examination revealed a small amount of fresh blood, but no surrounding crepitus or induration. Rectoscopic examination was not performed.



Fig 1: CT scan of abdomen and pelvis showing free air around rectum

Initial haematological investigations revealed a haemoglobin of 11g/dl, white cell count  $0.3 \times 10^9$ /litre, neutrophil count  $0.05 \times 10^9$ /litre and a C-reactive protein of 171mg/L. A provisional diagnosis of neutropenic sepsis was made. She was managed with analgesia, intravenous fluids and broad spectrum intravenous antibiotics (piperacillin and tazobactam 4.5g 3-times per day). An urgent CT of abdomen and pelvis was

arranged for that morning. It showed rectal wall thickening with air in the pelvis but no tumour or diverticulae (see figure 1).

### Explanation:

Stercoral perforation of the colon is caused by progressive ischemic necrosis of the bowel wall by a faecal mass. It is the least likely diagnosis here as it usually occurs on the antimesenteric border of the sigmoid colon and is usually associated with a history of chronic constipation and megacolon.

Typhlitis is a potentially life threatening inflammatory bowel process that is a recognised complication of systemic chemotherapy. It can progress to bowel necrosis and perforation but is usually characterised by involvement of the caecum or ascending colon and the rectum is rarely involved.

Clostridial gas gangrene infection occurs with tissue inoculation in a low oxygen tension environment. Approximately 80% of patients without trauma have a malignancy of which 40% are hematologic, however the vast majority of cases are preceded by trauma of which there was no history of in this case<sup>1</sup>.

Perineal Necrotizing fasciitis is a rare condition with an estimated 500 cases each year in the UK<sup>2</sup>. It can affect healthy individuals of any age but carcinoma and immunosuppression are known to increase susceptibility<sup>3</sup>. The initial lack of obvious skin findings make this condition difficult to diagnosis but exquisite pain, especially pain that is disproportionate to what would be expected from the clinical findings is seen<sup>2,4</sup>. Where concurrent signs of sepsis exist, a high index of suspicion is required.

As the disease progresses, the skin may begin to appear smooth, shiny and swollen. Blistering and serous bullae may develop, and a haemorrhage into bullae may occur and giving the appearance of a haematoma as in our case. Crepitus, induration and foul smelling watery discharge secondary to liquefactive necrosis can also become apparent<sup>2</sup>. On CT scans, fascial thickening, fat stranding and gas tracking may be seen in nearly 80%<sup>2,5</sup> of cases, and was seen in this case as well.

## Discussion

Necrotizing fasciitis is a lethal soft tissue infection characterised by rapidly progressive inflammation and necrosis of the subcutaneous fascial tissues. The adjacent skin and muscle are relatively spared until late in the course of the disease. Treatment with surgical debridement must be instigated without delay or the patient inevitably succumbs to sepsis and multi-organ failure<sup>2</sup>.

A 24 hour delay in treatment has been shown to increase mortality by 18% and further surgery is usually indicated with an average of 3.8 debridements needed overall<sup>5,6</sup>. Surgical treatment should be instigated in conjunction with broad spectrum intravenous antibiotics and intensive care. The antibiotics selected should be effective against gram-positive, gram negative and anaerobic organisms. Adjuvant therapies like hyperbaric oxygen, intravenous immunoglobulin and activated protein C are of uncertain value.

Following surgery the patient is invariably left with a large tissue defect. Perineal wounds are particularly complex and present multiple challenges including the risk of infection from faecal contamination. Thus diverting colostomies are advised and a Vacuum Assisted Closure (VAC) system may facilitate wound healing<sup>5</sup>.

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## Competing Interests

None declared

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## REFERENCES

1. San Ildefonso A, Maruri I, Facal C, Casal E. Clostridium septicum infection associated with perforation of colon diverticulum. *Rev Esp Enferm Dig* 2002;94(6):361-6.
2. Hasham S, Matteucci P, Stanley PR, Hart NB. Necrotising fasciitis. *BMJ* 2005;330(7495):830-3.
3. Kumar S, O'Donnell ME, Khan K, Dunne G, Carey PD, Lee J. Successful treatment of perineal necrotising fasciitis and associated pubic bone osteomyelitis with the vacuum assisted closure system. *World J Surg Oncol* 2008;6:67.
4. Young MH, Aronoff DM, Engleberg NC. Necrotizing fasciitis: pathogenesis and treatment. *Expert Rev Anti Infect Ther* 2005;3(2):279-94.
5. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. *Ann Surg* 1996;224(5):672-83.
6. Wong CH, Chang HC, Pasupathy S, Khin LW, Tan JL, Low CO. Necrotizing fasciitis: clinical presentation, microbiology, and determinants of mortality. *J Bone Joint Surg Am* 2003;85-A(8):1454-60.

## Interview with Prof Robert Moots

Robert Moots is Professor of Rheumatology at the University of Liverpool and Director for Research and Development at the University Hospital, Aintree. He is also a Consultant Rheumatologist at the hospital.

He graduated from St Mary's Hospital, London University in 1985 and also worked at Harvard Medical School. He became a Consultant Rheumatologist at University Hospital Aintree in 1997 and the youngest full-time professor of Rheumatology and Head of Department in 2003.

Professor Moots has published extensively in rheumatology, winning the prestigious Michael Mason prize for rheumatology research. He advises the UK Department of Health and NICE. His research interests are inflammatory rheumatic diseases, in particular innate cellular immunity in rheumatoid arthritis, immunotherapy, new therapeutic targets and clinical trials.

### **How long have you been working in your speciality?**

I've been working as a consultant in rheumatology since 1997, when I returned to the UK from the USA. Of course I was a trainee in rheumatology for a few years before then.

### **Which aspect of your work do you find most satisfying?**

It's hard to single out any one thing. The great fun of being Professor is that no two days are the same. My job varies so much from looking after patients, to teaching, running research and also communicating and sharing research findings with other clinicians and scientists throughout the world – giving me the opportunity to visit countries, where I would not normally have visited.

### **What achievements are you most proud of in your medical career?**

Clinically, I often deal with rare rheumatic diseases, or situations where normal treatments have failed and other doctors have said there is "no more that can be done". Each patient that I see in this situation, who then goes on to recover and have a normal happy life, gives me a great satisfaction. Academically, building up a successful research team of talented individuals in Liverpool, the first academic rheumatology unit in that city, has been a great privilege.

### **Which part of your job do you enjoy the least?**

Trying to balance the demands of patient care with the many other calls on my time can be rather wearing. But nothing is worse than the ever expanding administration tasks and bureaucracy!

### **What are your views about the current status of medical training in your country and what do you think needs to change?**

When I visit other countries to lecture, I always try to see how medicine runs there. I attend clinics and hospitals, see patients and learn how practice compares to the UK. I am pleased to note that the standard in the UK remains amongst the highest of all countries.

### **How would you encourage more medical students into entering your speciality?**

It's hard to imagine why students and doctors could consider any specialty other than Rheumatology! Rheumatology provides the opportunity to see patients of all ages, develop a close rapport with patients as the diseases tend to be chronic and prevalent, perform cutting edge research to understand pathophysiological process underlying the diseases and access drugs that can make a revolution to lives with great outcomes.

### **What qualities do you think a good trainee should possess?**

Be keen to learn, open, honest and bright. I also like trainees to challenge accepted wisdom – a considered critical approach is needed to move things forward and to keep us on our toes.

### **What is the most important advice you could offer to a new trainee?**

Don't accept non-evidence based dogma. Don't learn bad habits. Be critical and try to improve things. Try to spend some time away from your unit and ideally out of your country – seeing how medicine works in other environments to get life and work in a better perspective.

### **What qualities do you think a good trainer should possess?**

Good trainers should be excellent clinicians, inspirational leaders and listeners with patience. If you know someone like this, you should really treasure them!

**Do you think doctors are over-regulated compared with other professions?**

No – but I fear that we are getting there in the UK.

**Is there any aspect of current health policies in your country that are de-professionalising doctors? If yes what should be done to counter this trend?**

With a recent change in government in the UK and major changes to the Health Service planned, it's a little too early to tell. We have to be vigilant though.

**Which scientific paper/publication has influenced you the most?**

For much of my working life, I was focused on the T cell as the major driver for diseases such as rheumatoid arthritis. The paper that changed that was: Edwards SW, Hallett MB. Seeing the wood for the trees: the forgotten role of neutrophils in rheumatoid arthritis. *Immunol Today*.1997 Jul;18(7):320-4. This crucial paper from Steve Edwards, the world leader in neutrophil biology opened my eyes to a whole new field of work. I didn't know at the time that I would eventually have the privilege of working with Steve.

**What single area of medical research in your specialty should be given priority?**

That's an easy one – it should be whatever my group are working on at the time.(I just wish that were the case!)

**What is the most challenging area in your specialty that needs further development?**

Many rheumatic diseases such as rheumatoid arthritis can be treated extremely successfully (with patients enjoying a full remission) if they can access the right drugs at the right time. There is still much variability in time to diagnosis and in provision of appropriate medications – the challenge is to ensure that best practice can be rolled out more effectively.

**Which changes would substantially improve the quality of healthcare in your country?**

There needs to be a greater understanding of the importance of rheumatic diseases in the UK. These conditions are prevalent, may cause significant morbidity (and indeed mortality), cost the nation considerably in reduced productivity and in disability payments – yet many of these conditions can be treated most effectively.

**Do you think doctors can make a valuable contribution to healthcare management? If so how?**

Its crucial that doctors are fully engaged in management. We are in the best position to be advocates for our patients but cannot do this effectively without understanding the health care system and take the lead in ensuring this works for the best.

**How has the political environment affected your work?**

The consequences of the recent change in Government in the UK are likely to be considerable for the National Health Service. This will involve major changes to the work of staff at all levels. It is too early to know the full extent of this – but we all wait with trepidation

**What are your interests outside of work?**

With so much to do, its hard to find the time for much else apart from relaxing with my family. I travel a lot and especially enjoy taking my children with me. My 10 year old has heard me lecture so much that I suspect she can give my talk for me (and do it better). She has also taken to asking questions at the end of my lecture, which always scares the chairperson of the meeting!

**If you were not a doctor, what would you do?**

I'm not sure that I would be fit for anything else!