EASILY MISSED?

Motor neurone disease

Saiji Nageshwaran,[1] Lucy Medina Davies,[2] Imran Rafi,[1 2] Aleksandar Radunović[3]

[1]Department of Population Health Sciences and Education, St George's, University of London, London SW17 0RE, UK
[2]Clinical Innovation and Research Centre, Royal College of General Practitioners, London, UK
[3]Barts Motor Neurone Disease Centre, Royal London Hospital, London, UK
Correspondence to: S Nageshwaran saiji@doctors.org.uk

Cite this as: *BMJ* 2014;349:g4052
doi: 10.1136/bmj.g4052

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. To suggest a topic, please email us at practice@bmj.com

thebmj.com

Previous articles in this series

- Bladder cancer in women (*BMJ* 2014;348:g2171)
- Intestinal malrotation and volvulus in infants and children (*BMJ* 2013;347:f6949)
- Copper deficiency (*BMJ* 2014;348:g3691)
- Subdural haematoma in the elderly (*BMJ* 2014;348:g1682)
- Lisfranc injuries (*BMJ* 2013;347:f4561)

A 59 year old man initially presented with weakness in his right leg and occasional trips. He had a longstanding history of mild low back pain and had a magnetic resonance image performed under the orthopaedic team that showed some cervical spondylolisthesis sparing the spinal cord. Four months after this, he went back to the general practitioner with progressive difficulty buttoning his shirt.

What is motor neurone disease?

Motor neurone disease is a devastating, incurable neurodegenerative disease of the motor neurones that primarily affects people in their 60s or 70s.[1] Of the four subtypes of motor neurone disease, the most common is amyotrophic lateral sclerosis.[2] The subtypes vary clinically because they predominately affect different areas and have varying rates of progression.

Why is motor neurone disease missed?

Although motor neurone disease is a relatively well known rare disease, most GPs will diagnose only one or two cases in their career. There is a lack of awareness of the symptoms at presentation, when symptoms are often subtle.[3] The disease affects different anatomical regions, and it is estimated that about half of all patients with motor neurone disease are initially referred to non-neurology secondary care clinics. These are typically ear, nose, and throat clinics, because of bulbar symptoms such as dysarthria, and orthopaedics because of limb symptoms such as foot drop, which are often attributed to damage from spinal disease. A lack of continuity of care can compound the delay in diagnosis further,[3] because it is the progressive and multisystem nature of the symptoms that are the most indicative of the diagnosis.

The diagnosis is a difficult clinical one, and rates of misdiagnosis are high outside motor neurone disease specialist centres. Therefore, it is recommended that if motor neurone disease is suspected, doctors refer urgently directly to someone with a special interest in the disease.

Why does this matter?

The median survival for patients with motor neurone disease has been reported as 30 months but varies with subtype.[2 3] The diagnostic delay thus represents a substantial proportion of patients' overall survival. Treatments that modify the disease and support services are available for patients once a diagnosis is made, so it important to recognise the symptoms and signs early. Good clinical care of symptoms through specialist multidisciplinary teams and motor neurone disease centres improves both quality of life and life expectancy.

How is motor neurone disease diagnosed?

Clinical features

Motor neurone disease causes a painless progressive weakness. It is helpful to think of symptoms in terms of systems affected.

Limb involvement is present at onset in about 70% of patients.[4] This can be subtle, with a mild foot drop or a loss of manual dexterity leading to trips and difficulty with buttons or jar lids, respectively. On examination, there is a mixture of upper and motor neurone signs. Wasting and fasciculations can be seen.

At presentation, 20% of patients have bulbar features,[4] with dysarthria usually preceding dysphagia. Patients might also mention excessive salivation or a choking sensation when lying flat. Patients' voices can become weak and slurred, particularly when tired.

Respiratory involvement tends to be a late feature of motor neurone disease. Chest wall weakness causes hypoventilation and carbon dioxide retention, resulting in type II respiratory failure. This can present as lethargy, early morning headache, or dyspnoea.

Cognitive symptoms, especially changes in behaviour such as apathy and loss of social awareness, might be present at diagnosis and are increasingly recognised as important.[4 5]

Investigations

Neurophysiological studies—for example, electromyography and nerve conduction studies—and magnetic resonance imaging are often used as an adjunct to diagnosis and to exclude differential diagnoses. The diagnosis is largely clinical, however, and is usually made by an experienced neurologist.[1 2 5]

How is motor neurone disease managed?

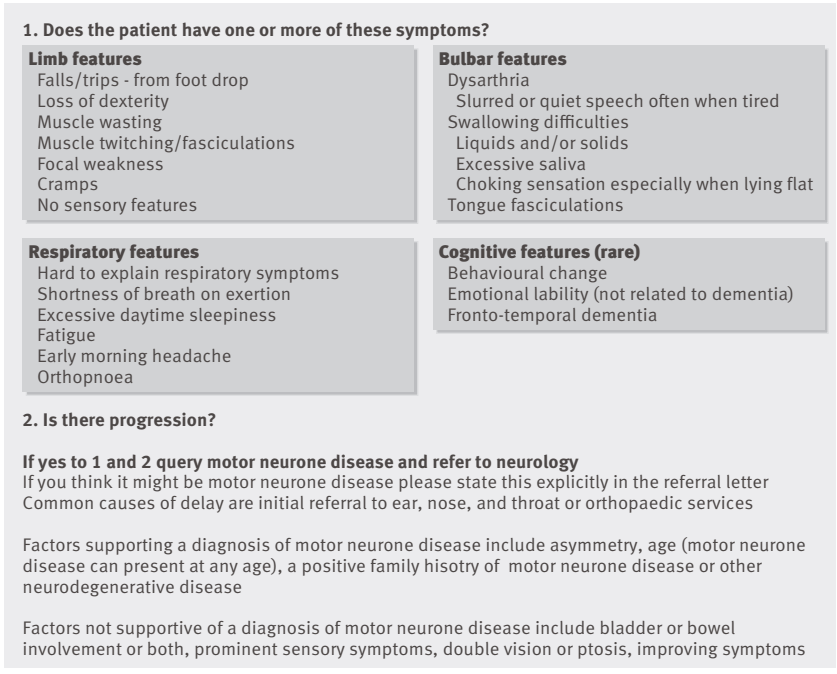
Urgent referral of patients with symptoms and signs suggestive of motor neurone disease to a neurologist (see figure), preferably one within the motor neurone disease care

KEY POINTS

- Motor neurone disease is relatively rare and should be considered in patients presenting with painless progressive weakness or progressive dysarthria
- Awareness of the limb, bulbar, respiratory, and cognitive features of motor neurone disease might help reduce diagnostic delay
- If suspected, refer urgently for specialist neurology review
- A multidisciplinary team approach to care is required once the diagnosis is made

HOW COMMON IS IT?

- The incidence of amyotrophic lateral sclerosis is estimated to be 2.6 per 100 000 person years across Europe[2]
- A GP working full time for 30 years might expect to see one or two cases in his or her career[1 2]
- Diagnostic delays of 12-19 months from presentation have been reported. Two retrospective studies involving 130 patients showed that 27-61% of patients eventually diagnosed with motor neurone disease had been misdiagnosed, contributing to about 9-13 months of this delay[3]



Features suggestive of motor neurone disease. The figure is adapted from an algorithm created by the Royal College of General Practitioners with the Motor Neurone Disease Association, which is based on expert consensus of opinion from clinicians in the field[6]

centre, is crucial so that a multidisciplinary team approach to their care can be initiated if necessary. Riluzole, a glutamate release antagonist, and non-invasive ventilation are currently the only treatments for motor neurone disease approved by the National Institute for Health and Care Excellence.[7] A Cochrane review (four randomised controlled trials involving 1477 patients) concluded that riluzole probably prolongs survival by two or three months[8]; another Cochrane review (one randomised clinical trial, 41 patients) suggests that non-invasive ventilation prolongs survival (perhaps by many months) and improves or maintains quality of life in those with better bulbar function.[9] GPs have an important role as care coordinators once the diagnosis is made. This includes identifying and treating symptoms, supervising treatment, facilitating frank discussions about end of life care and advanced decisions, and making referrals to palliative and other community services.[1 2 10 11]

DELAYS IN DIAGNOSIS FROM A PATIENT'S PERSPECTIVE

"I just need to know now, I'm really struggling to work but until I get a diagnosis I can't afford to just stop working. I know it sounds silly but now I've stopped crying and, as the prof said, we are one step away from knowing. I feel like I'm close to getting control back. Not that I want it to be MND [motor neurone disease] because it's almost like a death sentence, but not knowing is like a living hell that, for me, is worse."

Contributors: SN and LMD prepared the first and final draft of this article. IR and AR revised the article, adding necessary general practice and neurology input, respectively. We have all approved the final version and accept accountability for the work.
Competing interests: We have read and understood the BMJ policy on declaration of interests and have no relevant interests to declare.
Provenance and peer review: not commissioned; externally peer reviewed.
Patient is hypothetical.

1 McDermott CJ, Shaw PJ. Diagnosis and management of motor neurone disease. *BMJ* 2008;336:658-62.
2 Hardiman O, van den Berg LH, Kiernan MC. Clinical diagnosis and management of amyotrophic lateral sclerosis. *Nat Rev Neurol* 2011;7:639-49.
3 Mitchell JD, Callagher P, Gardham J, Mitchell C, Dixon M, Addison-Jones R, et al. Timelines in the diagnostic evaluation of people with suspected amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)—a 20-year review: can we do better? *Amyotroph Lateral Scler* 2010;11:537-41.
4 Leigh PN, Abrahams S, Al-Chalabi A, Ampong M, Goldstein L, Johnson J, et al. The management of motor neurone disease. *J Neurol Neurosurg Psychiatry* 2003;74:iv32-iv47.
5 Turner MR, Talbot K. Mimics and chameleons in motor neurone disease. *Pract Neurol* 2013;13:153-64.
6 Royal College of General Practitioners. Rare diseases red flags toolkit: painless, progressive weakness—could this be motor neurone disease? www.rcgp.org.uk/clinical-and-research/clinical-resources/~/media/Files/CIRC/Rare%20Diseases/RCGP-Red-Flags-Final-Nov-13.ashx.
7 National Institute for Health and Care Excellence. Guidance on the use of riluzole (Rilutek) for the treatment of motor neurone disease. 2001. www.nice.org.uk/nicemedia/live/11415/32139/32139.pdf.
8 Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2012;3:CD001447.
9 Radunovic A, Annane D, Rafiq MK, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2013;3:CD004427.
10 National Institute for Health and Care Excellence. Motor neurone disease: the use of non-invasive ventilation in the management of motor neurone disease. 2010. www.nice.org.uk/nicemedia/live/13057/49885/49885.pdf.
11 Radunovic A, Mitsumoto H, Leigh PN. Clinical care of patients with amyotrophic lateral sclerosis. *Lancet Neurol* 2007;6:913-25.

Accepted: 21 May 2014

UNCERTAINTIES PAGE

What is the optimal pharmacological management of retained placenta?

James M N Duffy,[1] Matthew J A Wilson,[2] Khalid S Khan[3]

[1]Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]School of Health and Related Research, University of Sheffield, Sheffield, UK
[3]Women's Health Research Unit, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, UK
Correspondence to: J M N Duffy
james.duffy@balliol.ox.ac.uk

Cite this as: *BMJ* 2014;349:g4778
doi: 10.1136/bmj.g4778

The third stage of labour is the period between childbirth and delivery of the placenta. It can be managed physiologically, with early cord clamping, cutting of the cord, and controlled cord traction, or it can be managed actively, with the addition of prophylactic oxytocics (oxytocin 10 IU intramuscularly). In the United Kingdom, the National Institute of Health and Care Excellence (NICE) defines the third stage of labour as prolonged if the placenta is retained after 30 minutes of active management or 60 minutes of physiological management.[1] Retained placenta affects 0.1-3.3% of births, depending on the population studied.[2]

The incidence of retained placenta is rising because an increasing number of women with risk factors, including advancing maternal age and previous caesarean section, are giving birth.[3] Retained placenta can result in severe maternal morbidity, including life threatening haemorrhage and sepsis.

Drugs, such as intraumbilical or intravenous oxytocin, are often used in the management of placental retention. Oxytocics cause myometrial contraction, which generates a shearing force that detaches the placenta from the uterine wall. However, after placental detachment, cervical

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com.

thebmj.com

Previous articles in this series

- Should we advise patients with sutures not to swim? (*BMJ* 2014;348:g3171)
- Whom should we "test and treat" for *Helicobacter pylori*? (*BMJ* 2014;348:g3320)
- Should doctors prescribe cannabinoids? (*BMJ* 2014;348:g2737)
- Is adrenaline safe and effective as a treatment for out of hospital cardiac arrest? (*BMJ* 2014;348:g2435)
- What is the most effective operation for adults with severe and complex obesity? (*BMJ* 2014;348:g1763)

constriction may trap the placenta within the uterus. Smooth muscle relaxants (such as glyceryl trinitrate) can release this entrapment and allow placental delivery. In practice, a variety of the drugs are used.

Despite active pharmacological management, if a retained placenta is not delivered, the placenta must be removed manually. This invasive surgical procedure physically removes the placenta from the uterine cavity and requires regional or general anaesthesia. The procedure can be complicated by haemorrhage, pain, infection, uterine inversion or perforation, and their sequelae. In the absence of bleeding, the timing of this intervention varies considerably. In Spain, obstetricians perform the procedure at 30 minutes, in the UK NICE recommends that it is carried out at 60 minutes, whereas in Dutch hospitals obstetricians wait 60 minutes or more.[4] The natural course of retained placenta suggests that placentas that remain in situ 60 minutes after delivery of the baby will remain undelivered if a further 30 minutes is allowed to elapse.[2]

What is the evidence of the uncertainty?

We searched Embase, Medline, the Cochrane Library, and the Current Clinical Trials databases from database inception to July 2014 to identify published and ongoing randomised controlled trials (RCTs) and systematic reviews on the effectiveness and safety of drugs for the management of retained placenta.

Intraumbilical oxytocin

Current NICE guidelines recommend the use of an oxytocin infusion, given through the placental umbilical vessels, to increase myometrial contraction when the placenta is undelivered at 30 minutes after childbirth.[1] This recommendation was based on a review that found a reduction in the rate of manual removal compared with placebo (relative risk 0.82, 95% confidence interval 0.67 to 1.00; nine RCTs, 650 participants).[1] However, after this guideline was produced, a high quality RCT that compared intraumbilical oxytocin with placebo found no significant difference in rates of manual removal of the placenta (0.98, 0.87 to 1.12; 577 participants).[5] When the review was updated with these new data, no significant difference was seen in rates of manual removal (0.85, 0.72 to 1.00; 10 RCTs; 1227 participants) (table).[6] There were also no significance differences in postpartum haemorrhage, defined as estimated blood loss over 0.5 L (1.03, 0.73 to 1.47; five RCTs; 860 participants); infection (1.33, 0.93 to 1.91; three RCTs; 577 participants); or surgical evacuation of retained products of placenta (0.89, 0.55 to 1.42; two RCTs; 814 participants).[6] Unfortunately, intravenous infusion of oxytocin, although common practice, has not been evaluated in RCTs.

Intraumbilical, intravenous, and oral prostaglandin

Other drugs to increase myometrial contraction that act on uterine receptors, including prostaglandins, have not been as rigorously scrutinised (table). A small RCT found no reduction in the need for manual removal of the placenta when intraumbilical prostaglandin was compared with placebo (0.91, 0.62 to 1.33; 99 participants; table). The trial reported no significance difference in postpartum haemorrhage, defined as estimated blood loss over 1 L (0.80, 0.50 to 1.27) but did not report infection, surgical evacuation of retained products of the placenta, or maternal mortality. A small RCT found no reduction in the need for manual removal of the placenta when intravenous prostaglandin was compared with placebo (1.20, 0.67 to 2.16; 95 participants; table). The trial reported no significance difference in postpartum haemorrhage, defined as estimated blood loss over 1 L (0.80, 0.44 to 1.46) but did not report infection, surgical evacuation of retained products of the placenta, or maternal mortality. A meta-analysis of two small RCTs of oral misoprostol, a synthetic prostaglandin, found a reduction in the need to perform manual removal compared with placebo (0.61, 0.41 to 0.90; 84 participants).[4] However, other relevant outcomes including postpartum haemorrhage, infection, surgical evacuation of retained products of placenta, and maternal mortality were not reported.

RECOMMENDATIONS FOR FURTHER RESEARCH

Participants: Women diagnosed with retained placenta after active or physiological management of the third stage of labour

Interventions and comparisons: Intervention that promotes uterine contraction (such as intravenous oxytocin or intraumbilical prostaglandin), followed by a second line intervention that promotes uterine and cervical relaxation (such as oral or sublingual nitroglycerin) if needed. The comparator should be standard care based on current practice (intraumbilical oxytocin)

Outcome: Primary: delivery of the placenta within 60 minutes, avoiding the need for manual removal of the placenta. Secondary: postpartum haemorrhage, adverse events, and side effects

Design: Multi-centre randomised controlled trial with factorial design

Meta-analysis of the effectiveness and safety of interventions to treat retained placenta[4 6-9]

Trials and outcomes	RCTs (N)	Participants	RR (95% CI)	P value
Intraumbilical oxytocin *v* placebo				
Manual removal of the placenta	10	1227	0.85 (0.72 to 1.00)	0.06
Postpartum haemorrhage (estimated blood loss >0.5 L)	5	860	1.03 (0.73 to 1.47)	0.86
Postpartum haemorrhage (estimated blood loss >1 L)	2	707	1.11 (0.71 to 1.74)	0.66
Infection	3	814	1.33 (0.93 to 1.91)	0.12
Surgical evacuation of retained products of the placenta	2	761	0.89 (0.55 to 1.42)	0.62
Maternal mortality	5	782	2.93 (0.12 to 71.59)	0.51
Intraumbilical prostaglandin *v* placebo				
Manual removal of the placenta	1	99	0.91 (0.62 to 1.33)	0.63
Postpartum haemorrhage (estimated blood loss >1 L)	1	99	0.80 (0.50 to 1.27)	0.34
Intravenous prostaglandin *v* placebo				
Manual removal of the placenta	1	95	1.20 (0.67 to 2.16)	0.54
Postpartum haemorrhage (estimated blood loss >1 L)	1	95	0.80 (0.44 to 1.46)	0.46
Oral prostaglandin *v* placebo				
Manual removal of the placenta	2	84	0.61 (0.41 to 0.90)	0.01
Intravenous glyceryl trinitrate *v* placebo				
Manual removal of the placenta	1	40	1.06 (0.80 to 1.41)	0.68
Surgical evacuation of retained products of the placenta	1	40	7.00 (0.38 to 127.32)	0.19
Intravenous oxytocin then sublingual glyceryl trinitrate *v* placebo				
Manual removal of the placenta	2	135	0.66 (0.51 to 0.86)	0.002
Postpartum haemorrhage (estimated blood loss >1 L)	1	111	1.88 (1.07 to 3.30)	0.03

CI=confidence interval; RCT=randomised controlled trial; RR=relative risk.

Intravenous glyceryl trinitrate

A small RCT found no reduction in the need for manual removal of the placenta when intravenous glyceryl trinitrate was compared with placebo (1.06, 0.80 to 1.41; 40 participants; table). The trial reported no significance difference in surgical evacuation of retained products of placenta (7.00, 0.38 to 127.32) but did not report postpartum haemorrhage, infection, surgical evacuation of retained products of the placenta, or maternal mortality.

Intravenous oxytocin combined with intravenous or sublingual glyceryl trinitrate

Two small RCTs have evaluated a strategy of using intravenous oxytocin to induce uterine contraction, followed by intravenous or sublingual glyceryl trinitrate to induce uterine and cervical relaxation. Meta-analysis showed lower rates of manual removal of the placenta, although higher rates of postpartum haemorrhage were observed (table). The included RCTs did not report infection, surgical evacuation of retained products of the placenta, or maternal mortality.

Is ongoing research likely to provide relevant evidence?

There is genuine uncertainty regarding drug treatments for the management of retained placenta. The box outlines the most relevant research needed to answer these questions. RCTs evaluating the effectiveness of drug treatments are feasible, but no such trials have been registered with the World Health Organization (WHO) International Clinical Trials Registry.

What should we do in the light of uncertainty?

Despite the uncertainty about the optimal management of retained placenta, WHO recommends the use of intraumbilical oxytocin infusion at diagnosis and manual removal of the placenta if retention persists.[10] If placenta accreta is thought to be the cause of retention, management should be in accordance with existing guidelines, including consideration of intrauterine balloon tamponade, pelvic embolisation, and hysterectomy.[11] Because there is currently no robust evidence to recommend any individual drug treatment, clinicians should participate in suitable clinical studies to identify the optimum management.

The authors are grateful to Sophie Mylan (foundation doctor, Barts and the London School of Medicine and Dentistry), who helped with data collection and analysis, and Marian Showell (trials search coordinator, Cochrane Menstrual Disorders and Subfertility Group), who helped develop the literature search strategy.

Contributors: The authors contributed equally to the conception, design, and interpretation of the data. All helped critically revise the manuscript and approve the final version. KSK is guarantor.

Competing interests: None declared.

1 National Institute for Health and Care Excellence. Intrapartum care. CG55. 2007. www.nice.org.uk/guidance/cg55.
2 Weeks AD. The retained placenta. *Best Pract Res Clin Obstet Gynaecol* 2008;22:1103-17.
3 Combs CA, Laros RK Jr. Prolonged third stage of labor: morbidity and risk factors. *Obstet Gynecol* 1991;77:883-67.
4 Stralen G, Veenhof M, Holleboom C, van Roosmalen J. No reduction of manual removal after misoprostol for retained placenta: a double-blind, randomized trial. *Acta Obstet Gynecol Scand* 2013;92:398-403.
5 Weeks AD, Alia G, Vernon G, Namayanja A, Gosakan R, Majeed T, et al. Umbilical vein oxytocin for the treatment of retained placenta (Release study): a double-blind, randomised controlled trial. *Lancet* 2010;375:141-7.
6 Nardin JM, Weeks A, Carroli G. Umbilical vein injection for management of retained placenta. *Cochrane Database Syst Rev* 2011;5:CD001337.
7 Bullarbo M, Bokstrom H, Lilja H, Almström E, Lassenius N, Hansson A, et al. Nitroglycerin for management of retained placenta: a multicenter study. *Obstet Gynecol Int* 2012;2012:321207.
8 Bullarbo M, Tjugum J, Ekerhovd E. Sublingual nitroglycerin for management of retained placenta. *Int J Gynaecol Obstet* 2005;91:228-32.
9 Visalyaputra S, Prechapanich J, Suwanvichai S, Yimyam S, Permpolprasert L, Suksopee P. Intravenous nitroglycerin for controlled cord traction in the management of retained placenta. *Int J Gynaecol Obstet* 2011;112:103-6.
10 WHO Reproductive Health Library. Umbilical vein injection for management of retained placenta: RHL commentary. 2012. http://apps.who.int/rhl/archives/mpcom/en/index.html.
11 Royal College of Obstetricians and Gynaecologists. Placenta praevia, placenta praevia accreta and vasa praevia: diagnosis and management. 2011. www.rcog.org.uk/files/rcog-corp/GTG27PlacentaPraeviaJanuary2011.pdf.

Accepted: 4 July 2014

ALL THINGS CONSIDERED

Seasickness: the bane of cruises

"I should never have come on this cruise," she groaned. "It was my husband who wanted us to go. I hate ships and loathe the sea, and now I feel sooo ... ill." This is Stage 1, or mild seasickness—nausea accompanied by self pity and, most importantly, the conviction that it is all someone else's fault.

In Stage 2, moderate seasickness, I am called out in the night to a darkened cabin where, as the ship gently rolls along, I can see the huddled shadow of a human form crumpled in the bed. "Get me off this ship," they moan between bouts of retching. "I don't care what it costs—charter me a helicopter—whatever it takes." Meanwhile, their partner stands in the corner of the cabin wringing their hands at the misery they have caused by booking this cruise, and the expense that they think is about to be incurred by a medical evacuation.

Stage 3 is the full monty. The patient is now quite still and has come to terms with their imminent demise. "Doc," they whisper, as if we are acting out the finale of a Jane Austen novel, "I just want this all to be over as quickly and painlessly as possible." They may have only vomited half a dozen times, but the soul is broken and the spirit is ready to depart.

We know very little about what does and does not work for seasickness, except that ondansetron, so valuable in hospital, is ineffective.

On one of our rougher cruises I saw little of the passengers for the first days apart from a glimpse of gluteals in a darkened cabin as I raced from door

to door giving injections. On day three, as we sailed serenely through calm seas, I came to sit with four rather redoubtable women who had at last appeared for dinner. I introduced myself as the ship's doctor. "Oh, but we know you," they chorused together. "You came and gave us injections last night."

Embarrassed by my lapse in memory, I spoke before I had time to think. "Yes," I replied, "but I fear that I know you all better by your buttocks than your faces."

There was a horrid moment of silence as the implication of my remark sank in and then, thank heavens, they all had the grace to laugh.

Christopher Bulstrode
emeritus professor of trauma and orthopaedics, Stanton St John, Oxfordshire, UK
Christopher.bulstrode@ndorms.ox.ac.uk

Cite this as: *BMJ* 2013;346:f3753