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Anti-microbial stewardship for urinary tract infection

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The current public concern about methicillin resistant *Staphylococcus aureus* (MRSA) has yet to extend to antibiotic resistance in general and its relationship to our stewardship of anti-microbial use. Since the 1970s, there has been an increase in both the number of anti-microbial prescriptions and in the preference for broad-spectrum agents. In Ireland in primary care, we are better than some but are worse than other European countries. Irish defined daily doses of antibiotic are 20 per 1,000 inhabitants, compared with 15 per 1,000 in the UK, 10 per 1,000 in the Netherlands and 32.2 per 1,000 in France.[1] Overall, anti-microbial resistance is lowest in the Nordic countries and Austria and highest in Portugal and Spain.

Whereas we all believe in the least toxic, least expensive agent with the narrowest spectrum of activity for the shortest possible time and in the avoidance of anti-microbial agents for viral infections, most of us break these principles repeatedly. Reasons may include pressure from patients to prescribe for all possible infections, marketing by pharmaceutical companies and a perceived need to cover all possibilities with empiric broad-spectrum therapy in all febrile patients in a litigious society. Provision of timely culture and sensitivity data should allow for better antibiotic stewardship. However, in hospital practice in some instances, it paradoxically can lead to broader spectrum therapy to cover all reported isolates, even when these culture results are of commensals or contaminants. We need greater wisdom and restraint in anti-microbial prescription or we will end up in a post-antibiotic age. For urinary tract infection (UTI), common errors include poor selection of agents, in appropriate therapy of asymptomatic bacteriuria in the elderly and in catheterised patients and failure to choose short course therapy for women with cystitis.

Anti-microbial therapy for community-acquired UTI in most instances must be given empirically, so knowledge of local anti-microbial sensitivity patterns is essential for general practitioners. In this issue, Ni Chulain et al provide valuable data on *in-vitro* susceptibilities to anti-microbial agents for consecutive urinary isolates of *Escherichia coli* (almost 1,000), in the West of Ireland over a defined time period. The majority (77.1%) were from general practice. Mid-stream urine (MSU) from patients with repeated difficulties with UTI may have been preferentially submitted, leading to an overestimation of the true prevalence of resistance. Pyuria and clinical findings are not reported, so some contaminants may have been included, due to delay in transport and failure to refrigerate. Despite these caveats, the paper provides a valuable description of *in vitro* resistance that should influence anti-microbial prescribing for UTI, in the context of a need to improve antibiotic stewardship.

This paper reports that more than 50% of *E. coli* are resistant to ampicillin and amoxycillin, more than 40% are resistant to sulphonamides and 30% to trimethoprim and to tetracycline. Although therapy may still succeed for lower tract infection in some cases in the face of *in-vitro* resistance, due to high and prolonged urinary excretion (as much as 50% success in the case of trimethoprim),[2] these agents can no longer be relied upon for UTI, in the absence of a definitive MSU report showing that the pathogen is susceptible.

For co-amoxiclav, resistance rates varied from 7.9% in the community to 12.5% in hospital, with approximately one in five of the total exhibiting intermediate susceptibility. Co-amoxiclav can still be relied upon in most instances, but it is likely that the prevalence of resistance will increase in the near future above a threshold of 20%, at which time it will also have to be abandoned for empiric use in UTI. As a beta-lactam, it has disadvantages that go beyond *in-vitro* susceptibility, in that clinical studies have shown that penicillins and cephalosporins have higher failure rates in comparison to non-cell wall active agents, even when the isolate is fully sensitive. The relationship between *in-vitro* susceptibility and clinical response in UTI is not straightforward. Randomised controlled comparisons of beta-lactam agents to non-cell wall active agents have consistently shown the superiority of the latter for UTI, and *in vitro* susceptibilities do not explain the variation. This comparison holds up when nalidixic acid is compared to cephalexin,[3] when amoxycillin is compared to co-trimoxazole,[4] and when ciprofloxacin is compared to co-amoxiclav.[5] This concept derived

from randomised controlled trials does not influence anti-microbial choice for UTI in Ireland at present.

The ciprofloxacin resistance rate of 6% in hospital isolates and 2.5% in the community also indicates that fluoroquinolones can be relied upon empirically in most instances. However we are concerned that the effectiveness of this valuable class of anti-microbial agents will also be lost. In the USA, ciprofloxacin was the only agent that demonstrated a consistent stepwise increase in resistance in urinary isolates from 1995 (0.7%) to 2001 (2.5%).[6] Similarly in the Netherlands, resistance to norfloxacin increased from 1.3% in 1989 to 5.8% in 1998.[7] Rates of resistance to community UTI isolates have reached 17% in Italy,[8] 25% in Turkey[9] and 23% in Spain.[10]

This increasing resistance to fluoroquinolones may result in the loss of a very valuable anti-microbial agent, especially for patients with life-threatening infections. Efforts should therefore be made to curtail fluoroquinolone use. More widespread use of fluoroquinolones for UTI may add to pressures resulting from their increasing use for respiratory tract infection. Used either alone or with penicillin, fluoroquinolones are justified for community-acquired pneumonia (CAP) of moderate or greater severity, but not for mild pneumonia, bronchitis, exacerbation of chronic obstructive pulmonary disease (COPD) and sinusitis. In UTI, their use should be limited to septic patients with moderate to severe pyelonephritis. For these patients admission to hospital and an additional agent such as an aminoglycoside is also justified, while awaiting the results of blood and urine cultures in the emergency room. For others with cystitis or mild or silent upper tract infection without sepsis, alternatives are strongly encouraged, of which older, less expensive urinary antiseptics should take precedence. It is not generally appreciated that nalidixic acid is a quinolone.[11] If resistance is selected for it, then in some but not all cases, this will spill over to ciprofloxacin, ofloxacin and moxifloxacin.

In contrast, nitrofurantoin does not share cross-resistance with more commonly prescribed anti-microbial agents. The consistent susceptibility of *E. coli* to nitrofurantoin may be due to nitrofurantoin's narrow spectrum of activity, limited indication (treatment of acute cystitis), narrow tissue distribution (low or undetectable serum concentrations), and limited contact with bacteria outside the urinary tract. It has the advantage of low cost, good tolerability, and safety in pregnancy. Efficacy has been well demonstrated for nitrofurantoin in clinical studies. Disadvantages include its four times per day administration and that it is not effective for the patient with bacteraemia.

Fosfomycin also had good clinical trials to validate its use, with very good response rates and consistently very low *in-vitro* resistance rates internationally, but was discontinued some time ago in Ireland.[12, 13]

In women with lower tract symptoms, who are without fever or renal tenderness, short course therapy of three days duration or even single dose therapy will suffice. Women with bladder symptoms of greater than seven days duration or who have had a recent failure of therapy for UTI are at risk of silent upper tract infection and, like men, should be treated for seven to 10 days.[14]

Symptomatic lower urinary tract infection (cystitis) will occur at least once in about one third of all adult women. A rare minority will have such frequent relapses that continuous prophylaxis is justified. In contrast to adult males and children, the proportion with underlying structural disorders of the renal tract is so low that referral for urological evaluation and imaging of the upper tract should be limited only to those women who have had a relapse of pyelonephritis.

In elderly patients of both sexes, asymptomatic bacteriuria is much more frequent than symptomatic UTI and should not be treated. There is a high frequency of spontaneous cure and re-infection. Anti-microbial therapy will not alter this and is only recommended if the patient has symptoms. In contrast asymptomatic bacteriuria in children or in pregnant women should be treated, if confirmed on a repeat MSU. Asymptomatic catheter-acquired UTI should not be treated as this will lead to emergence of more resistant organisms.

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Antimicrobial resistance in *E. Coli* associated with urinary tract infection in the West of Ireland

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ABSTRACT

Background Knowledge of antimicrobial resistance patterns in *E. coli*, the predominant pathogen associated with urinary tract infection (UTI) is important as a guide in selecting empirical antimicrobial therapy.

Aims To describe the antimicrobial susceptibility of *E. coli* associated with UTI in a region in the West of Ireland.

Methods A collection of 934 *E. coli* isolates associated with UTI were tested for susceptibility to a panel of antimicrobial agents by the disc diffusion method of the National Committee for Clinical Laboratory Standards.

Results More than 50% of *E. coli* were resistant to ampicillin, more than 40% resistant to sulphonamide and more than 30% resistant to trimethoprim. From 7.9% (community) to 12.5% (hospital) are resistant to co-amoxiclav with approximately 20% of isolates of intermediate susceptibility. In general practice most *E. coli* remain susceptible to nitrofurantoin (96.7%), nalidixic acid (93.9%) and ciprofloxacin (94.7%). For all agents rates of resistance were higher in hospital as compared with general practice isolates. Three isolates with the phenotype of Extended Spectrum Beta-lactamase (ESBL) resistance were detected.

Conclusions Ampicillin/amoxicillin are not suitable for empiric therapy of UTI in general practice or hospital patients in this region. There is doubt as to the role of trimethorpim or co-trimoxazole for empiric therapy of UTI. Nitrofurantoin, nalidixic acid and ciprofloxacin are active against the great majority of UTI associated *E. coli*.

INTRODUCTION

Urinary tract infection (UTI) is one of the more common infectious diseases presenting in both the community and hospital. *E. coli* is the most common organism associated with urinary tract infection accounting for more than 70% of UTIs in many series.[1,2] Uncomplicated UTI is frequently managed empirically without laboratory investigation. Agents commonly used for treatment of UTI include beta-lactam antimicrobial agents such as amoxicillin and co-amoxiclav, and agents such as nitrofurantoin and nalidixic acid that are used exclusively for treatment of UTI. Guidelines from the Infectious Disease Society of America recommend co-trimoxazole (trimethoprim-sulphamethoxazole) for three days, as the current standard of therapy for uncomplicated cystitis while acknowledging that trimethoprim alone is equivalent.[4] Ofloxacin and probably other fluoroquinolones such as ciprofloxacin are considered equivalent to co-trimoxazole but for therapy of uncomplicated cystitis these agents are considered unnecessary for routine empirical therapy unless rates of resistance to co-trimoxazole/trimethoprim exceed 10 to 20% among bacteria associated with urinary tract infection.[4]

A previous publication examining 171 uropathogenic *E. coli* from this region in 1997 documented high levels of resistance to ampicillin (54%) and trimethoprim (29%).[3] There are few recent data in the peer-reviewed literature on susceptibility patterns among uropathogenic *E. coli* isolates in Ireland. We have studied 934 consecutive, non-duplicate *E. coli* isolates associated with urinary tract infection in the period September 2002 to January 2003 to determine rates of antimicrobial resistance in this region. Susceptibility testing included antimicrobial agents commonly used for treatment of UTI in Ireland. Cefpodoxime is not generally used in Ireland but was chosen to represent extended spectrum cephalosporins because it is particularly useful in screening for the antimicrobial resistance phenomenon know as extended-spectrum beta-lactamase production.[5] A number of other antimicrobial agents (such as chloramphenicol, cefoxitin, kanamycin and streptomycin) were included because they are of interest as markers for the extent of dissemination of antimicrobial resistance determinants.

Table 1
ANTIMICROBIAL SUSCEPTIBILITY OF E.COLI ISOLATES ASSOCIATED WITH URINARY TRACT INFECTION

ANTIMICROBIAL AGENT	HOSPITAL ISOLATES		COMMUNITY ISOLATES	
	% RESISTANT	% SUSCEPTIBLE	% RESISTANT	% SUSCEPTIBLE
Ampicillin	52.1	43.1	52.1	45.6
Amoxicillin/Clavulanic Acid	12.3	63.5	7.9	74.33
Nalidixic Acid	12.3	86.7	5.9	93.3
Ciprofloxacin	4.3	92.9	2.5	95.3
Nitrofurantoin	5.2	93.4	3.2	96.5
Trimethoprim	35.5	63.0	30.5	69.1
Sulphonamides	44.1	55.5	42.3	57.7
Cefpodoxime	4.7	93.8	2.1	95.8
Cefoxitin	1.9	96.2	1.4	97.6
Gentamicin	2.4	97.6	1.4	98.5
Kanamycin	8.1	88.6	6.5	92.6
Streptomycin	36.0	57.8	32.6	62.7
Tetracycline	30.8	69.2	30.9	68.6
Chloramphenicol	10.4	89.6	7.2	92.7

Where % susceptible and % resistant do not equal 100% the remaining isolates were categorised as intermediate.

MATERIALS AND METHODS

Specimens were submitted from hospital inpatients and from general practitioners. *E. coli* were considered clinically significant if present at a count of greater than 100,000/ml and in pure culture. Consecutive isolates were collected from September 2002 to January 2003. Identification as *E. coli* was based on characteristic pink colony colour on Oxoid chromogenic urinary tract infection (UTI) medium. Antimicrobial susceptibility testing was performed by the disc diffusion method of the National Committee for Clinical Laboratory Standards (NCCLS, now know as the Clinical Laboratory Standards Institute).[6] The following antimicrobial agents were tested ampicillin (10μg), co-amoxiclav (20/10μg), nalidixic acid (30μg), nitrofurantoin (300μg), sulphonamide (300μg), trimethoprim (5μg), gentamicin (10μg), cefoxitin (30μg), cefpodoxime (10μg), cefpodoxime/clavulanic acid (10/1μg), kanamycin (10μg), streptomycin (10μg), tetracycline (30μg), chloramphenicol (30μg) and ciprofloxacin (5μg). *Escherichia coli* ATCC® 25922 and ATCC® 35218 were used as controls. Isolates resistant to cefpodoxime were tested for production of ESBL's by the NCCLS ESBL disc method with cefpodoxime and cefpodoxime/clavulanate. Isolates positive on this disc test were confirmed by ESBL Etest strips with cefotaxime, ceftazidime and cefpirome with and without clavulanic acid.[5]

RESULTS

Nine hundred and thirty-four consecutive isolates (934) were collected. The majority of isolates (77.1%, 723 isolates) originated from general practice. The remaining 22.9% of isolates were from hospital inpatients. The results are summarised in Table 1. Key observations include high rates of resistance to ampicillin (in excess of 50%) in both hospital and community *E. coli* isolates. The rates of resistance to trimethoprim and sulphonamide at greater than 30% and greater than 40% respectively are also very high. For co-amoxiclav, although only 7.9% (GP) to 12.5% (hospital) of isolates are resistant approximately 1 in 5 isolates (16.9% of GP and 24% of hospital isolates) exhibit intermediate susceptibility. Of agents commonly used to treat UTI and included in this study, only nitrofurantoin and ciprofloxacin are active against more than 90% of hospital and general practice isolates but nalidixic acid retains

activity against more than 90% of isolates of *E. coli* from general practice. Three isolates were confirmed as producing extended spectrum β-lactamase like enzymes. Two of these isolates are from patients in the community and one is from a hospitalised patient. Further characterisation of the enzymes present in these strains is in progress.

In total, 27% of isolates obtained from hospital inpatients and 31% of isolates obtained from patients in the community were susceptible to all antimicrobial agents tested. Multi-drug resistance is common with resistance to between 5 and 10 antimicrobial agents tested observed in 26.5% of isolates from hospital patients and 20.9% of isolates obtained from General Practice. A small number of isolates (2.8% of isolates from hospital and 1.1% of isolates from General Practice) were resistant to more than 10 antimicrobial agents. At least one of the panel of oral antimicrobial agents commonly used for treatment of UTI and included in this study (ampicillin, co-amoxiclav, trimethoprim, nitrofurantoin, nalidixic acid and ciprofloxacin) were active against all but two of the isolates. Both of these isolates were isolated from specimens submitted from General Practice and were resistant to 12 or more antimicrobial agents.

DISCUSSION

Urinary tract infection, particularly cystitis is a very common condition that most doctors are called upon to treat from time to time. Approximately one in three women will have at least one UTI before the age of 24 years.[7] Empirical antimicrobial therapy is a widely accepted approach to management of UTI. Data on which to base a rational decision regarding choice of antimicrobial agent are required. Some caution is required in interpretation of our data however as it is possible, particularly in relation to specimens from general practice, that the specimens submitted may represent a subset of patients with complicated infection or infection that has failed to respond to initial empiric therapy. Furthermore this study did not include uropathogens other than *E. coli*. Such factors could lead to overestimation of the prevailing level of antimicrobial resistance in patients with UTI. It is interesting to note that overall the findings are very similar to a recent multi-centre UK study.[1] Rates of resistance to streptomycin, kanamycin, chloramphenicol and tetracycline are of limited therapeutic interest as these agents are not routinely used for treatment of urinary tract infection and with the exception of tetracycline are rarely used now in human health care. The rates of resistance to these agents are of interest primarily as a marker of the extent to which antimicrobial resistance determinants have disseminated in bacterial populations and the extent to which the may persist even when the agents have been all but eliminated from use in human health care.

Although recognising the limitations and possible bias of this study it is important to attempt some practical recommendations for empiric therapy. We consider that ampicillin and the related agent amoxicillin cannot be considered as suitable agents for empiric therapy of UTI. The status of co-amoxiclav as an empiric choice is less clear-cut as the great majority of non-susceptible isolates are intermediate rather than frankly resistant. Similar rates of resistance to aminopenicillins and to co-amoxiclav were recently reported from UTI associated *E. coli* in the UK.[1] On balance we would caution against general use of co-amoxiclav for empiric therapy of UTI given the high rate of intermediate susceptibility and recent evidence that, even in the context of full susceptibility, co-amoxiclav is inferior to ciprofloxacin for short course (that is three days) therapy of uncomplicated cystitis.[8]

More than 90% of isolates are also susceptible to the beta-lactam cefpodoxime. Susceptibility to cefpodoxime can be taken as confirming susceptibility to parenteral cephalosporins such as cefotaxime or ceftriaxone. Cefpodoxime susceptibility does not confirm susceptibility to oral cefuroxime. A recent UK study suggests that less than 70% of uropathogenic *E. coli* are susceptible to oral cefuroxime.[1] There is some concern that the relatively low microbiological cure rate observed with co-amoxiclav for short course therapy of uncomplicated cystitis may be a general property of penicillins and cephalosporins. It is also important to note that a small number of isolates resistant to broad-spectrum cephalosporins and with a resistance phenotype consistent with Extended Spectrum Beta-lactamase (ESBL) production were detected in this study. Studies to define the molecular mechanisms of resistance in these isolates are ongoing. As with amoxicillin and co-amoxiclav, the routine use of cephalosporins for short course therapy of UTI may be best avoided. The penicillins and cephalosporins may be useful when there are relative or absolute contraindications to other agents.

High levels of resistance to trimethoprim and sulphonamide cast doubt on the suitability of trimethoprim alone, or the combination of trimethoprim-sulphamethoxazole (co-trimoxazole) for empiric therapy. These findings are also similar to recent UK data showing that only 73.3% of *E. coli* are susceptible to trimethoprim and only 62.3% are susceptible to suphamethoxazole.[1] In this context trimethoprim and co-trimoxazole can not be regarded as reliable agents for empirical therapy of UTI. These agents remain valuable when susceptibility is confirmed by laboratory testing.

Gentamicin remains active against most community and hospital uropathogenic *E. coli* isolates but its clinical use is limited by toxicity and the requirement for parenteral administration.

The susceptibility of over 90% of *E. coli* isolates to nitrofurantoin is also consistent with the recent UK data. Nitrofurantoin therefore has retained its role in treatment of uncomplicated cystitis in patients who can adhere to the four times per day dosing regimen.

The IDSA guidelines suggest that in circumstances where trimethoprim resistance is very common fluoroquinolone antimicrobial agents are the drugs of choice for empiric treatment of UTI.[3] In keeping with recent UK data, our data confirm that resistance to fluoroquinolone agents is uncommon. Resistance to the closely related but less potent compound nalidixic acid (a quinolone) is also uncommon in isolates from the community but rather more common in hospital isolates. Therefore nalidixic acid and fluoroquinolones can be expected to be effective for empiric treatment of UTI in the majority of cases. In the context of our data the more general use of fluoroquinolones such as ciprofloxacin or ofloxacin for empiric therapy of UTI would be consistent with IDSA guidelines and with clinical trial data on efficacy.[4,8] This approach will ensure effective first line empiric therapy of UTI in the vast majority of cases. However this must be balanced against the obligation of the profession to prescribe antimicrobial agents in ways that minimise emergence of resistance. There are well-founded concerns that more extensive use of fluoroquinolones will result in increasing resistance to these agents.[2] Use of the older quinolone agent, nalidixic acid may drive emergence of resistance to fluoroquinolones even more quickly than use of the fluoroquinolones themselves. This is because acquired resistance to quinolones/fluoroquinolones typically occurs in a step wise manner with only one mutation step required for emergence of resistance to nalidixic acid but with two mutation steps required for emergence of resistance to fluoroquinolones.[9]

Given the serious implications in terms of potential for emergence of resistance and the costs of a policy of more general use of fluoroquinolone agents we are cautious in making such a recommendation. Well structured multi-centre surveillance based on sentinel practices such as that described by Hummers-Pradier *et al*. is desirable to provide a more authoritative basis for recommendations regarding empiric therapy of UTI.[10] At present it may be appropriate to use nitrofurantoin where it is practical to do so, to seek initial laboratory confirmation where the delay in initiation of therapy is acceptable and to limit empiric fluoroquinolone use to patients with more severe symptoms, those at high risk of complications and those who have failed to respond to or are unlikely to adhere to therapy with nitrofurantoin. It is important also to bear in mind that fluoroquinolones are not recommended for use in children or during pregnancy.

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Changes in outcome following surgery for colorectal cancer: one surgeon's experience

ABSTRACT

Background Colorectal cancer (CRC) has the second highest mortality rate of all cancers in Ireland. Developments in imaging, surgical technique, and perioperative care in the last two decades have altered management.

Aims To determine whether outcome following surgery for CRC in the mid-west has changed over a 22-year period.

Methods Four hundred and twenty-two patients were divided into two time periods: Group A (1980-1991, n=203) and Group B (1992-2002, n=219) and demographic, inpatient, and survival data were reviewed.

Results The mean age was 67 years, 59% were male. Group B patients had less advanced disease at presentation (Dukes' stage D 14% vs 22%, $p<0.05$), fewer perioperative complications (13% vs 23%, $p<0.05$), and fewer local recurrences (6.8% vs 11.8%, $p<0.05$) than Group A. No difference in 30-day mortality rate or survival was detected.

Conclusions Although perioperative CRC management has improved, methods of earlier diagnosis and improvements in adjuvant therapy should be explored to improve survival.

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**Our friend and mentor Peter Delaney died in 2002*

INTRODUCTION

Ireland has the fourth and ninth highest number of colorectal cancer (CRC) cases for men and women in the European Union, making up 8.9% of all cancers diagnosed.[1] CRC has now become the leading non-cutaneous cause of cancer in Ireland, with an age adjusted rate of 49.8 per 100,000.[2] By contrast, the age adjusted rates per 100,000 for European and United States populations are 44 and 46.3 respectively.[2] In addition, 12.6% of all cancer deaths were attributable to CRC in 1999, making it the second most common cause of death from cancer.[3] Up to 20% of Irish patients still present with metastatic disease[4], emphasising the need for better prevention and early detection of tumours through strategic measures such as screening.

The implementation of endoscopic based screening programmes has gained widespread acceptance in many countries with numerous trials showing both a decrease in incidence and mortality from colorectal carcinoma.[5-8] Thus, American Cancer Society recommendations for screening include one of the following, beginning at age 50; a faecal occult blood test (FOBT) and flexible sigmoidoscopy (repeated every five years with FOBT annually if normal), or colonoscopy (repeated every 10 years if normal), or double-contrast barium enema (repeated every five to 10 years if normal). A digital rectal examination should be done at the same time as sigmoidoscopy, colonoscopy, or double-contrast barium enema.[9]

The publication of colorectal cancer management guidelines by the Royal College of Surgeons in Ireland has provided clinicians in Ireland with a benchmark of clinical care and emphasises the importance of a multidisciplinary approach to ensure acceptable rates of anastomotic leak, operative mortality, recurrence, and survival. However, the overall five-year survival for CRC is approximately 36.5% and the long-term outcome for CRC patients has not significantly changed over the past two decades despite apparent improvements in diagnosis, surgical options, and adjuvant therapy.[10] The total survival rate from cancer registries includes patients presenting with advanced disease many of whom are treated non-operatively.[2,3] However, in patients who undergo surgery for colorectal cancer, a significant survival advantage is seen. Patients who have surgery have a five-year survival of 53.4% compared to 14.1% in patients who do not.[4] Although previous Irish surgical data have been published from individual units,[11,12] no previous large series (from a single surgeon's perspective) of Irish patients examining changes in outcome over time has been published. The purpose of this study therefore, was to evaluate clinical and pathological factors in patients treated by a single colorectal surgeon over a period of 22 years and identify any trends and changes in outcomes over this time period.

MATERIALS AND METHODS

Patient population

A retrospective analysis of patients undergoing treatment for primary colorectal carcinoma at the Midwestern Regional Hospital, Limerick over a 22-year period from 1980 to 2002 was performed. Eight hundred and twenty-six patients who underwent a major abdominal procedure under the care of a single surgeon (PVD) were initially identified from operating-theatre records and their medical records (or microfilmed charts) were retrieved. Seventy-seven patient records were unavailable for analysis due to lost or destroyed records or poor quality of microfiche data.

Records were then examined to ensure accurate and complete demographic and operative details and to exclude non-colorectal cancer cases. A total of 422 patients with adequate records were identified. The demographic, clinical, pathologic, and follow-up data were then collected and entered into a database. In order to identify any trends over the 22 years, the group of 422 patients was then divided into two time periods; 1980 – 1991 (Group A) and 1992 – 2002 (Group B). Approval to conduct the study was obtained from the internal ethical review committee.

Demographic and clinicopathological characteristics

Group A comprised 203 patients and Group B 219 patients. The male to female ratio was 1.5:1. The mean age of patients was 66.8 years and the median age was 68 years, with an age range of 31 to 99 years (Table 1). One-third of patients were over 75 years of age at presentation and 16% were less than 55 years at presentation. The two groups did not differ significantly with respect to age or gender. Elective or emergency surgery (defined as the presence of obstruction or perforation at presentation) and type of operation were recorded. Operations were sub-categorised according to the region of the colon or rectum (Table 2). All rectal tumours were histologically proven adenocarcinomas and located 12 cm proximal to the anal verge as shown by rigid rectosigmoidoscopy. Tumours requiring low-anterior resection were approximated to 5cm from the dentate line. Dukes' stage, presence of metastases and subsequent liver resection, and pre- or post-operative chemoradiation or hepatic artery infusion were also recorded.

Table 1
PATIENT DEMOGRAPHICS

	GROUP A	GROUP B
Number	203 (48%)	219 (52%)
Male Gender	58%	61%
Mean Age, years	65.4	68.1
Median Age, years	66	68
Age Range, years	31-90	31-99

Table 2
OPERATION TYPE BY GROUP

	GROUP A N (%)	GROUP B N (%)
Right Hemicolectomy	38 (18.7)	44 (20.1)
Transverse Colectomy	4 (2.0)	5 (2.3)
Subtotal Colectomy	3 (1.5)	11 (5.0)
Total Colectomy	4 (2.0)	4 (1.8)
Left Hemicolectomy	13 (6.4)	8 (3.7)
Sigmoid Colectomy	3 (1.5)	6 (2.7)
Anterior Resection (AR)	67 (33.0)	61 (27.9)
Low Anterior Resection (LAR)	20 (9.9)	30 (13.7)
Abdominoperineal Resection (APR)	20 (9.9)	20 (9.1)
Hartmann's Procedure	14 (6.9)	16 (7.3)
Exploratory Laparotomy	2 (1.0)	1 (0.5)
Bypass	13 (6.4)	13 (5.9)
Transanal Resection	2 (1.0)	0

Table 3
MORBIDITY & MORTALITY

	GROUP A	GROUP B	OVERALL
Complications, %	23.2	13.2*	18.0
30-Day Mortality, %	6.4	7.8	7.1
Complication Type, %			
Symptomatic Anastomotic Leak	2.5	3.2	2.8
Wound infection	5.4	1.0*	2.8
Cardio-pulmonary	6.9	1.4*	4.0
Sepsis	1.0	1.4	1.2
Other	4.9	2.3	3.3

$p<0.05$ vs Group A

Morbidity and mortality

Morbidity was defined as any major complication that developed after surgery prolonging hospitalisation or requiring additional intervention. Complications included symptomatic anastomotic leak, wound infection, cardiopulmonary, thromboembolic, renal complications, and sepsis or any other major complication such as intestinal obstruction or rectovaginal fistula formation. The use of post-operative contrast enemas was not routinely employed to identify clinically unsuspected leaks. Operative mortality was defined as in-hospital death or death within 30 days of the procedure. Subsequent local or distant recurrence and time to recurrence also was examined. Local recurrence (LR) was defined as recurrence within the pelvis, with or without distant recurrence.

Follow-up and statistics

Follow-up and survival information was obtained from clinic notes, hospital records, patients' general practitioners, or infrequently from patients or surviving relatives. Statistical analyses were performed using Student's t test, or Chi-squared analysis where appropriate with statistical significance defined as $p<0.05$. Survival rates were analysed by the Kaplan-Meier actuarial method, with statistical significance determined by the log-rank statistic using SPSS statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Presentation and operation type

Fifty-five patients (13%) presented as emergencies with either intestinal obstruction or perforation. Of these patients 45.4% were over 75 years of age. Rates of emergency presentation did not differ between the two time periods (12.3% vs 13.6%, p=ns). All procedures were categorised into 13 different types and are outlined in Table 2. Left-sided lesions were treated with 21 left hemicolectomies (5.0%), nine sigmoid colectomies (2.1%), 30 Hartmann's procedures (7.1%) and 22 total/subtotal colectomies (5.2%). Eighty-two right hemicolectomies (19.4%) and nine transverse colectomies (2.1%) were performed for right-sided lesions. Of the 220 rectal lesions, anterior (n=128) or low anterior resections (n=50) were performed in 81% (n=178). Eighteen per cent of rectal cancers were treated with abdominoperineal resections and two transanal excisions were also performed. There were a total of 29 other procedures comprising 26 palliative bypass procedures and three exploratory laparotomies. Although some trends existed in the number of low anterior resections and subtotal colectomies performed, no significant differences in any operation type between the two groups were observed. There was no clear-cut policy on the use of a protective stoma for rectal surgery and no differences were seen between the two groups. Thirteen patients who developed liver metastases underwent liver resection. Two patients had an extended right lobectomy, three had right and left lobectomies each, and there were three segmental and two wedge resections performed.

Dukes' Stage and Chemotherapy/Radiotherapy

Figure 1 illustrates the two groups according to Dukes' Stage. Of tumours, 6.7% were Dukes' Stage A, 50.4% were Stage A, 25.2% were Stage C, and 17.7% were Stage D. Patients from the earlier time period (Group A) had a greater proportion of lesions that were Dukes' Stage D compared to Group B (22.2% vs 13.6%, $p<0.02$), demonstrating that patients in the later time period had their disease identified at an earlier stage in its progression. Overall, 33% of patients underwent chemotherapy during the study period, but a significantly greater proportion of patients in Group B received chemotherapy compared to Group A (47.8% vs 14.8%, $p<0.05$). A total of 26 patients received post-operative hepatic artery infusion. Of these patients, 8.2% received radiotherapy, and the groups did not differ when radiotherapy rates were compared. There were insufficient data available to further define which patients received neo-adjuvant versus adjuvant radiotherapy.

Morbidity and mortality

Table 3 demonstrates complications in both groups. A total of 76 patients (18%) developed complications. Patients in Group A developed a significantly greater proportion of complications compared to Group B (23.2% vs 13.2%, $p<0.02$), demonstrating a downward trend in the incidence of complications for patients in the later time period. Twelve patients developed symptomatic anastomotic leaks for an overall leak rate of 2.8% and leaks were relatively evenly distributed between group A and B (2.5% vs 3.2%). Of patients in Group A, 5.4% had documented wound infections compared to 1.0% in Group B ($p<0.002$). Cardiopulmonary events were seen with greater frequency in the earlier time period (6.9 % vs 1.4%, $p<0.05$), and septic complications were similar between the groups. The proportion of other complications which included longer term occurrence of intestinal obstruction or rectovaginal fistula formation was similar between the groups.

Thirty patients in the series died within 30 days of their procedure for an overall 30-day mortality rate of 7.1% (Table 3). The 30-day mortality rate between groups A and Group B did not differ significantly (6.4 vs 7.8%, p=ns). Twelve out of 55 patients who underwent emergency surgery died for an emergency operative mortality rate of 21.8%. Eighteen patients undergoing elective surgery died for an elective operative mortality rate of 4.9%. No difference in either elective or emergency operative mortality rate was observed between the two time periods.

Recurrence

The local recurrence rate was 9.2 % and a further 10.7% developed distant recurrences. Interestingly, Group A patients had a local recurrence rate of 11.8% and distant recurrence rate of 6.8%, whereas Group B had a local recurrence rate of 6.8% and a distant recurrence rate of 13.7% and these differences were statistically significant ($p<0.05$) (Figure 2a). The local recurrence rate for rectal lesions in the series as a whole was 10.5%. The recurrence rate after anterior resection (AR) in Group A was significantly greater compared to Group B (18% vs 3.3%, $p<0.05$) (Figure 2b). Recurrences after abdominoperineal resections (APR) and low-anterior resections (LAR) did not differ significantly between groups A and B. The mean and median time to overall local recurrence was 24.3 and 12 months.

Follow-up and survival

At the time of data analysis, 44.5% of patients were alive. The overall mean and median cumulative survival was 116 months and 84 months respectively (Figure 3a). One- and three-year survival was 78 and 66% respectively. No difference in survival between the two groups was found (Figure 3b). Figure 4 demonstrates overall survival according to Dukes' Stage, with five-year survival rates of 83% for Dukes' A, 74% for Dukes' B, 48% for Dukes' C, and 13% for Dukes' D.

DISCUSSION

According to the most recent figures from the National Cancer Registry in Ireland[2], colorectal carcinoma has a considerable and measurable impact on healthcare costs ranging from increased hospital activity to number of years of life lost due to premature death. CRC accounted for an average of 12 years of life lost or 11% overall, making it second only to lung cancer. In terms of hospital activity, the longest average length of stay was for CRC-related admissions at 16-17 days compared to, for example,

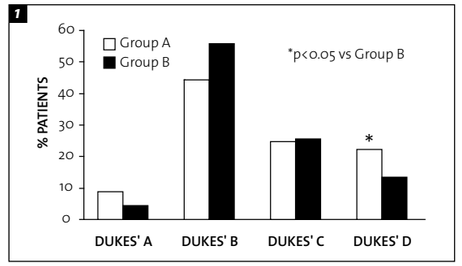
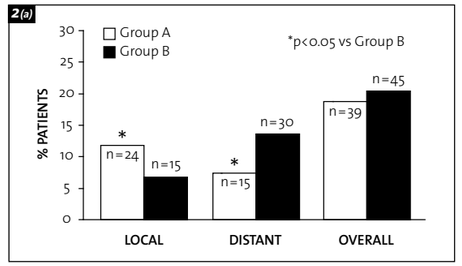


Figure 1 — EFFECT OF TIME PERIOD ON DUKES' STAGING

Group A had a significantly greater proportion of Dukes' stage D patients compared to patients in the earlier time period (Group B).



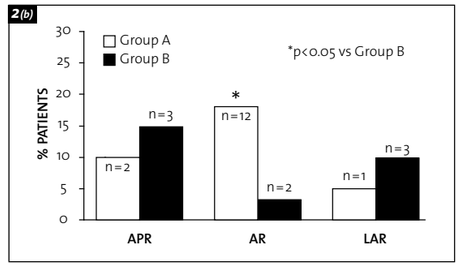
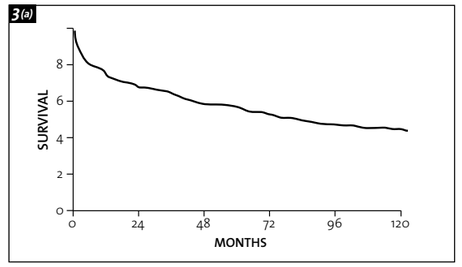


Figure 2 — EFFECT OF TIME PERIOD ON RECURRENCE RATES

Group A had a significantly greater proportion of patients with local recurrence compared with Group B. Group B had higher rates of distant recurrence compared to Group A (Figure 2a). Local recurrence rate after anterior resection (AR) was significantly higher in Group A compared to Group B but unchanged for abdominoperineal resection (APR) and low anterior resection (LAR) (Figure 2b).



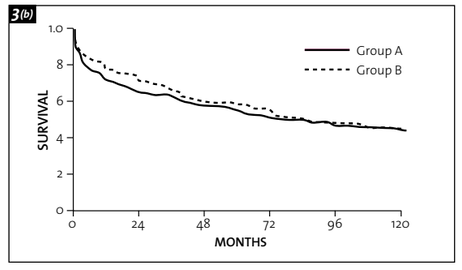


Figure 3 — KAPLAN-MEIER ACTUARIAL SURVIVAL CURVES – ENTIRE SERIES

Kaplan-Meier actuarial survival curves demonstrating overall cumulative survival for the entire series (Figure 3a) and between groups A and B (Figure 3b). The overall mean and median cumulative survival was 116 months and 84 months, respectively. One- and three-year survival was 78 and 66%, respectively.

15 days for gastric cancer, and eight days for bladder cancer. Of CRC inpatients, 42% underwent right hemicolectomy accounting for the greatest number of inpatient procedures (11%).

This study reports a 22-year experience with 422 cases of surgically-managed colorectal carcinoma divided into two time periods, Group A (1980-1991) and Group B (1992-2002). There was no difference in age, gender, presentation type or type of operation performed. Group A however, was more likely to have advanced disease at diagnosis, develop post-operative complications, and develop local recurrence. The 30-day mortality between the two groups was not significantly different and the overall mean and median survival for both groups also did not differ. The incidence of obstructing lesions requiring emergency surgery was similar between the groups. This suggests that despite improvements in perioperative and surgical intensive care, emergency admissions of this type continue to be major sources of morbidity and mortality.

Importantly, patients belonging to the earlier time period were significantly more likely to present with Dukes' D stage in comparison with patients in the later time period (22.2% vs 13.6%, p<0.02), demonstrating that patients in the later time period had their disease identified at an earlier stage in its progression. It is unclear why the groups differ in this regard, because age at presentation as well as presentation type did not differ significantly, but improved patient access and diagnostic imaging techniques in the later time period may be responsible. McCallion et al reported an apparent proximal shift in tumour distribution over a 20-year period using data collected from all CRC cases in the Northern Ireland tumour registry.[13] This was thought to be due to a rise in the incidence of right-sided lesions found on colonoscopy and also a rise in the aging population who tend to have a greater proportion of right-sided lesions. They concluded that flexible sigmoidoscopy may lose its importance as a screening tool as a result. Our data do not show any such change in the tumour distribution; however this may be partly explained by the absence of an age difference between the two groups.

During the study period a total of 220 operations were performed for rectal lesions (52%) and these were distributed equally between both groups. In our series of patients who underwent anterior resections the symptomatic leak rate was 2.3%.

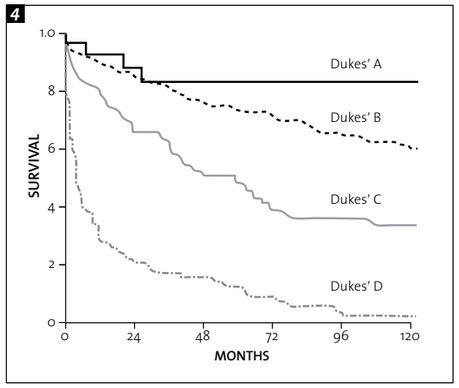


Figure 4 — KAPLAN-MEIER ACTUARIAL SURVIVAL CURVE – BY DUKES' STAGE

Kaplan-Meier actuarial survival curves comparing Group A and Group B patients by Dukes' staging. 5-year survival rates were: 83% for Dukes' A, 74% for Dukes' B, 48% for Dukes' C and 13% for Dukes' D.

The accepted leak rate in the RCSI guidelines is approximately 8% for anterior resections and up to 15% for low anterior resections.[10] Our study compares favourably with these and other published studies with reported leak rates from 3% to 21%.[14-17] It should be noted that routine contrast enemas were not used post-operatively, therefore our series does not include asymptomatic or sub-clinical leaks. Of the 50 patients who underwent a low anterior resection, six developed a leak (12%). These rates did not differ between the two groups. Due to ambiguity in some of the medical records on the use of a protective stoma versus a therapeutic stoma post leakage, we do not have sufficient data to determine whether prophylactic stomas may have played a role in the low leak rate, however there was no policy of routine use in every case.

The local recurrence rate in the series as a whole for rectal lesions was 10.5%. After rectal surgery, patients in the earlier time period (Group A) had a greater local recurrence rate compared to Group B patients, but these differences were not statistically significant (13.8% vs 7.2%, p=0.17). When we compared local recurrence rates after anterior resection (AR), Group B was significantly lower compared to Group A (3.3 vs 18.0%, p<0.05) (Figure 2b). Greater emphasis on surgical technique, especially with the introduction of total mesorectal excision (TME), which came into widespread usage in the late 1980s (including our unit), has been shown to lower local recurrence rates.[18] In our series, the lower recurrence rate after AR in Group B supports this. In recent years, more emphasis has been placed on the oncological importance of the circumferential resection margin and distal mesorectal spread of tumour.[19] TME is now widely accepted as the optimal technique in the resection of rectal cancer,[20] and the low local recurrence rate and improved survival strongly support the necessity to remove the entire mesorectum to achieve complete tumour clearance in cancers of the middle and lower rectum.[21]

A total of 77 patients developed complications for an overall complication rate of 18%. Group A patients developed a significantly greater proportion of complications compared to Group B (23.2% vs 13.2%, p<0.02), demonstrating a downward trend in the incidence of complications for patients in the later time period. Twelve patients developed wound complications (2.8%), with a greater number in Group A (5.4% vs 1.0%, p<0.002). This likely reflects a more standardised approach towards perioperative antibiotic coverage, as well as improved post-operative wound care management in the later time period. The overall 30-day mortality rate of 7.1% compares favourably with RCSI guidelines and published reports.[10,22] No significant differences existed between the two groups. Twelve out of 55 patients who underwent emergency surgery died giving an overall emergency operative mortality rate of 21.8%. Slightly fewer patients belonged to Group B (five out of 12), but the two groups did not differ significantly in this regard. The elective operative mortality rate was 4.9% and similarly, both groups had comparable mortality for elective surgery. When cumulative survival rates were examined in overall terms as well as between the two groups, patients in the earlier time period had similar survival compared to the patients who underwent surgery in the later time period (Figure 3).

Because of the potential for cure of early-stage disease, the definition of populations at risk and screening of asymptomatic patients are important considerations. Decreases in colorectal cancer incidence and mortality rates have been largely attributed to the detection and removal of precancerous polyps, the early detection of tumours through screening, and improved treatments.[23,24] A prospective, randomised study of faecal occult blood suggested that annual tests reduce colorectal cancer-related deaths by 33% through 18 years of follow-up.[5] Additional trials have also demonstrated a 15% to 21% reduction in colon cancer-related death from biennial faecal occult blood testing.[25] Examination of the entire colon by colonoscopy remains the gold standard for visualisation, biopsy, and, when possible, removal of colonic neoplasms. The results of the American National Polyp Study show that the removal of all adenomas in the colon decreases the incidence of colorectal cancer by 76% to 90%.[8]

While our study reflects progress in the treatment of colorectal cancer, we conclude that a widespread screening programme in Ireland should be implemented in order to achieve comparable declines for overall death rates, and improved survival rates, which would have long term positive effects on the burden of costs. Although the most cost-effective approach remains to be identified, screening for colorectal cancer has the potential to decrease mortality by detecting cancers at earlier stages and allowing the removal of adenomas, thus preventing the subsequent development of cancer. Finally, the present series demonstrates that increased attention to surgical technique and improvements in surgical care over time have led to significant gains in the outcome of subsets of patients with colorectal cancer.

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Factors associated with self-reported depression and self-esteem among school-going adolescents from a geographically defined region in Ireland

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ABSTRACT

Background Recent reviews indicate that mental health problems in the young are increasing.

Aims To measure the prevalence of, and risk factors associated with, depression and low self-esteem among Irish post-primary students.

Method 1,428 students, randomly selected from a sample of post-primary schools, were given an anonymised questionnaire. Analyses included bivariate and multivariate logistic regression.

Results Questionnaires were completed by 992 (69.9%) respondents. 206 (20.8%) had a high depression score. Being from a single parent family (OR 2.8, 95% CI 1.5 –5.4, p<0.001); having low self esteem (OR 13.44 95% CI 8.9 – 20.3, p<0.001); being female (OR, 3.7, 95% CI 2.5-5.6 p<0.001) and having a low fitness level (OR 1.8, 95% CI 1.2-2.8 p<0.006) were independently associated with a high depression score.

Conclusions The level of self-reported depression was high among these respondents and risk factors identified include having low self-esteem, being female, being from a single parent family and having a low fitness level.

INTRODUCTION

In 2002, the North Eastern Health Board (NEHB) undertook a study which examined the prevalence of smoking, alcohol and drug use among school-going adolescents in the region.[1] As part of this study, information on how the adolescents felt about themselves using a self-administered depression and self-esteem questionnaire was also collected. This paper presents the findings and identifies risk factors associated with depression and self-esteem scores among this cohort. Identification of these risk factors in this cohort of young adolescents is important given that recent reviews indicate that mental health problems in young people are increasing and the number of young people taking their own lives is rising.[2-5] This increase in suicide has lead to calls for the identification of young people at risk, with a view to the development of prevention programmes.[4] A recent study in Ireland showed that there are large numbers of young people at risk of mental health disorders and suicidal ideation and raised the question of the importance of mental health promotion in the Irish education system.[6] Furthermore, it has been shown that depression in adolescents is a strong risk factor associated with depression in adulthood and preventive efforts should be selectively targeted at adolescents who have been exposed to identifiable risk factors.[7] The aim of this study was to estimate the prevalence of self-reported depression and self-esteem among school-going adolescents in a geographically defined region. A further aim of the study was to identify risk factors associated with depression and self-esteem.

METHODS

A random stratified sampling technique was employed to select post-primary schools in counties Cavan, Monaghan, Louth and Meath. Of a total of 58 post-primary schools, 24 were selected to participate in the study. The principal of each school was contacted and his or her permission was sought. After written consent was received, each school was visited and the purpose of the survey was explained. Confidentiality was guaranteed and the students were made aware that participation in the survey was voluntary. Three classes from each school were

then randomly selected to participate. Anonymous questionnaires incorporating two standardised scales for measuring depressive symptomatology (CES-D questionnaire) and self esteem (Rosenberg Self-Esteem Scale) were distributed to students during a class period by a Research Officer. Questionnaires were collected by the Research Officer following their completion. Demographic data such as age, sex, social class and fitness levels were also collected by questionnaire. The completed questionnaires were then coded, and analysed using JMP statistical analysis package.[8] In addition, multivariate logistic regression analysis was carried out using STATA, version 8.[9]

Instrument used to measure depression - the CES-D scale

The Centre for Epidemiological Studies-Depression (CES-D) Scale comprises of a 20-item self-reported measure designed to measure symptoms of depression.[1] The CES-D has been shown to correlate substantially with other self-report depression measures and to adequately differentiate depressed from non-depressed groups.[11] The CES-D has demonstrated its usefulness as a screening instrument at both adult and adolescent levels and has been successfully used with large adolescent school samples.[10] Although a score of 16 or more has been commonly used in adult samples as indicating high levels of depressive symptomatology, Roberts et al found that this criterion yielded rates in excess of 50% for adolescents, compared with 16-21% for general adult population samples.[12] Chabrol et al found that a higher criterion score of ≥ 24 provided a sensibility rating of 0.74 and a specificity rating of 0.73 when used in adolescents.[13] Therefore, for the purposes of this study, a CES-D score of ≥ 24 was used to demonstrate significant levels of depressive symptomatology.

Instrument used to measure self-esteem - the Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem (RSE) Scale is a self-report measure in which respondents rate their agreement with ten statements that describe how they feel about themselves. This scale was originally developed to measure adolescents' global feelings of self-worth and is generally regarded as being the standard against which other measures of self-esteem are compared. Extensive and acceptable reliability (0.82-0.88) and validity data exist for the RSE.[14]

RESULTS

Response rates

Questionnaires were administered to 1,428 students, of these, 992 (69.6%) completed the questionnaire sufficiently to allow computation of a depression and self-esteem score. Given that there were no statistically significant differences in demographic profile (age, sex and social class profile) between the final 992 respondents and the total representative sample of 1,428 respondents, this study will concentrate on these 992 respondents.

Demographic profile of respondents

Of the 992 respondents there were significantly more males (N=603) than females (N=389), (60.7% vs 39.2% p<0.01); the median age was 15 years (range 13 to 17 years) and there was no significant age difference between the males and females. The gender ratio may be explained by the fact that among the schools that were randomly selected, there was a higher proportion of males than females in attendance. Based on their parents' current occupation, a total of 323 (32.6%) belonged to social class 1-2(Professional, Managerial/Technical and Farmers owning 100 acres of more). In general approximately 29.6% of the population of this region belongs to social class 1-2.[15] However, the higher than expected proportion from these groups may be explained by the fact that adolescents from social classes 1-2 are more likely to attend class and therefore had been in attendance to complete the questionnaire.[16] A total of 73 (7.4%) of the respondents reported that they lived in a single parent family. Similarly, given that the proportion of single parent households with children in Ireland is nearer 12%, the lower than expected proportion of responders from single parent families may be explained by the fact that adolescents from one-parent families are more likely to miss school more often than adolescents from two parent families.[15-16]

Fitness Levels

The adolescents were asked to rate their fitness on a 1-10 scale with 1 equal to 'Very Unfit' and 10 equal to 'Very Fit'. A fitness score was completed by 966 (97.4%) of the respondents. The average fitness score recorded by the respondents was 6.2. The average fitness score recorded by the male respondents was significantly higher than the average fitness score recorded by the female respondents (7 vs 5, p<0.001). When the fitness scale was dichotomised into 'low fitness level' (i.e. with a fitness score below the inter-quartile range) and into 'high fitness level' (i.e. with a score within and above the inter-quartile range), a total of 243 (25.1%) had a low fitness score with a significantly higher proportion of females (N=135) than males (N=107) among those who had a low fitness score (35.4% vs 18.3%, p<0.001).

Table 1

FACTORS ASSOCIATED WITH A CENTRE FOR EPIDEMIOLOGICAL STUDIES IN DEPRESSION (CES-D) SCORE INDICATIVE OF SIGNIFICANT LEVELS OF DEPRESSIVE SYMTOMATOLOGY

VARIABLE	CRUDE OR	ADJUSTED OR*	P-VALUE FOR ADJUSTED OR
Sex (being Female)	6.55	3.72	p<0.001
Single Parent Family	2.93	2.86	p<0.001
Low Self-Esteem Score	16.73	13.44	p<0.001
Low Self-Reported Fitness Level	2.68	1.85	p<0.006

** Odds ratios, adjusted for age, social class all other predictive variables above.*

Table 2

FACTORS ASSOCIATED WITH A LOW ROSENBERG SELF-ESTEEM (RSE) SCORE

VARIABLE	CRUDE OR	ADJUSTED OR*	P-VALUE FOR ADJUSTED OR
Sex (being female)	4.57	2.34	p<0.001
Single Parent Family	1.74	0.83	p=0.59
High CES-D score indicative of significant levels of depression	16.73	13.37	p<0.001
Low Self-Reported Fitness Level	2.03	1.20	p=0.39

**Odds ratios, adjusted for age, social class all other predictive variables above.*

Main Outcome Measures

(a) CES-D Depression Score

A total of 206 (20.8%) of the respondents had a depression score above the cut-off score point that indicated that they had significant levels of depressive symptomatology on the CES-D. A significantly higher proportion of the females, 152 (39%) than males, 54 (9%) scored a reading that indicated that they had significant levels of depressive symptomatology (39% vs 9%, p<0.001). Table 1 identifies the factors associated with a depression score indicative of significant levels of depressive symptomatology. As shown, after controlling for confounding factors, being female, living in a single parent family, having a low self-esteem score and having a low self-reported fitness level were all significantly associated with having a depression score indicative of depressive symptomatology. Those from a single parent family were almost three times more likely to have a depression score indicative of depressive symptomatology and this was independent of age, sex and social class of the respondent. Those who had a low self-esteem score were more than thirteen times more likely to have a depression score indicative of significant levels of depressive symptomatology compared to those with a normal/high self-esteem score. Respondents who reported that they had a low fitness level were also almost twice as likely to have a depression score above the cut off and therefore indicative of significant levels of depressive symptomatology compared to those who had a high fitness level.

(b) RSE score

The mean RSE score among this cohort of patients was 28.9 (S.D. 5.66). The male respondents had a statistically significant higher mean self-esteem score than the female respondents, (30.5 vs 26.4, p<0.001) which indicated that the male respondents on average rated their self-esteem higher than the female respondents.

When the self-esteem score was dichotomised into 'low self-esteem' (i.e. with a self-esteem score below the inter-quartile range) and into 'normal/ high self-esteem score (i.e. with a score within and above the inter-quartile range), a total of 215 (21.6%) had a low self-esteem score. A significantly higher proportion of the females than males had a 'low' RSE score (37.5% vs 11.6%, $p<0.0001$). As shown in Table 2 when the factors previously identified as associated with a high depression score were placed in the model to identify factors associated with a 'low self-esteem score', only being female and having a high depression score remained significant factors after controlling for the other factors in the model. This suggests that although being from a single parent family was independently associated with having a high depression score, it was not independently associated with a low self-esteem score. Furthermore whilst a low fitness score was independently associated with a high depression score, a low fitness score was not independently associated with self-esteem score.

DISCUSSION

The CES-D questionnaire was used to determine self-reported depression among this cohort of students. Over 20% of the respondents had a depression score above the cut-off point and therefore indicative of significant levels of depressive symptomatology. This finding is very similar to the findings by Lawlor and James which showed, using the Youth Self-Report questionnaire, that 21.3% of a sample Irish 16-year-olds attending post-primary school have psychological problems[17]. Females had a higher average depression score than the males with a significantly higher proportion of the females compared to the males having a CES-D reading indicating significant levels of depressive symptomatology and this is in keeping with international studies on self-reported depression among adolescents which show a higher prevalence of self-reported depression among female adolescents.[18,19] It is very interesting to note that several factors other than sex were independently associated with depression scores among this cohort of students. These factors included living in a single parent family whereby those adolescents who lived in a single parent family were almost three times more likely to have a higher depression score than those adolescents who lived in a two-parent family. This finding is supported by other international studies, which show that parental separation increases the risk of adolescent mental health problems.[20] Census results from 1996 and 2002 show that between 1996 and 2002, the number of households containing a lone parent with children increased by 24.5%[14]. This increasing rate of marital breakdown in Ireland has therefore, serious implications for the mental health of our adolescents. Family support measures in Ireland need to be enhanced if the trend in family breakdown is to be reversed. As some of the risk factors for adolescent mental health are outside the sphere of health services, a public health approach, which involves other agencies of the state is required to reduce the burden of mental health illness in adolescents. Given that a previous follow-up study on the risk for depression in Finnish adolescents[6] showed that self-reported perceptions of psychosocial well-being have predictive value and therefore, it seems reasonable to suggest that preventive efforts should be selectively targeted at adolescents who have been exposed to identifiable risk factors. An Irish study by James and Lawlor[21] on early school leavers showed that 24% of early school leavers experienced psychological problems and recommended that this vulnerable group be provided with psychological support and treatment if necessary. However, our study suggests that the psychological support and treatment should be made available before the adolescents leave school and perhaps in the school setting since the prevalence of high depression scores is evident before these adolescents leave the school setting.

The Rosenberg Self-Esteem questionnaire was used to measure self-esteem among this cohort of students and it was found that the mean self-esteem score for the males and for the females in this study were broadly in keeping with a national study carried out by Nic Gabhainn and Mullan on the self-esteem norms for young (aged 10-17) Irish people.[22] Similarly to this study, it was found that the females on average, had a lower self esteem score than the males. When the data were categorised into low self-esteem and normal/high self-esteem, it was found that over a fifth (21%) of the adolescents reported a low self-esteem score. When multivariate analysis was carried out it was also found that, after controlling for other factors, such as age, sex, and social class, self-reported depression was the only factor independently associated with self-esteem. Those adolescents with a high depression score had a lower self-esteem score than those with a low depression score and this was particularly evident among the female adolescents.

It was also interesting to note that when asked about self-reported fitness level the majority of the adolescents rated their fitness level reasonably high (i.e. an average of 6.2 on a 1-10 continuous scale). However, a significant minority of the respondents (25%) had a 'low fitness level'. It is interesting to note that a low self-reported fitness level was one of the factors that was positively correlated with a high depression score whereby those who had a low self-reported fitness level were almost twice as likely to report a high depression score. This finding is not surprising given that a substantial body of literature attests to the benefits associated with fitness and psychological health.[23] Therefore, health promotion strategies to encourage fitness levels and exercise among adolescents may have a beneficial effect on the psychological health as well as the physical health of adolescents. Previous studies involving adolescents have shown that an important predictor of physical activity behaviour was participation in community sports.[24] Therefore perhaps one potentially effective way to increase physical activity among these adolescents would be to facilitate greater access to community-based physical activity outlets such as fitness programmes designed specifically for adolescents. To help with this process, schools could establish links with community sports leaders so that students become more aware of the physical activity opportunities in their community.

LIMITATIONS OF THE STUDY

This study was a cross-sectional study and therefore a causal relationship between risk factors and outcome measures can only be inferred. Data on confounding factors such as timing of parental separation[25] and parental depression[26] that may be associated with both single parent families and depression are lacking in this study. However, the finding that the high depression scores are highest among adolescents from single parent families compared to adolescents from two parent families is consistent with both Irish[6] and international studies.[20] This study used self-administered questionnaires to measure depression and self-esteem and therefore, the findings may not be as reliable as that information obtained by interview or clinical assessment. However, self-report measures are found to be reliable with adolescents[27] and our findings are similar to previous studies suggesting that it is likely that our measures of depression and self-esteem are reliable.

CONCLUSION

To conclude, this study has shown that the prevalence of self-reported depression as measured by CES-D scale is high among this cohort of adolescents with greater than 1 in 5 of the respondents reporting a high CES-D depression score (i.e. over the cut-off point that is indicative of significant levels of symptomatology). Moreover, a high CES-D depression score was associated with being female, being from a single parent family, having a low self-reported fitness level and low self-esteem score. This paper has also shown that the average self-reported self-esteem score of the male and female adolescent responders in this study are similar to those found in a larger Irish study with over 21% of the respondents reporting to have a 'low self-esteem score'. Given that the risk of depression in adulthood is strongly associated with depression in adolescence, it is of great importance that preventive efforts are selectively targeted at those adolescents who are exposed to those risk factors associated with a high depression score, such as being from a one-parent family and having a low self-reported fitness levels. Effective mental health promotion strategies should be included as part of the school curriculum.

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Non-orthopaedic paediatric trauma in a regional hospital

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ABSTRACT

Background In the Republic of Ireland there are no paediatric surgeons outside Dublin. Most paediatric trauma is managed in general hospitals by general or orthopaedic surgeons.

Aim In this study we audited our experience with paediatric trauma in a regional setting.

Methods We carried out a retrospective review of all non-orthopaedic paediatric trauma patients admitted to our institution over a two-year period. The method of injury, management and outcome were recorded and the TRISS (revised trauma injury severity score) method was used to calculate the probability of survival.

Results One hundred and fifty four paediatric patients were admitted following trauma. Falls, RTAs and burns were the commonest reasons for admission. Twenty nine of these patients (19%) required surgical procedures. There were no unexpected deaths.

Conclusion The majority of paediatric trauma admissions were for minor injuries. A number of seriously injured children were successfully treated with no unexpected deaths.

INTRODUCTION

Paediatric trauma is a major health problem affecting children over one year of age. Multiple reports indicate that serious trauma in the paediatric age group will remain a continuing problem in the future.[1] In the United States of America (USA) it has been suggested that all severely injured children should be managed in regional paediatric trauma centres to ensure best possible care and outcome.[2] The British Association of Paediatric Surgeons (BAPS) recommends that a specialist paediatric surgical unit consisting of four specialist paediatric surgeons and one paediatric urologist should cater for the specialist paediatric needs of a population of 2.5 million and the general paediatric surgical needs of 1.2 million.[3] In the Republic of Ireland the number of specialist paediatric surgeon posts fall short of this recommendation with the result that specialist paediatric surgical services for the country are based primarily in Dublin. Elsewhere most paediatric general surgery and much specialist paediatric surgery e.g. urology, is performed by general and other surgeons with paediatric training as defined by the Senate of Surgery of Great Britain and Ireland.[4] Many seriously injured children are cared for by general surgeons in general hospitals which deal with both adult and paediatric trauma.

The Mid-Western Regional Hospital, Limerick is the largest hospital in the HSE Mid-Western area, which consists of the counties of Limerick, Clare and North Tipperary. This area has a population of 339,591 with 71,968 (21%) under the age of 14 years (2002 population census, CSO).[5] Three general surgeons and one urologist, all with paediatric training provide general paediatric surgery and paediatric urology services in the Mid-Western Regional hospital for this HSE area. These consultants work in collaboration with twelve consultant anaesthetists and six consultant radiologists, all with paediatric experience, and five consultant paediatricians. Paediatric surgical admissions are cared for in a dedicated paediatric unit staffed by trained paediatric nurses and also in a surgical day unit. The adult intensive care unit is used for paediatric admissions when necessary as there is no dedicated paediatric intensive care or high dependency unit.

METHODS

We carried out a retrospective audit of all paediatric trauma patients admitted to our institution between January 2000 and December 2001. Inclusion criteria were that the patients were less than 14 years of age and admission was as a result of accidental injury. Children with orthopaedic trauma alone were excluded from this study; this accounted for 629 admissions.

Patients' charts were reviewed for demographic data and information related to mode of injury, investigations, treatments and outcomes. The injury severity score (ISS) and the revised trauma score

(RTS) were calculated. The ISS, first introduced by Baker et al in 1974, is derived from the abbreviated injury scale (AIS) which is a numerical method for grading injuries by severity on an ordinal scale ranging from 1 (minor injury) to 6 (maximum injury).[6] The ISS is used to summarise multiple injuries in a single patient. The ISS is defined as the sum of squares of the highest AIS grade in the three most severely injured body regions. Six body regions are defined; the thorax, abdomen and visceral pelvis, head and neck, face, bony pelvis and extremities, and external structures. ISS ranges from 1-75. If an injury is assigned an AIS of 6 (unsurvivable injury), the ISS is automatically assigned to 75. The RTS, is a physiological scoring system which uses three specific physiologic parameters; the Glasgow Coma Scale, systemic blood pressure, and the respiratory rate. Parameters are coded from 0-4 based on the magnitude of the physiologic derangement.[7] RTS is determined by adding each of the coded values together. RTS range from 0-12.[7]

The TRISS method was used to calculate the probability of survival (Ps) among these patients.[8] This test combines both anatomic and physiologic measures of injury severity (ISS and RTS, respectively) and patient age in order to predict survival from trauma. This method recognises the difference between blunt and penetrating injury. The logistic regression equation predicts the probability of survival.

The observed and expected survivals were compared using Z statistics, which quantify the difference in the actual number of deaths (or survivors) in the test subset, and the predicted number of deaths (or survivors) based on the baseline norm from the American Major Trauma Outcome Study (MTOS).[8,9]

RESULTS

One hundred and fifty four paediatric patients (96 male, 58 female), were admitted with trauma during the two-year period. The median age was four years (range 2 months-14 years). Falls were the commonest cause of injury, accounting for 56.4% of all admissions, this was followed by injuries sustained in road traffic accidents (RTAs) which accounted for 21.4% (n=33) of admissions, burns 9.7% (n=15), gunshot injuries 1.9% (n=3) and miscellaneous injuries 10.3% (n=16) (Figure 1). There were four pedestrian injuries out of 33 RTAs.

One hundred and three patients had either a primary or secondary diagnosis of head injury.

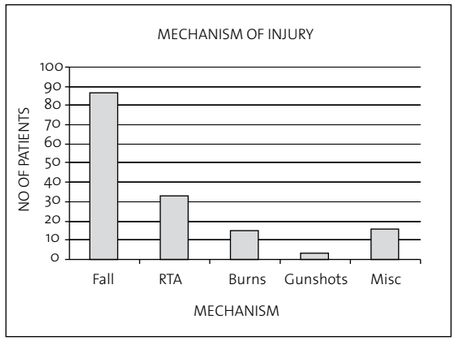

Figure 1 — MECHANISM OF INJURY

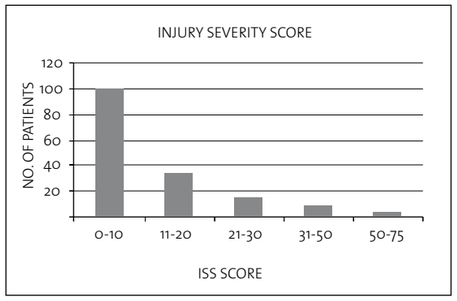

Figure 2 — MEAN ISS SCORE. ISS RANGES FROM 1-75; THE HIGHER THE ISS SCORE THE GREATER THE DEGREE OF INJURY

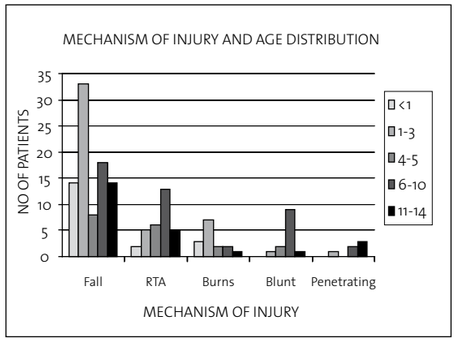

Figure 3 — AGE DISTRIBUTION OF ALL TRAUMA ADMISSIONS

Median Glasgow Coma Score (GCS) was 7.5 (range 3-15). Thirty-six patients (23.4%) had a computerised tomography (CT) brain scan; only one of whom had a GCS of less than ten. Eight scans had positive findings, three patients had an extradural haematoma (EDH), two had skull fractures, two had oedema with contusion and one patient had a severe intracerebral haemorrhage, this patient subsequently died.

Mean ISS was 11 (±6.36,SEM) (Figure 2). Twenty nine patients (19%) required 30 surgical procedures: wound exploration n=21 (14%), exploratory laparotomy n=5 (3%), chest drain insertion n=3 (2%), and scrotal exploration n=1 (0.6%). Fourteen patients with suspected serious blunt abdominal trauma had radiological imaging; CT scan was performed in six patients and abdominal ultrasound in eight. One patient had a positive diagnostic peritoneal lavage (DPL) and underwent a laparotomy on the basis of the DPL findings. Only four of the 14 patients who had an abdominal scan required an exploratory laparotomy. The other 10 were managed conservatively.

Seventeen patients (11%) were referred to specialist units: 13 (8.4%) to plastic surgery, 3 (1.9%) to neurosurgery and 1 (0.64%) to a spinal unit. There was one death (0.6%) due to a severe head injury. The majority of admissions were for minor trauma. There were no unexpected deaths in our study but there were four unexpected survivors (probability of survival score< 0.5). Of the unexpected survivors two patients suffered from blunt trauma injuries, one resulted in a head injury, skull fracture, bilateral pneumothorax and liver haematoma, the other patient with a duodenal perforation. The other two unexpected survivors were injured in RTAs, one patient sustained a mesenteric tear, jejunal perforation and wound dehiscence requiring a second laparotomy, the other RTA patient sustained liver and spleenic lacerations, fractured C3-4 and a head injury. Applying TRISS methodology from the major trauma outcome study the Z statistic for survival in our study was 0.132 (p>0.5).

DISCUSSION

The care of injured children begins with the understanding that they have special needs. Children can compensate better following haemorrhage than adults but pose problems in management due to their small size and other unique anatomic features.[10]

In the ideal world all paediatric trauma cases would be admitted to a specifically designated paediatric centre, however in most countries this is not feasible. In the USA there has been considerable concern about the issue of adult trauma centres looking after the paediatric trauma patients. However, even in the USA it is not logistically possible to have paediatric trauma centres for children in every state and most paediatric trauma patients are treated by adult general and trauma surgeons.[11] The situation is similar in the UK and Ireland where specialist paediatric surgeons provide specialist services in neonatal and complicated paediatric surgery, but a large percentage of paediatric trauma cases are treated in regional centres. In the Republic of Ireland (population 4 million) there are only four specialist paediatric surgeons, three less than the number recommended by the British Association of Paediatric Surgeons (BAPS).[3] BAPS also recommends that non-specialist or general paediatric surgery can be provided safely by appropriately trained general surgeons in hospitals that serve a population of 200,000 or more.[3] The Senate of Surgery of Great Britain and Ireland has recommended that non-specialist or general paediatric surgery may be undertaken by a general surgeon who has received appropriate training and that this surgeon would be known as a general paediatric surgeon.[4]

A review of the literature published on survival of paediatric trauma cases treated in dedicated paediatric centres compared to regional centres with paediatric commitment shows mixed results. Various studies reported greater survival rates in designated paediatric centres,[12,13,14] when compared to regional centres, yet other studies have reported comparable rates.[15,16] For example Osler et al, in 2001 compared 55,113 paediatric trauma cases from 22 dedicated paediatric trauma centres and 31 adult trauma centres.[15] They reported lower mortality rates in those treated in the designated centres, yet discovered that patients admitted to the adult trauma centres were more severely injured. When the analysis controlled for injury severity score, paediatric trauma score, age and mechanism of injury and when The American College of Surgeons verification status was applied the difference was eliminated and comparable mortality rates were reported. The results from these published studies highlight the importance of developing a detailed national paediatric trauma registry. In Ireland such a registry would allow for comparison of results from different centres, allowing for future planning and development of paediatric services.

For this study we used TRISS methodology to evaluate the outcome of paediatric trauma patients presenting to our hospital. It has been proven in previous studies by Eichelberger[17] and Kaufmann[18] that TRISS methodology is applicable to children and provides a reliable method of predicting outcome and evaluating quality, comparable to an adult population. In our study most of the children were in the minor trauma group, however there were 24 children with an ISS score of more than 20 indicating severe injury. We did not encounter any unexpected deaths in our group.

Conversely, there were four unexpected survivors with probabilities of survival of less than 0.5. There was only one death; this patient had a serious head injury with a GCS of three on arrival.

In our study group falls were the commonest cause of injury accounting for 57% of cases followed by RTAs (21.4%). These figures are consistent with the published findings from other centres.[19,20] When the different age groups were compared falls were the commonest cause of injury in preschool children and RTAs were more prevalent in children older than five years of age (Figure 3). Head injury was the commonest reason for admission. In this study group, the threshold for CT scanning children with head trauma was quite low; only one patient had a GCS of less than 10. Interestingly this policy of low threshold for CT brain scanning seems worthwhile as eight scans were positive for intracranial injury. This policy of low threshold for brain CTs is consistent with the NICE guidelines for the management of head injury in children.[21]

The positive patient outcomes seen in this small study group reflects the paediatric training experience of the various consultants involved in the management of these children. To maintain paediatric competence in the regions in Ireland there is a need to include rotations in paediatrics in the higher training curricula of the various disciplines involved, especially general surgery.

Another issue for debate in centres without paediatric surgeons is whether injured children should be under the direct care of paediatric physicians or general surgeons. We agree with the opinion of Knudson et al that the care of injured children should remain the responsibility of surgical teams for optimum outcome.[2] Appropriately trained surgeons not only have the knowledge and skills to adequately resuscitate the patient but also are the most appropriate clinicians to decide which patient may need surgical intervention. The decision to treat an injured patient conservatively requires the judgement of an experienced surgeon who is capable of intervention should his or her decision prove wrong. Ten of the fourteen patients with blunt abdominal injuries and positive scans (free intraperitoneal fluid) were successfully managed conservatively. In our study 19% of patients required some sort of surgical intervention and three were transferred to neurosurgeons, two of these required neurosurgical intervention.

CONCLUSION

The purpose of our study was to evaluate the morbidity and mortality of trauma patients in the paediatric age group admitted to our hospital. Although the majority of patients had suffered minor trauma, the outcome of severely injured children was favourable with no unexpected mortalities. Appropriately trained general surgeons with experience in paediatric surgery can safely care for injured children in regional hospitals that have considerable paediatric infrastructure. We suggest that a rotation in paediatric surgery should be mandatory in the higher surgical training curriculum to enable the next generation of regional surgeons to continue to look after injured children. In addition a national paediatric trauma registry would allow for continuing audit of practices and outcomes.

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Increasing rates and changing patterns of hospital admissions for patients with inflammatory bowel disease in Ireland: 1996 – 2001

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ABSTRACT

Background The inflammatory bowel diseases require frequent hospital visits. The literature suggests that the incidence of IBD may be increasing.

Aim To investigate the pattern of admissions of patients with inflammatory bowel disease (IBD) to hospital over a five-year period (between 1996 and 2001).

Methods We obtained national data regarding admission rates for patients with IBD from the Economic and Social Research Institute (ESRI) during the years 1996 and 2001. Local data were gathered from the Hospital In-Patient Enquiry (HIPE) scheme for the same years.

Results Over this five-year period, there has been a substantial increase in the rate of admission with IBD (58% for Crohn's disease and 25% for ulcerative colitis), in particular in the number of day-case admissions for patients with Crohn's disease (125%). There has been little change in the number of patients undergoing surgery for their disease (Crohn's disease; 24% vs 20% and Ulcerative colitis; 17% vs 16.6%) and in the length of hospital stay.

Conclusion Despite an increase in the rate of admission with IBD, there has been little change in the rates of surgical intervention and length of stay. The most dramatic increase was seen in the day-case admissions for patients with Crohn's disease and may reflect the use of anti-TNFα (infliximab) in the treatment of this disease.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic spontaneously relapsing and remitting diseases requiring both frequent attendance at hospital and hospital admissions. They pose a considerable burden on health resources globally and have a significantly negative impact on the quality of life of the patients affected. In recent years, there has been a global increase in the reported incidence of IBD.[1-3] In addition, novel treatments have been introduced to the management repertoire for patients with IBD, some requiring day-case admission. In particular, with the introduction of biological therapy in the form of Infliximab, the management of patients with Crohn's disease has moved increasingly towards day-case treatment. Bearing these factors in mind, the aim of our study was to assess the pattern of admission and outcome for patients with IBD between 1996 and 2001 in Ireland. We also aimed to assess the admission rates and outcome for patients with IBD in our unit during this five-year interval.

METHODS

To carry out this study, national data were obtained from the Economic and Social Research Institute (ESRI), where all data from the local HIPE (Hospital In-Patient Enquiry) schemes are accumulated. HIPE is a computer-based health information system designed to collect clinical and administrative data regarding discharges and deaths from acute public hospitals. The coding scheme used to identify diagnoses and surgical procedures is the International Classification of Diseases - 9th Revision - Clinical Modification, known as ICD-9-CM. In Ireland, 60 acute public hospitals participate in HIPE. Maternity hospitals are beginning to participate as well as some private hospitals. HIPE national coverage varies considerably since data collection began in 1970. Coverage is now over 95% since 1995. HIPE statistics identifies single and repeated admissions for individual patients.

RESULTS

A) National data

In Ireland, between 1996 and 2001, the total number of admissions per year (in-patients and day-case) for patients with Crohn's disease increased from 1077 to 1706, an increase of 58%. During the same interval, the total number of admissions for ulcerative colitis increased from 1537 to 1922, a 25% increase (Figure 1). In 1996, ulcerative colitis resulted in more admissions than Crohn's disease (1537 vs 1077). However, these numbers have approximated in 2001 (1922 vs 1706).

For Crohn's disease, the total number of in-patient admissions increased by 31%, from 762 to 998. Interestingly, there was a marked increase of 125% in the total number of day-case admissions for these patients, from 315 to 708 (Figure 2). We evaluated the proportion of patients with Crohn's disease who underwent a major surgical procedure during admission to hospital. The surgical procedures included colonic resections, fistula and stomal surgery. There has been little change in the number of patients requiring surgery for Crohn's disease. In 1996, 179 of 762 admissions (24%) required surgery compared to 200 out of a total of 998 (20%) in 2001.

For ulcerative colitis, the total number of in-patient admissions increased by 22% from 709 to 862. The number of day-case admissions increased by 28% from 828 to 1060 (Figure 2). This increase in day-case admissions is considerably less than that observed for those with Crohn's disease. We evaluated the proportion of patients with ulcerative colitis who underwent a major surgical procedure during hospital admission. In 1996, 121 patients out of a total of 709 (17.1%) in-patients with ulcerative colitis required surgery compared to 143 of 862 (16.6%) in 2001. The surgical procedures included colonic resections and stomal surgery.

B) Data from Beaumont hospital

Beaumont Hospital is a 629-bed teaching hospital and a tertiary referral center for patients with gastrointestinal disease. The trends for patients with IBD in Beaumont Hospital were similar to the national trends above. The total number of admissions to Beaumont Hospital for patients with Crohn's disease has increased from 38 to 144 (279%) between 1996 and 2001. For ulcerative colitis, the numbers have increased from 63 to 142 (125%) during the same five-year period (Figure 3). Interestingly, there was a substantial difference in the number of admissions for Crohn's disease compared to ulcerative colitis in 1996 (38 vs 63). Again these figures have approximated in 2001 (144 vs 142).

Within the group of patients with Crohn's disease, the number of in-patient admissions increased from 23 to 55, a 139% increase. However, regarding day case admissions there has been a dramatic 493% increase from 15 to 89 within the same timeframe (Figure 4). The number of patients undergoing surgery has changed little during this time despite an increase in the number of admissions. In 1996, eight of the 23 in-patients underwent surgery for Crohn's disease compared to 10 of 55 patients in 2001. The surgical procedures included colonic resections, fistula surgery and stomal revisions.

For ulcerative colitis, there has been a 119% increase in the number of in-patient admissions between 1996 and 2001, 21 to 46. The number of day-case admissions for ulcerative colitis increased by 129%,

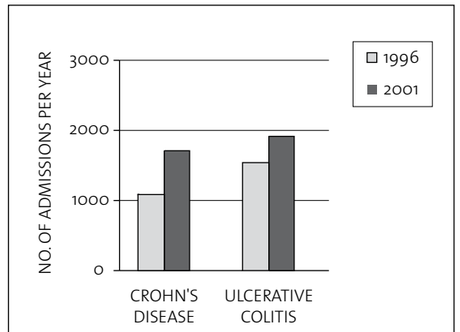

Figure 1: This graph shows the overall number of admission for patients Crohn's disease and ulcerative colitis in Ireland, in the years 1996 and 2001. The graph includes in-patient and day-case admissions.

Figure 1 — TOTAL NUMBER OF IN-PATIENTS AND DAY-CASE ADMISSIONS FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE IN IRELAND: 1996 - 2001

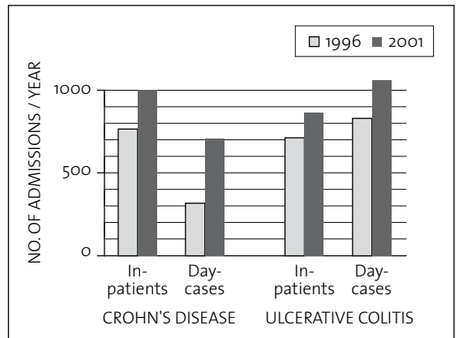

Figure 2: This graph shows the total number of admissions for patients with Crohn's disease and ulcerative colitis in Ireland, in the years 1996 and 2001. The graph specifically distinguishes between in-patient and day-case admissions for the patient groups in each year.

Figure 2 — TOTAL NUMBER OF ADMISSIONS FOR PATIENTS WITH CROHN'S DISEASE AND ULCERATIVE COLITIS IN IRELAND: IN-PATIENTS AND DAY CASES

from 42 admissions to 96, (Figure 4). In 1996, nine of the 21 in-patients with ulcerative colitis underwent surgery compared to 15 of 46 in 2001. The surgical procedures included colonic resections and stomal surgery.

In Ireland, the average length of stay has remained at 11 days for patients with Crohn's disease and has reduced marginally from 12 to 11 days for patients with ulcerative colitis. In our institution, the average length of stay for patients with Crohn's disease has reduced from 14 to 13 days and from 22 to 18 days for patients with ulcerative colitis.

C) Results of audit from Beaumont Hospital, 2001

During 2001, 92 patients were admitted as in-patients to Beaumont Hospital for further management for their inflammatory bowel disease. Forty-five patients had Crohn's disease, 35 had ulcerative colitis and two had indeterminate colitis.

Of the 45 patients with Crohn's disease, 44 had ileocolitis, colitis or a combination of both with one patient having gastric Crohn's disease. Sixteen patients underwent surgery during their admission (seven elective, nine emergency), 50% of whom required surgery for either stricturing or fistulating disease. Seventy five per cent had a bowel resection of some type (Table 1).

Thirty-five patients were admitted with ulcerative colitis, the majority of whom had either left-sided disease or pancolitis. Fifteen of these patients underwent surgery, seven on an elective basis and eight as an emergency. The commonest indication for surgery was failure of medical therapy. The commonest surgical procedure was a total colectomy (Table 2).

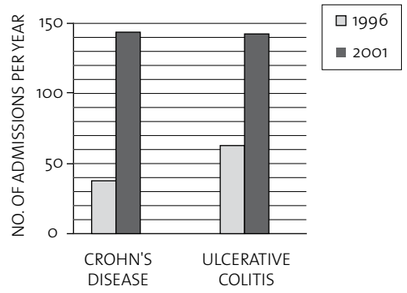

Figure 3 — TOTAL NUMBER OF IN-PATIENTS AND DAY-CASE ADMISSIONS FOR PATIENTS WITH INFLAMMATORY BOWEL DISEASE IN BEAUMONT HOSPITAL: 1996 - 2001

This graph shows the overall number of admissions for patients with Crohn's disease and ulcerative colitis in Beaumont hospital, in the years 1996 and 2001. The graph includes in-patient and day-case admissions.

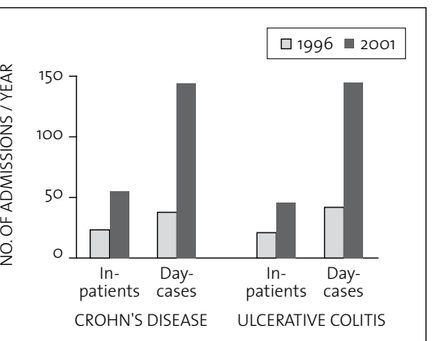

Figure 4 — TOTAL NUMBER OF ADMISSIONS FOR PATIENTS WITH CROHN'S DISEASE AND ULCERATIVE COLITIS IN BEAUMONT HOSPITAL: IN-PATIENTS AND DAY-CASES

This graph shows the total number of admissions for patients with Crohn's disease and ulcerative colitis in Beaumont hospital, in the years 1996 and 2001. The graph specifically distinguishes between in-patient and day-case admissions for the patient groups in each year.

DISCUSSION

The results of this study illustrate several points regarding the pattern of admission to hospital of patients with IBD in recent years. Overall, there has been an increased rate of admission during the relatively short time interval of this study. Despite this increase, there has been little change in the number of patients requiring surgery for their disease. There has been a reduction of four days in the length of stay for patients with ulcerative colitis in our institution but overall little change in the average length of stay for patients with IBD in Ireland. In addition, there has been a considerable increase in the number of day-case admissions, in particular related to patients with Crohn's disease. These observations however must be taken in the context that they depend completely on the accurate and complete documentation and collection of data for the HIPE system. We know however that over 95% coverage is estimated since 1995 in the HIPE system.

One potential reason for these trends is an increase in the incidence and prevalence of IBD globally and this has been supported in the literature over the last decade. Many studies have been carried out across Europe and the United States over the last number of years suggesting an increase in the incidence of IBD. A review from Sweden supports this increase during the past decades and quotes a prevalence of 0.5% in the northern part of the world at present.[1]

Armitage *et al* has reported an increasing incidence of both juvenile-onset Crohn's disease and ulcerative colitis in Scotland between 1981 and 1995.[2] Similarly, Hildebrand *et al* also reported an increase in the incidence of Crohn's disease in northern Stockholm. The incidence in their population was higher than that reported from other areas. Their results suggested a shift in presentation and diagnosis from ulcerative colitis towards Crohn's disease, but also a net increase in IBD.[3] An increase of IBD in children will obviously have a knock-on effect in the adult population. Pajares *et al*, having reviewed the epidemiology of IBD in Spain describe how IBD has gone from being considered a rare disease in Spain to being a relatively frequent one.[4] Other groups have demonstrated a similar trend with regard to the incidence of IBD.[5,6] The rising prevalence is thought to be due to a combination of increased incidence and in addition increased survival.[7]

A second explanation may be an increase in the recognition of these disease entities with increased awareness and easier availability of diagnostic tests. Despite this suggestion, some centres are still reporting a high prevalence of undetected disease. Howarth *et al* from Nottingham followed patients who were faecal occult blood positive and demonstrated that in comparison with detected disease, undetected ulcerative colitis is relatively common in these patients, but fortunately, usually presents with other symptoms to alert the clinician.[8] Other studies have supported the existence of this group of patients with undetected IBD, being picked up during routine screening examinations or during epidemiological studies addressing this exact issue.[9,10]

The use of new biological therapies requiring day case admission, specifically, anti-TNFα in the management of active Crohn's disease is likely to have made a significant impact on the number of day-case admissions. It is important to note that patients admitted for routine endoscopy on a day-case basis are not included in these numbers, and therefore almost completely represent patients admitted for anti-TNFα infusion. Rubenstein *et al*, from Chicago followed patients with Crohn's disease who had been treated with Infliximab and evaluated their use of hospital services. Their study showed a reduction in the number of hospitalisations and a decrease in the use of surgical service.[11] In combination with improvements in the medical management of patients with active IBD better nutritional management may have had an impact on the rate of surgical intervention in the management of these patients.

Table 1
DATA ON SURGICAL INTERVENTION FOR PATIENTS WITH *CROHN'S DISEASE*

INDICATIONS FOR SURGERY		SURGICAL PROCEDURES	
Stricture	5	Right Hemicolectomy	7
Fistulae	5	Small bowel resection	3
Small bowel obstruction	2	Total colectomy	2
Failed medical therapy	2	Anal fistulotomy	2
Abscess	1	Abscess drainage	1
Toxic megacolon	1	Refashioning of Ileostomy	1

This table outlines the indications for surgery and the surgical procedures performed, on those patients with Crohn's disease from Beaumont Hospital who were included in this audit.

Table 2
DATA ON SURGICAL INTERVENTION FOR PATIENTS WITH *ULCERATIVE COLITIS*

INDICATIONS FOR SURGERY		SURGICAL PROCEDURES	
Failed medical therapy	10	Total colectomy	11
Pouch surgery	2	Pouch surgery	2
Perforation	2	Proctectomy and ileostomy	1
Stricture Dilation (in a previously formed pouch)	1	Stricture Dilation	1

This table outlines the indications for surgery and the surgical procedures performed, on those patients with ulcerative colitis from Beaumont Hospital who were included in this audit

In conclusion, there has been an increase in hospital admission for IBD over the last five years in Ireland, most dramatically in the day-case admission for patients with Crohn's disease. Average length of stay has stayed relatively static and the numbers requiring surgery have changed little during this period.

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Cardiac rehabilitation services in Ireland: the impact of a coordinated national development strategy

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ABSTRACT

Background The national Cardiovascular Health Strategy including specific plans for cardiac rehabilitation was launched in Ireland in 1999. A survey of cardiac rehabilitation services was conducted in 2003 to evaluate progress on service provision.

Aim To establish levels of service provision, service formats and geographic distribution of cardiac rehabilitation services in 2003 and compare them with the status pre-Strategy (1998).

Method All hospitals in Ireland (n=39) admitting cardiac patients to a coronary or intensive care unit were surveyed by postal questionnaire.

Results All hospitals provided information and all reported providing Phase I cardiac rehabilitation. Seventy-seven per cent (30 of 39) provided Phase III rehabilitation in 2003 (i.e. outpatient cardiac rehabilitation services) compared with 29% (12 of 41) in 1998. Of those hospitals currently without programmes, 78% (seven of nine) had plans in place for programme establishment. All programmes had trained cardiac rehabilitation coordinators, multidisciplinary teams and multiple components as recommended in the Strategy. In 82% of hospitals, intervention was provided at Phase II (immediate post-discharge period) while 26% of hospitals provided intervention at Phase IV (long-term maintenance period).

Conclusions There have been substantial achievements towards the Cardiovascular Health Strategy target of providing cardiac rehabilitation services for all relevant hospitals in Ireland over the past five years. Service provision of cardiac rehabilitation can benefit from collective efforts made across centres to encourage the prioritisation of cardiac rehabilitation in national health policy initiatives.

INTRODUCTION

Cardiovascular mortality rates in Ireland have been decreasing steadily in recent years. Although Ireland's rates remain among the highest in Europe, the gap between cardiovascular mortality rates for Irish men and women under the age of 65 and the European Union average is narrowing.[1] The Second Report on the Implementation of the Cardiovascular Health Strategy[1] states that in this context the number of people living with chronic cardiovascular disease is increasing, resulting in an increased need for ongoing disease management, secondary prevention and cardiac rehabilitation.

Cardiac rehabilitation has been defined by the World Health Organisation[2] as the 'sum of activities required to influence favourably the underlying cause of the disease, as well as to ensure the patient the best possible physical, mental and social conditions so that they may through their own efforts preserve, or resume when lost, as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form of therapy but must be integrated with the whole treatment, of which it only forms one facet'. Core components of cardiac rehabilitation programmes typically include a combination of exercise, psychological and educational interventions.[3,4] Cardiac rehabilitation programmes are typically organised in four phases.[5] Phase I refers to the acute treatment of patients admitted to the intensive care unit and the in-hospital stage in recovery. Phase II follows discharge from hospital and is a period of convalescence for the patient. Phase III typically involves a 4-12 week outpatient programme incorporating exercise and education classes and is usually commenced between the fourth and eight

week post-discharge, depending upon the amount of cardiac damage.[6] Phase IV refers to the period of long-term maintenance and typically involves community-based exercise sessions.

In the past, service provision for cardiac rehabilitation in Ireland has been poor. A European Union survey of cardiac rehabilitation activity conducted in 1995 found that Ireland ranked among the lowest in relation to the number of cardiac rehabilitation programmes per head of population.[7] Following this, a first national survey of cardiac rehabilitation services in 1998 found that only twelve hospitals (29% of all hospitals admitting cardiac patients) provided outpatient programmes.[8] In 1999 the national Cardiovascular Health Strategy[9] was launched which aimed to coordinate and prioritise activities in relation to cardiovascular disease management. As a result additional resources were made available to cardiac rehabilitation services and ten recommendations were made specifically concerning cardiac rehabilitation. The first of these recommendations (R9.1) stated that 'every hospital that treats patients with heart disease should provide a cardiac rehabilitation service.'

The aim of the present study was to establish the level of service provision of cardiac rehabilitation in 2003. Geographic distribution of current programmes is outlined, staff profiles, programme formats and patient throughput are described and comparisons are made with service provision in 1998. This facilitates the assessment of the extent to which recommendation R9.1 has been achieved and evaluates the impact of the national Cardiovascular Health Strategy on cardiac rehabilitation service provision.

METHOD

All general hospitals admitting cardiac patients to a coronary or intensive care unit in Ireland (n=39) were surveyed by postal questionnaire to cardiac rehabilitation coordinators or clinical nurse managers of the coronary or intensive care unit as appropriate. Information was sought on the cardiac rehabilitation phases (phases I-IV) provided by the hospital; components of each phase and staffing levels. Where Phase III outpatient programmes were provided, programme formats (i.e. number of sessions and patients per group) and the number of new patients attending in the previous year were queried. Where outpatient programmes were not provided, information was sought on plans to develop programmes. Following telephone reminders the final response rate was 100%.

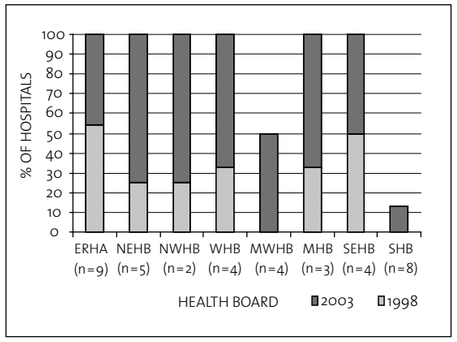

Figure 1. — PERCENTAGE OF HOSPITALS PROVIDING OUTPATIENT CARDIAC REHABILITATION SERVICES IN 1998 AND 2003 *(number of relevant hospitals per health board provided in brackets)*

RESULTS

Seventy-one per cent of hospitals admitting cardiac patients provided an outpatient (Phase III) cardiac rehabilitation programme in 2003 compared with 29% in 1998 (Figure 1). There was 100% provision in six of the health board areas. The Mid-Western Health Board provided services in 50% of hospitals while the Southern Health Board had the least developed cardiac rehabilitation services with only 13% (one of eight) of hospitals providing cardiac rehabilitation services. Of those hospitals currently without outpatient services, seven of nine had advanced plans to develop programmes and six of nine of these hospitals already had a cardiac rehabilitation coordinator in place. Hospitals without outpatient services cited lack of funding, lack of staff and lack of available space as the greatest barriers to programme development.

The number of new patients entering phase III programmes in 2002 was available from 71% of centres who provided programmes in the previous year (Table 1). The remaining hospitals were unable to provide throughput figures. Programmes in the Eastern Regional Health Authority enrolled most patients (1164 in total) while the smallest number was seen in the Midland Health Board area (50 in total). Across all centres providing information in 2002, a total of 2448 patients were enrolled compared with 696 in 1996. This demonstrates a substantial increase in patient throughput. Most centres (96%) placed no age restrictions on entry to the programme.

Phase III programmes lasted for a median of 8 weeks, including a median of 24 exercise sessions and a median of eight education sessions (Table 2). Typically six to eight patients were seen in exercise and education sessions. A wide range of components was offered by phase III programmes and matched core components recommended by national and international guidelines.[3,4,5] Almost all centres (ranging from 96-100%) provided education on cardiac disease, exercise, smoking cessation, medications, nutrition and stress management. Eighty per cent provided psychological advice; 77% provided sexual counselling and 53% provided support for vocational rehabilitation. Table 3 shows the mean amount of time spent on each component across centres. Most time was spent on cardiac education, relaxation training and nutrition education.

The multidisciplinary team comprised a variety of health professionals. There is evidence of a substantial increase in professional input to programmes since 1998 (Table 3). All centres had a designated cardiac rehabilitation coordinator who held at minimum a diploma level qualification or higher in cardiac rehabilitation training. Staff members who provided most time to the programme were cardiac rehabilitation coordinators, cardiac rehabilitation nurses, dieticians, physiotherapists and secretarial staff. Time designated to the programme by all professional categories has increased from a mean of 45.9 hours per week in 1998 to a mean of 113.1 hours per week in 2003. Despite these increases, centres have reported several concerns with staffing levels. Thirty per cent of centres reported needing increased time from a psychologist; 30% needed increased dietician time; 23% reported concerns about lack of cover for annual leave and 6% reported the need to appoint a vocational counsellor.

Service provision levels of phases I, II and IV provided by each hospital were also established. Phase I cardiac rehabilitation was provided in 100% of hospitals. Clinical management issues (e.g. education on diagnosis, diagnostic testing, blood pressure, medications and family history) and risk factor management issues (e.g. education on smoking, weight reduction advice, lipid lowering advice and risk factor assessment) were addressed by almost all centres. Psychosocial management issues were addressed by a majority of hospitals: 85% provided psychological advice; 82% provided sexual counselling and 67% provided vocational counselling. Post-hospital management issues proved to be the weakest components of phase I intervention. While 100% of hospitals provided discharge advice, three-quarters (74%) issued an individual patient plan for self-care and lifestyle change and 52% provided home needs assessment. The Heart Manual [10] (a six-week home-based post MI rehabilitation programme) was issued in phase I in 36% of hospitals.

Phase II cardiac rehabilitation was provided in 82% of hospitals. Risk factor education was the main intervention with 72% of all hospitals providing smoking cessation education and 66% providing nutrition education in Phase II. Psychosocial management was again less widely addressed: 49% provided psychological advice, 46% provided sexual counselling and 33% provided vocational counselling. In a majority of hospitals, care was delivered by telephone (64%) while individual outpatient (41%) and group outpatient (33%) appointments were offered in a number of centres. The Heart Manual was issued in phase II in 23% of centres. Home visits was the least frequent method of care delivery (13%).

Twenty-six per cent of hospitals reported that they provided a formal phase IV programme while outpatient appointments post-phase III were offered in 33% of hospitals. Some hospitals referred patients to support groups (26%) and community exercise classes (21%). About half of hospitals had links with general practitioners (56%); 33% linked with health promotion teams and 18% had links with community leisure centres.

DISCUSSION

The second national survey of cardiac rehabilitation service provision in Ireland has shown that over three quarters of hospitals admitting cardiac patients now provide an outpatient cardiac rehabilitation programme. This is a marked increase since 1998 when only 29% of hospitals provided programmes. It demonstrates that substantial progress has been made in achieving Recommendation R9.1. of the national Cardiovascular Health Strategy. It is envisaged that 100% service provision will be reached in the near future since seven of nine hospitals without outpatient programmes have plans to develop them. However, hospitals have reported several obstacles in achieving their plans such as lack of funding, staffing and available space.

The increases in programme numbers has been paralled by increases in patient throughput. There have also been marked increases in the time dedicated to programmes by health professionals since 1998. All categories of health professionals

Table 1
NEW PATIENTS ENTERING PHASE III CARDIAC REHABILITATION PROGS. BY HEALTH BOARD AREA IN 2002 AND 1996

HEALTH BOARD AREA	INFORMATION AVAILABLE IN 2002*	NEW PATIENTS IN 2002	INFORMATION AVAILABLE IN 1996**	NEW PATIENTS IN 1996
ERHA	6 (8)	1164	4 (6)	526
NEHB	3 (4)	197	1 (1)	75
NWHB	2 (2)	192	1 (1)	22
WHB	3 (4)	293	0 (1)	-
MWHB	2 (2)	135	-	-
MHB	1 (3)	50	0 (1)	-
SEHB	3 (4)	417	1 (2)	73
SHB	0 (1)	-	-	
TOTAL:	20 (28)	2448	7 (12)	696

**(Total number of hospitals with programmes in 2002)*
***(Total number of hospitals with programmes who replied in 1996)*

Table 2
STRUCTURE, FORMAT & DURATION OF PHASE III CARDIAC REHABILITATION PROGRAMMES PROVIDED (N=30)

	MEAN (SD)	MEDIAN	RANGE
Duration of programme (weeks)	8.6 (2.3)	8	(6-18)
Number of exercise sessions	19.7 (8.0)	24	(2-30)
Number of education sessions	9.4 (4.1)	8	(2-24)
Number of participants per exercise group	6.2 (1.4)	6	(4-10)

Table 3
EDUCATION COMPONENTS OF PHASE III CARDIAC REHABILITATION PROGRAMMES

COMPONENT	DURATION OF COMPONENT (MINS) MEAN (SD)	MEDIAN	RANGE
Cardiac education	71.3 (45.9)	60	(30-260)
Relaxation training	71.3 (58.4)	60	(15-280)
Nutrition	67.8 (31.9)	60	(30-150)
Exercise education	60.2 (36.0)	60	(0-180)
General psychological advice	45.4 (43.1))	45	(0-200)
Smoking cessation	35.2 (23.8))	30	(0-90)
Medication	26.3 (34.6)	45	(0-120)
Sexual counselling	25.4 (24.5)	17.5	(0-90)
Vocational counselling	18.0 (24.5))	0	(0-90)
Diabetic advice*	9.5 (16.5)	0	(0-60)

** Where required*

Table 4
NUMBER OF HOURS PER WEEK PROVIDED TO PHASE III PROGRAMMES BY PROFESSIONAL CATEGORY

PROFESSIONAL	HOURS PER WEEK IN 1998 MEAN (SD)	HOURS PER WEEK IN 2003 MEAN (SD)
CR Co-ordinator	28.2 (14.1)	37.2 (25.7)
CR Nurse	7.5 (12.7)	19.8 (24.6)
Dietician	3.1 (8.1)	13.0 (14.8)
Physiotherapist	2.8 (5.1)	17.7 (16.8)
Psychologist	1.7 (4.4)	2.9 (6.6)
Occupational therapist	0.7 (2.3)	2.8 (7.7)
Pharmacist	0.5 (0.5)	2.3 (5.5)
Social worker	1.3 (4.7)	2.6 (7.6)
Vocational counsellor	<1 centre	0.8 (3.6)
Secretary	0.1 (0.2)	10.3 (12.5)
Smoking cessation officer	-	1.7 (7.3)
Cardiac liaison nurse	-	1.1 (6.7)
Diabetic nurse	-	0.1 (0.34)
Health promotion tutor	-	0.7 (0.4)
TOTAL:	45.9 (-)	113.1 (67.8)

are now giving more time to cardiac rehabilitation programmes. Furthermore, additional types of health professionals are involved in the multidisciplinary team, such as smoking cessation officers, cardiac liaison nurses, diabetic nurses and health promotion tutors. Despite these additions, concerns over staffing levels remain and in particular centres have highlighted need for increased hours from psychologists and dieticians.

In phase III, all centres addressed a majority of core components as recommended by national and international guidelines. A minority of centres did not offer psychological advice or education on sexual and vocational rehabilitation in phase III and these issues were also less well addressed in phase I and phase II. The diagnosis of coronary heart disease has major psychological consequences [11] and evidence shows that patients can benefit from psychological intervention. A recent meta-analysis of psychoeducational programmes for coronary heart disease patients found a 34% reduction in cardiovascular mortality and 29% reduction in the recurrence of myocardial infarction.[12] Post-discharge issues were also less widely addressed both after the phase I period (where issues such as home needs assessment and use of the Heart Manual were not widely addressed) and after the phase III programme (where only 26% of centres provided Phase IV intervention). As the aim of cardiac rehabilitation is to facilitate long-term life-style changes,[13] interventions dealing with the issues of long-term maintenance would be desirable. Notwithstanding this, the fact that all hospitals provided Phase I cardiac rehabilitation and 82% provided Phase II means that those patients not attending a phase III outpatient programme can benefit from cardiac rehabilitation intervention during these earlier stages.

The rapid expansion in cardiac rehabilitation services is evident following a focused health service strategy in which cardiac rehabilitation was prioritised. This suggests that service provision of cardiac rehabilitation can benefit from collective efforts made across centres to encourage the prioritisation of cardiac rehabilitation in national health policy initiatives. The next challenge is to ensure optimum levels of service uptake among cardiac patients. A recent study estimating the total number of patients referred to and completing cardiac rehabilitation programmes in the UK in 2000[14] found that only 45-67% of patients were referred while just 27-41% attended. The adoption of a standardised audit system would allow centres to track patient uptake

of services and assess patient outcomes. Inability to provide figures by almost one in three centres on patient throughput suggests that administrative aspects of the cardiac rehabilitation services are currently underdeveloped. This underscores the importance of introducing a standardised audit system to facilitate routine data collection. The development of a standardised cardiac rehabilitation audit tool in Ireland is now at an advanced stage. This will facilitate an evidence-based continuous improvement approach to the provision of cardiac rehabilitation services in Ireland.

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Laparoscopic adrenalectomy, an initial experience of fifteen cases

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ABSTRACT

Background Laparoscopic adrenalectomy is an attractive alternative to open surgery, but making the transition can be difficult.

Aim To evaluate the initial experience of a general surgical team at a single institution at making the transition.

Methods The details of 15 patients undergoing laparoscopic adrenalectomy were prospectively recorded over a 21-month period.

Results Fifteen glands were removed from fifteen patients. Nine of these were left-sided. The mean gland size was 3.4 cm. Pathology included six non-functioning adenomas, four Conn's syndrome, two Cushing's syndrome and three phaeochromocytomas. Mean operating time was 74 minutes (range 31-172 minutes), with one conversion to open procedure. There were no morbidities and no mortality.

Conclusion Our initial experience demonstrates this approach to be the ideal technique for removal of benign adrenal tumours with significant advantages for the patient.

INTRODUCTION

The first case of laparoscopic adrenalectomy was reported in 1992[1] since when laparoscopy has become the approach of choice for adrenalectomy, especially in cases of benign tumours and isolated metastasis from lung cancer. As with laparoscopic cholecystectomy there are a number of arguments in favour of this technique; incisions are small, most referred disease is benign and there is excellent visualisation because of the magnification of an anatomically demanding area. Reported advantages over conventional adrenalectomy include decreased blood loss, lower requirement for post-operative analgesia, shorter hospital stay and reduced costs.[2-8] This study reports our initial experience of this procedure.

PATIENTS AND METHODS

Study Group

Details of patients undergoing laparoscopic adrenalectomy were prospectively documented between October 2001 and June 2003 at Beaumont Hospital, Dublin. The indications for surgery were benign inactive adrenal tumours of 6cm or less in size or hormonally active tumours of the adrenal. Hormonally inactive tumours larger than 6cm have a higher risk of malignancy[9] and therefore were also excluded. Although large glands do pose particular problems in relation to safety of dissection, and are considered by many authors to be a contraindication, a number of reports exist of lesions up to 13cm successfully treated with laparoscopy.[3,8] Glands which demonstrated any radiological features suggestive of malignancy (local invasion, irregular borders, obliteration of fat planes, lymphadenopathy or other intra-abdominal metastasis) were similarly excluded. All patients with hormonally active glands were investigated by the endocrinology service, and similarly all 'incidentalomas' were seen in consultation with the endocrinology service and proven to be biochemically inactive.

The three patients with phaeochromocytomas were commenced on α-blockade with phenoxybenzamine until orthostatic hypotension was apparent and then beta-blocked with atenolol. Patient demographics, pathology and operative characteristics were recorded. All patients were reviewed at a clinic six weeks following surgery.

Operative technique

Patients were placed in the lateral decubitus position, with the affected side elevated and extended. Pneumoperitoneum was then achieved at 15mmHg through a Verres entry 2cm below the costal margin of the affected side, medial to the anterior axillary line. A 10mm trocar was inserted though this incision to accommodate a 25° angled laparoscope. One

further 10mm port and one further 5mm port were then inserted along the costal margin caudad to the camera. A Harmonic Scalpel (Ultracision; Ethicon Endo-Surgery) was used to dissect the area around the adrenal gland and was excellent for maintaining a dry field and for facilitating identification of the adrenal vein. The adrenal gland was removed with the surrounding fat intact using an extraction bag. In all but two cases the initial incision had to be enlarged to facilitate extraction.

For left-sided lesions the following approach was used;

i) mobilisation of splenic flexure followed by medial mobilisation of spleen by division of lienorenal and diaphragmatic ligamentous attachments,
ii) identification of the splenorenal groove which guides the operator to the renal vein,
iii) dissection and ligation with titanium clips of the left adrenal vein,
iv) completion of adrenal dissection staying outside the peri-adrenal fat to minimise bleeding or breach of the gland.

For right-sided lesions the technique involved;

i) division of the lateral ligaments of the liver to partially mobilise the right lobe of liver,
ii) identification of the right renal vein and inferior vena cava prior to clipping and division of the right adrenal vein,
iii) completion of mobilisation of the adrenal gland.

RESULTS

Fifteen patients with a mean age of 54 years (range 38-70 years) underwent laparoscopic transperitoneal adrenalectomy (Table 1). Of the fifteen, nine patients were female and six were male with a mean age of 49 years and 54 years respectively. The average tumour size was 3.4cm (range 0.8-8cm).

The mean operative time (incision to closure) was 74 minutes, with a range of 31 – 172 minutes. Post-operative discharge time had a mean of 3.1 days (range 2-7 days). One male patient with bilateral adrenal hyperplasia, who had previous upper abdominal surgery for trauma, was converted to an open procedure due to inability to identify the gland. There was no morbidity and no mortality.

DISCUSSION

The results of 15 initial cases of laparoscopic adrenalectomy at our institution are presented. There is a learning curve for this procedure and with

Table 1
DEMOGRAPHIC, TUMOUR AND OPERATIVE CHARACTERISTICS

Patients	15
Sex, Male/Female	6/9
Side, left/right	9/6
Adrenal Disease:	
Adenoma	6
Conn's Syndrome	4
Cushing's Syndrome	2
Phaeochromocytoma	3
Mean Age, years (range)	54 (38-70)
Mean Size, cm (range)	3.4 (0.8-8)
Operative Time, minutes (range)	74 (31-172)
Conversion to open procedures	1
Length of stay, days (range)	3.1 (2-7)

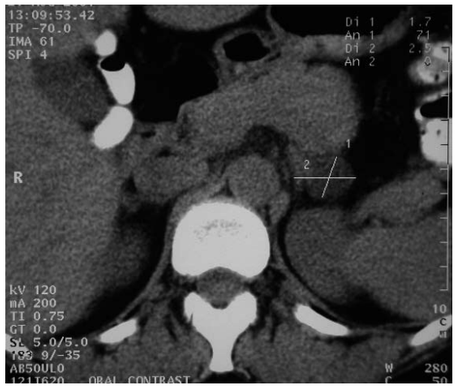

Figure 1 — CT IMAGE OF SMALL LEFT-SIDED ADRENAL ADENOMA

experience comes a reduction in surgical time,[10-12] peri-operative morbidity[13] and cost.[7] Meria et al (2003) found that most reported complications came at the beginning of the learning curve.[14] The only absolute contraindication to laparoscopic resection of adrenal tumours is invasive carcinoma requiring extensive excision, but the presence of a large right lobe of liver or previous abdominal surgery are only relative contraindications to surgery.[15] The latter accounted for the only conversion to open laparotomy in this series, and accounted for the longest operative time of 172 minutes.

Our experience leads us to conclude that left-sided lesions were less technically challenging than right-sided lesions. Although operative times were shorter for right-sided lesions (mean 59 vs 81 minutes), if we exclude the left-sided case which required conversion, the times are similar (mean 59 vs 63 minutes). In addition smaller lesions (Figure 1) were found to be subjectively less technically challenging than larger lesions.

Ultrasonic dissection presents a significant advantage by offering excellent haemostasis and better visualisation of tissue planes. This has been shown to reduce operative time and cost relative to conventional devices for this procedure.[16]

Laparoscopic resection of phaeochromocytomas is challenging due to their highly vascular nature, their tendency to be larger than non-secreting lesions and their potential for blood pressure surges due to intra-operative catecholamine release. Three patients with phaeochromocytomas were included in this study. These patients had effective and adrenergic blockade pre-operatively. There were no significant intra-operative or post-operative complications with respect to blood pressure or heart rate, although one patient required a nitroprusside infusion intra-operatively. During the mean follow-up of eight months there were no recurrences, the patients remain normotensive and long-term follow-up continues. Our early experience would support the growing evidence that phaeochromocytoma is not a contraindication to endoscopic resection.[17-19]

CONCLUSION

Our initial experience with laparoscopic adrenalectomy was encouraging. The procedure has an appreciable learning curve and therefore should only be performed against a background of significant laparoscopic experience. We believe it to be the operation of choice for benign or hormonally active adrenal disease.

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Intracapsular fractures of the femoral neck in younger patients

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ABSTRACT

Background Most femoral neck fractures in younger patients have a different mechanism, treatment, and prognosis from those in elderly patients.

Aims To evaluate the results of internal fixation of femoral neck fractures in patients aged between 20 and 60 years, and to determine reasons for failure.

Patients and Methods Thirty three patients aged between 20 and 60 years who sustained a femoral neck fracture between 1995 and 2000 were reviewed. This represents 5.6% of the total femoral neck fractures admitted to the unit during this period.

Results In 26 patients (78.8%) the fracture resulted from higher energy trauma. Of 23 patients with displaced fractures four patients (17.4%) developed avascular necrosis and one patient (4.3%) developed non-union. Factors influencing outcome were mechanism of injury, pre-operative fracture displacement, adequacy of fracture reduction and delay in surgery.

Conclusion Our study emphasises the importance of timely surgery and adequate reduction of displaced femoral neck fractures in younger patients.

INTRODUCTION

Fractures of the femoral neck occur in two different patient populations. A very small group (3-5%) are young patients subjected to higher energy trauma, usually motor vehicle crashes and falls from a height. The remainder occur in the elderly population and approximately 90% of these injuries are the result of a simple fall from the standing position.[1] The aims of our study were to evaluate the clinical and radiological outcomes of internal fixation of intracapsular fractures of femoral neck in patients between the ages of 20 and 60 years, and to determine the reasons for failure.

PATIENTS AND METHODS

Thirty-nine patients between the ages of 20 and 60 years were treated for intracapsular fractures of the femoral neck between 1995 and 2000. This represents 5.6% of the total femoral neck fractures admitted to the unit during this period including all age groups. Three patients were excluded from our study: one patient had osteogenesis imperfecta, another patient was mentally retarded and wheel chair bound pre-operatively, and the third patient had a fracture dislocation with an associated fracture of the acetabulum. Thirty-six patients eligible for the study were invited to attend a review clinic. Twenty nine patients attended the clinic. Of the seven patients who did not attend, four were contacted on the phone and their medical records were studied. No contact was possible with three patients.

The patients were assessed clinically and radiologically. Functional assessment was performed using the Harris hip score.[2] Pre-operative and post-operative radiographs were studied to determine the fracture type and reduction achieved. Radiographs were also assessed for non-union, evidence of avascular necrosis and loss of reduction. The Garden Index[3] was used to evaluate reduction of fracture. On the AP view the angle formed by the medial cortex of femoral shaft and the primary compressive trabeculae in the head and neck normally measures 160 degrees. An angle of less than 155 degrees was taken as an unacceptable varus reduction and one more than 180 degrees was considered as severe valgus reduction. Radiological evidence of avascular necrosis, non-union or conversion to arthroplasty was regarded as failure.

RESULTS

Of the 33 patients reviewed, 16 were male and 17 were female whose mean age was 46.3 years at the time of surgery. Mean follow-up was 37.7 months (range 18-76 months). The mechanism of injury was higher energy trauma in 26 patients (78.8%). Ten patients (30%) had an undisplaced fracture (Garden type 1 or 2), while 23 patients (70%) had a displaced fracture (Garden type 3 or 4). All patients with undisplaced fractures healed without any evidence of avascular necrosis or non-union, so further analysis is confined to the review of the patients with displaced fractures only.

Table 1
Results

METHOD OF FIXATION	TIMING OF SURGERY (HOURS)	NO. OF PATIENTS	SATISFACTORY REDUCTION (ANATOMICAL + VALGUS)	UNSATISFACTORY REDUCTION (RESIDUAL DISPLACEMENT + VARUS)	UNEVENTFUL HEALING (HARRIS HIP SCORE >80)	AVN	NON-UNION	EARLY OA
DHS	<12	1	1	-	1	-	-	-
	12-24	7	6	1	6	-	1	-
	>24	-	-	-	-	-	-	-
Screw fixation	<12	2	2	-	2	-	-	-
	12-24	11	8	3	8	2	-	1
	>24	2	1	1	-	2	-	-

Of the 23 patients with displaced fractures, 15 (65.2%) underwent screw fixation and eight patients (34.8%) were treated with sliding hip screw plate fixation with or without a Derotation screw. Three patients under went surgery within 12 hours of injury, 18 patients underwent surgery between 12 to 24 hours of injury and in two patients surgery was delayed for more than 24 hours. Intra-operative fracture reduction was anatomical in 14 patients and five fractures were fixed in acceptable valgus impaction. Fracture reduction was inadequate in four patients with three having residual displacement and one fracture was fixed in varus. Open reduction was performed in one patient due to failed closed reduction.

Seventeen of 23 patients (73.9%) healed without any radiological evidence of avascular necrosis, non-union or osteoarthritis. Four patients (17.4%) developed avascular necrosis while one patient (4.3%) developed non-union and underwent conversion to hemiarthroplasty (Table 1). One patient (4.3%) showed early osteoarthritic changes 68 months after surgery with mild symptoms. Impaction at the fracture site resulted in screws protruding laterally in two patients. These patients underwent removal of screws after the fracture union.

Five patients who developed avascular necrosis and non-union had displaced fractures. In three of these five patients, fractures resulted from high velocity injuries. Two had associated life threatening injuries which delayed their fracture fixation for three and seven days respectively. Four fractures were fixed with parallel screws and one fracture was fixed using dynamic hip screw plate. Four patients had inadequate reduction of their fractures, there was residual displacement in three fractures after fixation and one fracture was fixed in varus (Figure 1). One fracture pattern was of vertical shear type (Figure 2).

DISCUSSION

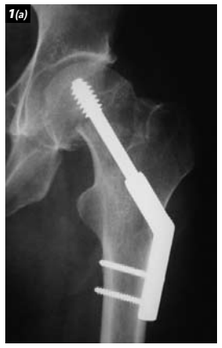
Protzman and Burkhalter[4] emphasised three basic differences between femoral fractures in younger patients and those in elderly patients. Firstly, they are uncommon. Secondly, the reported results of treatment are notably poorer compared to those in older patients. Also, there is a significant difference in the severity of trauma required to cause this fracture in young adults. Higher kinetic energy is necessary to produce a non-pathological femoral neck fracture in younger patients. These patients can have associated life threatening injuries. They related the non-union and avascular necrosis rates directly to the high energy trauma responsible for the fractures. In our series, three of four patients who developed avascular necrosis sustained their fracture following high energy trauma.

Avascular necrosis remains the main complication following internal fixation of intracapsular femoral fractures. Revascularisation of the femoral head after a fracture is a slow process. Calandruccio and Anderson[5] obtained autoradiographs of 113 femoral head specimens removed from the patients who had been given radioactive phosphorus before hemiarthroplasty for an acute intracapsular fracture. They reported that approximately 22% of the femoral heads were completely vascular, 47% were partially vascular, and 32% were completely avascular. Sevitt[6] performed arteriographic and histological studies on 25 femoral

heads obtained at autopsy of patients who had sustained an intracapsular fracture and they found total or partial necrosis in twenty one specimens.

There are three criteria for the successful treatment of femoral neck fracture in young patients: (i) fixation must be achieved within twelve hours of injury; (ii) anatomical reduction must be obtained through an open reduction if necessary; and (iii) the fracture must be stabilised with some form of multiple screw fixation. It is believed that circulation may improve after anatomical reduction and fixation through a reduction of the deforming forces on the remaining blood vessels.[7] Tooke and Favero[8] described 32 patients less than 50 years of age who had femoral neck fractures. Multiple devices were used for fixation and a capsulotomy was performed in only one hip. All patients with Garden 1 & 2 fractures healed without avascular necrosis. Patients with Garden 3 & 4 fractures had a 5.5% rate of non-union and a 33% rate of avascular necrosis. They reported only a single case of non-union, which they believed was due to failure to achieve adequate reduction. They emphasised the importance of achieving an anatomical reduction and performing reduction and internal fixation as soon as possible after injury. In our series, inadequate reduction was the significant factor among four of five patients who developed complications of AVN or non-union. One patient in our series who developed AVN had a fracture with vertical shear pattern. Pauwels[9] attributed non-unions in type 3 fractures to the increased shearing force of this vertical fracture.

Swiontkowski et al[10] presented 27 patients between the ages of 12 and 49 years who suffered femoral neck fractures. The fractures were treated with anatomical reduction, capsulotomy and fixation with 6.5mm A-O screws in a box pattern. The surgical procedures were done within eight hours of injury. All fractures in their series united. Avascular necrosis developed in 22% of the patients. They attributed the absence of non-union and low incidence of avascular necrosis to immediate reduction and internal fixation with compression. In our series, delay in surgery was a significant factor in two patients who developed avascular necrosis. On the other hand, Upadhyay et al[11] in a prospective randomised study found that a delay of more than 48 hours before surgery did not influence the rate of union or the development of non-union when compared with operation within 48 hours of injury.



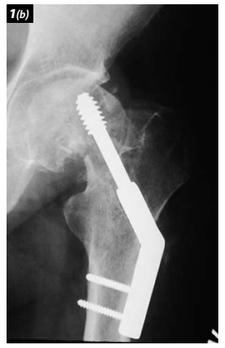


Figure-1 (a) — POST-OPERATIVE RADIOGRAPH OF A 53-YEAR-OLD MALE SHOWING FRACTURE FIXED IN VARUS

Figure-1 (b) — INADEQUATE REDUCTION LEADING TO NON-UNION

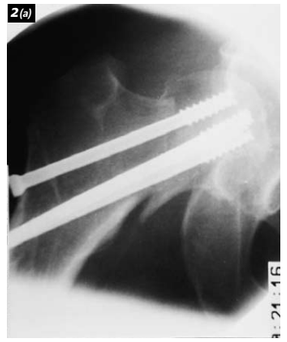
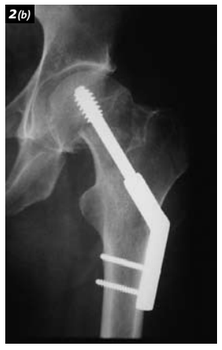


Figure-2 (a) — INTRA-OPERATIVE RADIOGRAPH OF A 53-YEAR-OLD FEMALE SHOWING INADEQUATE REDUCTION OF A VERTICAL SHEAR TYPE FRACTURE



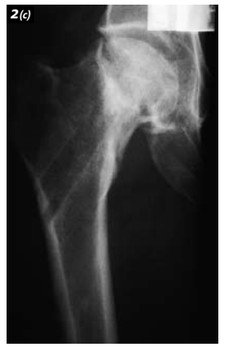


Figure-2 (b) — RADIOGRAPHS TAKEN 14 MONTHS AFTER SURGERY SHOWING SIGNS OF AVASCULAR NECROSIS AND PROTRUDED SCREWS

Figure-2 (c) — RADIOGRAPH TAKEN 19 MONTHS AFTER SURGERY SHOWING AVASCULAR NECROSIS

Anatomical reduction is optimal and should be achieved by open reduction if necessary. Cave[12] emphasised anatomical reduction in younger patients and recommended if one attempt at closed reduction fails, the surgeon should proceed directly to open reduction through an anterior approach. Valgus impaction provides a stable mechanical configuration.[13] Varus reduction is not acceptable. In our series all fractures fixed in valgus impaction united without any complication while one fracture that was fixed in varus developed non-union.

If multiple screw fixation is used as a method of fixation, the triangular and diamond patterns of fixation adapt well to the different forces applied to the hip in different body positions.[14] Bout et al[15] described the "three point principle" for the fixation of fractures. Both ends of the screws are anchored in the firm bone of lateral femoral cortex and subchondral bone of the head. The shafts of the screws are positioned to rest against the inner surface of the cervical cortex along the inferior and posterior borders. Subchondral screw fixation is recommended for better purchase.[16] Parker et al[17] compared parallel and crossed Garden screws and found that parallel screws were associated with lower incidence of non-union and avascular necrosis. In another study, Parker[18] described patient's age and pre-operative fracture displacement to be of the greatest value in predicting non-union. Although overall complication rate was higher among the patients in our series who underwent screw fixation as compared to those who underwent sliding screw fixation (30.8% as compared to 12.5%), there were other associated factors for failure, hence these results are difficult to compare.

CONCLUSION

Avascular necrosis and non-union are the most serious complications following displaced femoral neck fractures. High energy trauma, pre-operative fracture displacement, delay in surgery and failure to achieve adequate reduction are the factors contributing to these complications. Our study emphasises the importance of timely surgical intervention (preferably within 12 hours of injury) and adequate reduction while dealing with displaced femoral neck fractures in younger patients. Although these recommendations are extensively documented in the literature, they are sometimes overlooked resulting in serious complications.

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Olfactory function in people with genetic risk of dementia

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ABSTRACT

Background Screening for sensorial impairment is a secondary objective in the context of neurodegenerative diseases, including dementias. For example, olfactory dysfunction is among the first signs of Alzheimer's disease. There has been no study of olfactory function in Irish subjects at risk of dementia.

Aim To investigate olfactory function in non-demented Irish persons, who carry genetic risk factors for dementia.

Methods Thirty-eight Irish adult subjects, who are at risk of dementia, were recruited. Cognitive performance and olfactory function were assessed and apolipoprotein E (APOE) genotype determined.

Results Three and six subjects had a Mini Mental State Examination (MMSE) and Brief Smell Identification Test (B-SIT) score, respectively, outside the normal range. While five out of the fifteen ε-4 allele positive subjects had B-SIT scores outside the normal range, only one out of the twenty-three ε-4 allele negative subjects had; the difference in this frequency was significant (P=0.025). There was no significant difference (P=0.266) in the frequency of abnormal MMSE scores between ε-4 allele groups.

Conclusion Further investigation is required to explore the reasons for the higher prevalence of olfactory dysfunction in ε-4 allele positive subjects.

INTRODUCTION

Dementia is one of the most common and costly forms of cognitive impairment in the elderly. Dementia is a gradual, progressive decline in mental ability that affects memory, thinking processes, behaviour and physical activity. It is acquired and persistent and results in impaired activities of daily living. Different forms of dementia have been defined, but Alzheimer's disease (AD) is the leading form, which accounts for 65% of all dementias,[1] while vascular dementia is the second most frequent form of dementia.[2] Of concern, the incidence of AD is expected to grow exponentially in the next 50 years.[3] AD is a complex multifactor disease which involves environmental and genetic factors, particularly possession of an ε-4 allele of the apolipoprotein E (APOE) gene.[2] Other firmly established risk factors are increasing age, a family history, which raises the risk 2- to 5-fold,[4] and Down's syndrome.[5] The risk of AD increases further as more of these factors are combined.

While a curative treatment of cognitive impairment is currently impossible, current drug therapies, if started early enough, may slow down the progression of the condition. Therefore, it is important to plan prevention strategies and to diagnose early. The Mini Mental State Examination (MMSE) is a brief and widely used method for assessing cognitive mental status.[6] Several studies have examined the association of performance on the MMSE with APOE genotype, but the findings have been mixed.[7,8]

Screening for sensorial impairment is a secondary objective in the context of neurodegenerative diseases. Olfactory deficit, involving identification, recognition and detection of odours, is a sign of some neurodegenerative diseases.[9] Impaired olfactory detection predicts cognitive decline in non-demented older adults[10] and has also been observed in first-degree relatives of patients with AD.[11,12] Few studies have examined the association of performance in olfactory tests with APOE genotype, with some studies finding no effect of APOE genotype [10,11], while Wang *et al*[13] reported that in patients with mild cognitive impairment, those with ε-4 allele detected less odours than those without the ε-4 allele. Moreover, Murphy[14] reported significant deficits in odour identification in persons carrying an ε-4 allele, but who did not yet show evidence of dementia.[14] Therefore, the aim of the present study was to investigate olfactory function in non-demented Irish persons, who carry genetic risk factors for dementia.

SUBJECTS AND METHOD

Subjects

Thirty-eight subjects (26 women and 12 men; mean [SD] age, 58.0 [9.4] years) were recruited through an advertisement circulated among the members of the Alzheimer's Society of Ireland (n = 26) and at the Cork University Hospital (n = 12). Inclusion of first degree blood relatives of people with AD increased the frequency of ε-4 allele-positive subjects. The following exclusion criteria were applied: smokers (ex or current), local respiratory tract factors such as active rhinitis or sinusitis (allergic or infectious), history of septum surgery, depression, and stroke. 26.3%, 34.2% and 39.5% of subjects had attained primary, secondary and tertiary educational status, respectively.

Ethical Considerations

Before participation in this study, all subjects signed an informed consent document approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

Study design

This was an association study which examined the relationship between APOE genotype and cognitive performance and olfactory function in a cohort of Irish adults at risk of dementia. After recruitment, each participant was assessed for cognitive mental status and olfactory function. In addition a cheek swab was taken for DNA analysis. Cheek swabs containing buccal cells were used for DNA isolation by a PURGENE® genomic DNA purification kit (Promega Corporation, Madison, WI, USA). This isolation technique resulted in high molecular weight DNA (>20 kb) that was free of RNA contamination and had a 260/280 absorbance ratio >1.7. The isolated DNA was then stored at -20°C until required for analysis.

Assessment of cognitive performance and olfactory function were made prior to and independently of, the APOE genotype, and results were stored in a coded fashion.

DNA analysis

Restriction fragment length polymorphisms in the APOE gene were determined by polymerase chain reaction (PCR) followed by digestion of the amplified PCR product with *Hha I* restriction endonucleases as described previously.[15] Following restriction endonuclease digestion, APOE genotype was determined by ethidium-bromide-UVB illumination of the fragments separated on non-denaturing polyacrylamide gels (150 g/l). Additional *Hha I* restriction sites located throughout the amplified sequence do not interfere with the polymorphism detection as the five diagnostically important fragments of 91 base pairs (bp) (indicates presence of ε-2 or ε-3 allele), 83 bp (indicates presence of ε-2 allele), 72 bp (indicates presence of ε-4 allele), 48 bp (indicates presence of ε-3 or ε-4 allele) and 35 bp (indicates presence of ε-3 or ε-4 allele) were unique and easily identifiable.

Cognitive performance

As the present study was concerned with the overt signs of dementia, the standard version of MMSE,[6] which offers two alternative forms of measuring attention (serial subtraction; S7, and backward spelling; WB) was used. A cut-off score of 24 out of 30 distinguishes mild dementia from normal cognition, depending on age, and education, amongst other factors.[16]

Olfactory function

The shortened version of the University of Pennsylvania Smell Identification Test, namely the B-SIT,[17] was used in the present study. The B-SIT is a 12-item standardized, four-alternative, forced-choice odour-identification task, which takes less than five minutes. The stimuli are embedded in 'scratch and sniff' microcapsules fixed and positioned on strips at the bottom of each page. This B-SIT provides an accurate screen for olfactory dysfunction (test-retest reliability > 0.70).[17]

Statistical Analysis

Unpaired t-tests were used to compare mean age, MMSE scores and B-SIT scores among ε-4 allele positive and ε-4 allele negative subjects. The Fisher's exact test and χ^2 test was used to compare male to female ratio and percentage of subject attaining different levels of educational status, respectively, among ε-4 allele positive and ε-4 allele negative subjects. The Fisher's exact tests were used to compare the frequency of ε-4 allele positive and ε-4 allele negative subjects who had MMSE and B-SIT scores outside the normal range. In addition, logistic regression was used to assess the relationships between MMSE and ε-4 allele status as well as between BSIT and ε-4 allele status, after accounting for confounders (such as age and educational status).

RESULTS

Fifteen subjects were ε-4 allele positive. Of these, 12 were heterozygous (APOE-3/4 or APOE-2/4) and three were homozygous (APOE-4/4) for APOE genotype. The mean age, MMSE score, and B-SIT score, and percentage attaining different levels of educational status, as well as the ratio of men to women in the entire group and stratified by ε-4 allele status are shown in Table 1.

Three and six subjects had a MMSE and B-SIT score, respectively, outside the normal range. There was no significant difference ($P=0.266$) in the frequency of abnormal MMSE scores between ε-4 allele positive and ε-4 allele negative subjects. Similarly, when educational status and age were accounted for, there was still no significant (P=0.199) association between abnormal MMSE scores and ε-4 allele status. Only one out of the twenty-three ε-4 allele negative subjects had B-SIT scores outside the normal range, while five out of the fifteen ε-4 allele positive subjects had B-SIT scores outside the normal range; the difference in this frequency was significant (P=0.025). In addition, when age was accounted for, the significant (P=0.022) association between abnormal B-SIT scores and ε-4 allele status remained.

DISCUSSION

While a curative treatment of cognitive impairment is currently impossible, current drug therapies, if started early enough, may slow down the progression of the condition. Therefore, it is important to diagnose early. A widening of the approach to the early diagnosis of cognitive impairment is desirable.[18] The MMSE is a brief and widely used method for assessing cognitive mental status.[6] It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. Furthermore, it estimates the severity of cognitive impairment at a given point in time, follows the course of cognitive changes in an individual over time, and documents an individual's response to treatment.[19] A number of studies have examined the association of performance on the MMSE with APOE genotype,[7,8] possession of an ε-4 allele being an independent risk factor for AD [20] as well as possibly non-AD dementias.[21,22,23,24] In the present study, there was no association between MMSE scores and presence or absence of an ε-4 allele, even after adjustment for possible confounders. While this is in agreement with the findings of some studies,[8,25,26] it is in contrast with the findings of other studies which have reported low MMSE scores in those with the ε-4 allele.[7,27,28,29,30] However, the number of subjects in the present study who had MMSE scores outside the normal range was low (three out of 40) and this may have limited our potential for detecting a significant difference between APOE genotype groups.

Screening for sensorial impairment is a secondary objective in the context of neurodegenerative diseases. Impaired olfactory detection predicts cognitive decline in non-demented older adults[10] and has been also observed in first-degree relatives of patients with AD.[11,12] Few studies have examined the association of performance in olfactory tests with APOE genotype. In the present study, there was a significantly higher prevalence of olfactory deficit in non-demented Irish subjects who possessed at least one ε-4 allele compared to those who lacked the ε-4 allele. These findings are in agreement with those of Murphy[14] who reported significant deficits in odour identification in persons with the ε-4 allele, but who do not show yet evidence of dementia.[14] Furthermore, Wang *et al*.[13] reported that in patients with mild cognitive impairment, those with ε-4 allele detected less odours than those without the ε-4 allele.

The reason for the higher prevalence of olfactory deficit in ε-4 allele positive subjects in the present study is unclear. It is tempting to suggest that as the olfactory system may be the site of the first involvement of the AD process,[31] and may explain why olfactory dysfunction is among the first signs of AD,[31] the olfactory deficit in ε-4 allele positive subjects may have been due to preclinical AD. However, this is unlikely to have been the case, since the prevalence of AD in a group of individuals aged 60 to 69 years is 0.3% [32] and if possession of an ε-4 allele increases risk by up to three-fold, prevalence would still only be about 1%. Thus, the reason why about a third of ε-4 allele positive subjects had an olfactory deficit is still unclear. It is worth noting that olfactory impairment is not specific for AD type dementia,[17] and that, as mentioned already, APOE genotype is also a risk factor for other dementias.[21,22,23,24] However, the subjects in the present study were non-demented, as defined by the MMSE. Interestingly, recent studies in APOE knockout mice have provided evidence for a role for APOE in the olfactory process,[33] with APOE deficiency leading to substantial delay in olfactory nerve repair.[34] APOE has been shown to be expressed at high levels in human and mouse olfactory bulbs, particularly in the olfactory nerve layer and around the glomeruli.[35] These findings raise the possibility that APOE genotype may influence olfaction independent of AD or other dementias.

In conclusion, the findings of the present preliminary work suggest that there is a higher prevalence of olfactory dysfunction among Irish individuals at genetic risk of dementia. Further investigation is required to explore the relationships between APOE genotype, olfactory as well as cognitive deficits

Table 1
CHARACTERISTICS OF THE ENTIRE GROUP OF SUBJECTS AS WELL AS STRATIFIED BY APOLIPOPROTEIN ε4 ALLELE STATUS (Mean values and their standard deviations in parenthesis)

CHARACTERISTIC	ENTIRE GROUP	ε4 ALLELE POSITIVE	ε4 ALLELE NEGATIVE
n	38	15	23
Age (years)	58.0 (9.4)	58.0 (6.3)	58.0 (11.1)
Educational status (P/S/T) (%)	26.3/34.2/39.5	13.3/40.0/46.7	34.7/30.4/34.8
Male:Female	10:28	5:10	5:18
MMSE score	27.9 (2.6)	28.1 (3.4)	27.9 (2.1)
B-SIT score	9.5 (1.6)	8.9 (1.9)*	10.1 (1.2)

MMSE, Mini Mental State Examination; B-SIT, Brief Smell Identification Test; P, primary education; S, secondary education; T, tertiary education.
**Mean value significantly (P<0.05) less than that in ε4 allele negative group.*

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Recent alcohol intake and suicidality — a neuropsychological perspective

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ABSTRACT

Background Alcohol use disorders and suicidal behaviours are among the most prevalent and damaging of all psychiatric phenomena in Ireland and worldwide. Furthermore, alcohol use both chronic and acute has long been identified as a potent risk factor for suicidal behaviour.

Aims In this paper, the authors review the observational and experimental evidence for the acute neuropsychological effects of alcohol intake on suicidal ideation and behaviour.

Methods A selective review of the literature was conducted, using the PubMed database. Search terms employed included 'alcohol', 'suicide', 'binge' and 'acute alcohol intake'.

Results Cognitive mechanisms implicated include alcohol-induced deficits in attention-allocation, prospective cognition, autobiographical memory and disinhibition. Emotional mechanisms include alcohol-induced dysphoria, depression and aggression.

Conclusions This paper serves to highlight the importance of identifying and tackling acute alcohol intake and binge drinking as a risk factor for suicidal behaviour.

INTRODUCTION

Alcohol use disorders and suicidal behaviours are among the most prevalent and damaging of all psychiatric phenomena. Worldwide, alcohol accounts for 1.8 million deaths (3.2% of total) and 58.3 million (4% of total) of Disability Adjusted Life Years (DALYs) per annum.[1] The burden of alcohol related harm is not distributed equally, with industrialised countries most affected.[1,2] For example, lifetime prevalence of alcohol use disorders in the United States has been estimated as 20.1% for men and 8.2% for women, but these prevalence rates are much lower in countries where alcohol use is prohibited or restricted, such as the Islamic countries of the Middle East.[1,3] Alcohol use and related harm is now a major public health problem in Ireland, with levels of alcohol consumption the second highest in Europe.[2]

Pooled international data from the World Health Organization show that completed suicide rates for males increase from 22 per 100,000 in the 15 to 24-year-old age group to 50 per 100,000 in the over 75-year-old age group. The corresponding rates for females are 4.9 and 15.8 per 100,000. Parasuicide rates are highest in younger age groups, with the parasuicide to suicide ratio increasing from 4:1 in older people to as high as 200:1 in adolescents.[1]

Suicide has been identified as the leading cause of death for Irish men age 15 to 34 years, and tackling risk factors such as alcohol intake is of vital importance.[4]

There also exists a strong link between alcohol use disorders and suicidality, with both chronic alcohol abuse/dependence and acute alcohol intake being associated with substantially heightened risks of suicidal behaviour.[5-8] It has been estimated that one fifth to one third of the excess mortality associated with alcohol dependence is accounted for by suicide and that alcohol abuse/dependence may account for 15-25% of completed suicides. [9,10]

The relative risk of completed suicide in the alcohol dependent compared to the general population has been estimated as 60-120 and alcohol abuse/dependence is second only to depression in the list of the commonest psychiatric illnesses associated with completed suicide, and is sometimes identified as the most common psychiatric diagnosis.[5,10,11] A metaanalysis has demonstrated the lifetime risk of suicide among the alcohol dependent to be 7%, with corresponding risks of 6% for affective disorders and 4% for schizophrenia.[12] Furthermore, at a population level, rising per capita alcohol consumption and

higher levels of binge drinking have been seen to occur in conjunction with rising rates of completed suicides in some countries, such as Ireland, and the major anti-alcohol campaign in the former USSR in 1985 led to significant reductions in alcohol consumption and suicide rates.[2,13]

While these statistics strongly suggest an association between chronic alcohol abuse/dependence and suicide, they are based mainly on the results of epidemiological and case-control studies and provide little information on potential mechanisms explaining the interplay between them. In addition, relatively little research has focused on the acute effects of alcohol intake on suicidal ideation and behaviour, in both the alcohol dependent and non-alcohol dependent.

In this paper, we aim to review the most recent literature in the area, focusing primarily on the acute neuropsychological effects of alcohol intake on suicidal ideation and behaviour. Other factors in the relationship between acute alcohol intake and suicidality, such as the effects of gender, genetic factors and neurochemical and neuroanatomical perspectives are also important, but are beyond the scope of this paper. The adverse neuropsychological effects of recent alcohol intake described in this paper are likely to be potentiated considerably by psychiatric disorders such as depression and attention deficit hyperactivity disorder, organic brain disease such as vascular cognitive impairment and intellectual disability.[14,15,16]

Recent alcohol intake and suicidal behaviour-observational data

High blood alcohol concentrations (BACs) have been demonstrated in 46-77% of suicide attempters and 33-59% of suicide completers.[17-24] A more recent review found that 10-69% of completed suicides and 10-73% of suicide attempters tested positive for alcohol use.[25]

In a study of emergency room attenders, higher BACs were found among patients attending for assessment of suicidality than among those attending for other reasons, indicating a possible dose-response relationship between alcohol and suicidality.[7] A recent case-control study demonstrated recent drinking (within six hours) to be strongly associated with intentional injury (odds ratio of 10), and a stronger predictor of intentional injury than alcohol dependence.[26] Similar findings were reported by the Houston case control study, with odds ratios of a near lethal suicide attempt ranging from 2.4 for alcoholism to 7 for drinking within three hours of the attempt.[27]

Furthermore, alcohol intake in suicidal individuals has been associated with use of more lethal suicide means and recent alcohol intake has been associated with heightened suicide risk in the alcohol dependent.[5,6,20,22] Therefore, these findings imply a strong relationship between acute alcohol intake and suicidality. But what are the neuropsychological mechanisms by which this acute effect is mediated?

Cognitive and Emotional Mechanisms

A number of cognitive and emotional processes are potentially involved in mediating the effects of acute alcohol intake on suicidal ideation and behaviour. These different mechanisms may have an additive or overlapping effect.

It has been proposed that some individuals consume alcohol in an attempt to turn suicidal ideation into action.[20] This behaviour may be influenced by the individual's own perception of how alcohol will affect their mental state ('alcohol expectancies'). The individual may believe that alcohol will give them the motivation to attempt suicide or to make that attempt painless.[28] 'Alcohol expectancies' may also differ between males and females. Furthermore, if an individual drinks alcohol to relieve an unpleasant mental state but does not derive any benefit from drinking, they may then be propelled into suicidal ideation or behaviour.[28]

Alcohol intoxication can lead to deficits in attention-allocation, whereby the intoxicated individual is less aware of internal and external cues and less able to make sense of them, thus leading to a state of cognitive constriction. This leads to difficulties in problem-solving, with a restricted range of options available to the intoxicated individual, a state that has also been termed 'alcohol myopia'. When combined with other factors that may accompany intoxication, such as a dysphoric mood state and disinhibition, the individual may be more likely to see death and suicide as a potential solution to a problem and act on suicidal ideation, particularly if they have had suicidal ideas prior to becoming intoxicated.[29]

'Alcohol myopia' can also lead to disinhibition, due to deficits in the ability to assess the advantages and disadvantages of a particular course of action

or behaviour and impairing the individual's ability to identify effective coping strategies. These deficits can then lead to an increased likelihood of acting out behaviours that would normally have a high degree of inhibition conflict, such as self-harm and suicide attempts.[29]

Closely related to cognitive constriction and 'alcohol myopia' is prospective cognition. Suicide attempters have been demonstrated to be less fluent in coming up with positive events that might happen in the future, and it is possible that, in view of alcohol-specific effects leading to frontal lobe dysfunction, that intoxicated individuals may have similar deficits.[30]

Finally, deficits in autobiographical memory have been proposed to explain trait-dependent deficiencies in problem-solving skills.[30] In acute alcohol intake in some individuals, the combination of a dysphoric mood state and constricted cognition may possibly lead to the selective recall of unhappy autobiographical memories, thus perpetuating a dysphoric mood state and increasing the risk of suicidal ideation and behaviour.

The ascending limb of the BAC curve is associated with mild euphoria, disinhibition, aggression and increased psychomotor activity. While of no clinical relevance in normal individuals, this change in emotion in the suicidal individual may lead to a transient increase in the risk of suicidal ideation and behaviour. The descending limb of the BAC curve, however, with its associated dysphoria, depression and aggression is more likely to lend a malignant colour to the cognitive changes described before and increase the risk of suicidality.[28]

In relation to aggression, individuals who are angered and not given the opportunity to retaliate may turn to alcohol use.[31] Furthermore, intoxicated individuals may also be more likely to behave aggressively, due to a combination of emotional changes and the effects of disinhibition alluded to in the previous section.[32]

CONCLUSIONS

A large amount of observational data exist that suggest a strong link between recent alcohol intake and suicidality. Mechanisms by which this effect is mediated are undoubtedly numerous and complex and are not confined solely to the neuropsychological perspective described in this paper. A discussion of the effects of psychiatric disorders such as depression, organic disorders such as vascular cognitive impairment and developmental disorders associated with low intelligence and life-long cognitive problems was outside the scope of this review. However, the experimental evidence supporting this neuropsychological perspective is compelling and serves as a potent reminder of the dangers of alcohol intoxication and binge drinking in relation to suicidal ideation and behaviour. Further research on this neuropsychological perspective is needed to describe in more detail the cognitive and emotional mechanisms involved, and the role of other factors such as gender and personality type.

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Maternal brain death — an Irish perspective

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ABSTRACT

Background Brainstem death is a concept used in cases in which life-support equipment obscures the conventional cardiopulmonary criteria of death. Brainstem death during pregnancy is an occasional and tragic occurrence.

Aims To consider the ethical, legal and medical issues raised by maternal brainstem death.

Methods Medline and Embase search.

Results The death of the mother mandates consideration of whether continuing maternal organ supportive measures in an attempt to attain foetal viability is appropriate, or whether it constitutes futile care. There is no theoretical limit to the duration of time for which maternal somatic function may be sustained. However, successful prolongation of maternal somatic function in pregnancies of less than 16 weeks gestation has not been reported to date. There is no legal imperative to continue maternal somatic support where there is little likelihood of a successful foetal outcome.

Conclusion The difficult issues raised by maternal brainstem death mandates a consensus building approach to decision making in this context.

Key Words Maternal; Brain Death; Brainstem death; Foetus; Ethics; Legal.

INTRODUCTION

'Brain death' describes the irreversible loss of brainstem function in a patient receiving artificial organ support that delays the onset of cardiac arrest and somatic death.[1] It is an irremediable event which heralds the permanent loss of consciousness. Brain death is ultimately followed by circulatory arrest, and is internationally recognised as being equivalent to somatic death.[2] It is generally considered unethical and futile to continue to support vital organ function once a diagnosis of brain death has been made.[3] A potential exception is maternal brain death, where a live foetus is present. The mother and foetus are two distinct organisms, and the death of the mother mandates consideration of the appropriateness of continuing maternal somatic support in order to prolong gestation to attain foetal viability. Two recent cases have been reported in this country in recent years,[4-6] highlighting the need to carefully consider the issues raised by these complex and tragic situations.

BRAIN DEATH VERSUS SOMATIC DEATH

The irreversible cessation of brainstem function implies death of the brain as a whole.[1,7-10] This concept is used to determine when death has occurred in cases in which the provision of 'life-support' obscures the conventional cardiopulmonary criteria of death.[7-9] This concept is widely accepted in the medical field[2], and is legally recognised in most countries, including Ireland. The Memorandum on Brain Death reinforces this diagnosis in Ireland,[11] though 'death' as such is not defined in law in this country.[12,13] This concept provides the basis for cadaveric organ donation. However, there remain significant differences worldwide in the diagnostic criteria used for determination of brain death.[2] Some debate does exist in the medical literature regarding the equivalence of traditional 'somatic' and 'brain' death.[14-17] What is not in dispute is that fact that brain death is a totally irreversible, irremediable, and final event which heralds the permanent loss of arousal and consciousness. There is no recorded case of recovery following the diagnosis of brain stem death. These findings form the basis for the concept of the equivalence of somatic and brain death.

Brain death ultimately is followed by somatic death, often within days, despite meticulous supportive care.[18] While there are rare and exceptional case reports of survival for longer durations in the literature, it is generally considered unethical and futile to continue to support vital organ function once a diagnosis of brain death has been made.[3] However, in the tragic situation of maternal brain death, attempts have been made to sustain maternal somatic function with the aim of allowing the

pregnancy to continue until the foetus has attained viability. It is not generally considered to be maternal life support *per se* in that maternal brain death, and therefore legal death, has occurred.

MATERNAL BRAIN DEATH AND LIMITS OF FOETAL VIABILITY

The key determinant of success of attempts to sustain maternal somatic function is the duration of time required for the foetus to attain viability. However, there are insufficient data regarding the effects of maternal brain death on the limits of foetal viability. It does seem likely that the physiologic alterations and therapeutic interventions necessary to sustain maternal somatic function (e.g. the effects of vasopressor therapy on utero-placental blood flow) would impact adversely on the onset of foetal maturity.

Despite these reservations, it is useful to consider the data on premature delivery in the general population as a reference point in determining the limits of foetal viability in the setting of maternal brain death. A foetus born before 24 weeks has little prospect of surviving.[19] At 24 weeks, a foetus has approximately a 20 – 30% likelihood of survival with a 40% chance of suffering from severe handicap if born alive.[19] At 28 weeks, there is an approximately 80% chance of survival and a 10% risk of severe handicap. A gestational age of 32 weeks has generally been considered the earliest time at which delivery can be made with the best chance of survival and the least chance of handicap. At that stage there would be a 98% chance of survival with a less than 2% risk of handicap.[19]

LIKELIHOOD OF SUCCESSFUL MATERNAL SOMATIC SUPPORT

The determination of the likelihood of successfully maintaining maternal somatic function for the duration necessary to achieve a good foetal outcome is of central importance. The rarity of prolonged maintenance of somatic function following brain death is clear from earlier studies reporting the ventilation of patients post brain stem death until cardiac arrest supervened. In their series of 1200 brain dead patients, Jennett and Hessett were unable to find a single case of somatic survival beyond 14 days.[20] Hung and Chen, in a prospective study of 73 patients that met the clinical criteria for brainstem death, found that 97% developed cardiac asystole within seven days despite continued full cardiorespiratory support.[21] In an older study, Jorgensen reported that of 63 patients diagnosed as brain dead, 100% developed asystole within nine days.[22] Median time to cardiac arrest following brain death was 3.5 – 4.5 days in a UK study.[23] More recently, Shewmon, in his meta-analysis of somatic survival following brain death, did report multiple cases of prolonged maintenance of somatic function following brain death, but acknowledged that was very much the exception.[24]

The longest duration for which successful support of maternal organ function following maternal brain death has been achieved to date is 107 days.[25] The woman involved was a 30-year-old who suffered a massive brain injury at 15 weeks gestation. She was declared brain dead 10 days later, i.e. at 16.5 weeks. Vital organ support was provided for 15 weeks and two days (i.e. 107 days), and a live infant was delivered at approximately 32 weeks gestation. Maternal somatic function remained relatively stable up until organ support was discontinued following delivery of the infant. This raises the potential that support of maternal function could have been prolonged for longer in this case, had it been necessary.

In summary, it is possible, at least in theory, to sustain maternal somatic function for extended periods of time. However, the duration of successful maternal somatic support has not been extended in fifteen years, despite dramatic advances in organ support therapies in the interim. Of importance, the successful delivery of a live foetus has never been reported where pregnancies were less than 16 weeks gestational age at the time of maternal brain death.

ETHICAL ISSUES

Maternal brain death raises difficult ethical issues. While it is clear that the nearer the pregnancy is to term, the more likely that there can be a successful delivery by caesarean section, the outer limits of successfully maintaining a body on life support in the absence of brain stem function are unclear. In addition, there is no proven management strategy to maintain maternal somatic function; therefore this can be considered to constitute experimental therapy. The question arises as to whether attempting to sustain maternal somatic function for a prolonged duration following brain death is an ethical option. It seems that it can only be considered ethical if there is some – albeit poorly quantified – hope of success. An alternative viewpoint is that this constitutes medical experimentation with little or no hope of success. Other issues which require

detailed consideration with respect to the mother include the woman's right to autonomy, the need to respect a body following brain death and the woman's right to die with dignity. Balanced against these considerations regarding the mother are the ethical issues which centre on the foetus. A key issue is an examination of whose interest takes primacy, i.e. the interests of the foetus or those of the mother.

Finnerty et al have raised three possible approaches to these ethical issues.[26] The first approach is to view the subject as a terminally ill, autonomous patient; in this case, maternal wishes as expressed previously will prevail. With this approach, it is particularly important to determine the existence of any previously expressed maternal opinions (e.g. advanced directive, living wills, discussion with family). The second approach is to view the subject as a 'cadaveric incubator' with no autonomous rights; in this case the rights of the foetus prevail. The third approach is to view the patient as a voluntary organ donor if the patient had previously expressed positive views regarding organ donation; in this case it could be viewed that she is willing to act as an incubator for the benefit of the foetus.[26]

The interests and concerns of other family members, particularly the next-of-kin, also deserve consideration. Further issues may arise where there is uncertainty as to the identity of the next of kin, such as where the maternal next-of-kin is not the foetal next-of-kin. The immediate family must be centrally involved in decision-making, be offered counselling and made aware of their right to independent legal and medical advice.

LEGAL ISSUES IN THE IRISH CONTEXT

The legal rights conferred on the foetus are closely linked to the maternal right to therapeutic abortion, generally depend on gestational age, and vary across Europe. In the Irish Republic, the foetus has been accorded a legal right to life, as stated in Article 40.3.3 of the Constitution of the Republic of Ireland:

> *"The State acknowledges the right to life of the unborn and with due regard to the equal right to life of the mother, guarantees in its laws to respect, and as far as practicable by its laws, to defend and vindicate that right."*

Article 40.3.3 asserts the *right to life* of the unborn, and treats the foetus as a person having the same right to life as any other human being, and it makes no attempt to suggest that that right is limited or qualified by the stage of foetal development. Mills argues that the State, in its application of this Article, considers life to begin at implantation.[27] Article 40.3.3, in referring to the '*equal right to life of the mother*', necessarily implies that no interest of the mother, or of anyone else, short of a right to life, can overbear the right to life of the unborn. Given that the mother is legally dead, then in the strict legal sense, her right to life is no longer of relevance.

Sheikh and Cusack, in considering the medicolegal implications of this legal protection of the foetus, contend that there is an obligation to maintain a foetus to a viable gestational age.[5] It seems likely that a court would consider that if it can be said that there is exists a realistic prospect of delivery of a live baby, then no-one (whether the Health Authorities, the Hospital, a family member or the putative father) would be justified in removing life support when that would inevitably result in ending the life of the foetus. However, Sheikh and Cusack raise the possibility that, if maternal organ support were continued, and resulted in the birth of a seriously injured child, then that child could then institute legal proceedings for negligence.[5]

In contrast, if the available medical evidence suggested that is no realistic prospect of delivery of a live baby, then maternal somatic support would be considered futile, and would not be permitted.[5] This position is supported by the advice of the then Attorney General in the case of a maternal brain death at 14 weeks gestation in this country.[5,6] He stated that withdrawal of ventilation, nutrition and fluids would not require legal sanction given that the likelihood of successful foetal outcome was considered to be remote.[5,6] Therefore, even though the foetus has considerable legal rights in this country, there appears to be no legal imperative to continue maternal somatic support where there is little likelihood of a successful foetal outcome. However, this remains controversial, and has not been subjected to legal challenge.

Finally, the lack of a defined maximum period for sustaining maternal somatic function, coupled with the protection afforded to the foetus, raises the potential for the need to exclude pregnancy, even in its earliest stages, in all brain dead females of childbearing age prior to terminating somatic support.

MEDICAL INTERVENTIONS REQUIRED TO SUSTAIN MATERNAL SOMATIC FUNCTION

As already stated, there is no medical therapy or management strategy which prolongs maternal somatic function for prolonged durations of time following brain death. The intensive care physician is faced with extrapolating from the experience of sustaining organ function following brain death to allow for organ donation, and consulting case reports[3,25,26,28] and reviews[29] in the literature. A relatively predictable picture involving loss of cardiovascular stability, complete pituitary failure, sepsis and bradyarrythmias resulting in eventual cardiac arrest emerges.[3,25,26,28] Support of multiple organ systems, including the respiratory, cardiovascular and endocrine systems are near universal requirements. Nutritional support should be instituted early, preferably by the enteral route. Specific invasive procedures may be necessary, including placement of a tracheostomy to facilitate long-term mechanical ventilation, and placement of invasive lines including a central venous pressure line and an arterial line to facilitate management of cardiovascular instability. Pituitary failure is likely, mandating hormonal replacement with thyroid hormone, corticosteroids and vasopressin and management of diabetes insipidus. Insulin therapy may be required to manage glucose intolerance. Thermovariablity may be particularly difficult to manage, and may require heating and cooling blankets and repeated septic screens. Blood transfusion may be required for management of persistent anaemia. The efficacy of erythropoietin in this context is not known. Maternal thromboembolism must be considered a high risk, mandating prophylaxis with fractionated or unfractionated heparins.

Sepsis, in the absence of haemodynamic collapse, constitutes the greatest risk to maternal somatic function. Repeated episodes of sepsis, including recurring [ventilator associated] pneumonias, and [urinary catheter associated] bladder and kidney infections are likely. Blood stream infections are particularly likely, due to the presence of intravascular catheters. These infections are likely become increasingly resistant to antibiotic therapy over a time period of several months in the ICU. Strict asepsis, if possible involving isolation of the maternal body, within the ICU, is necessary to reduce the likelihood of developing sepsis. Consideration should be given to strategies to reduce the incidence of catheter-associated sepsis, although unproven in this context, including the use of antibiotic or bactericide coated catheters and/or using tunnelled central venous lines.

CONCLUSIONS

Maternal brain death raises difficult ethical and legal issues. A consensus building approach that involves broad based consultation including the immediate family, appropriate legal advice and external medical experts is central to resolving these issues. It is clear that there is no theoretical limit to the duration of time for which maternal somatic function may be sustained. However, successful prolonged maintenance of maternal somatic function is rare. The right to life conferred on the foetus from the earliest stages of gestation in this State may only be usefully exercised if there exists some expectation of successful delivery of a live baby. If no realistic prospect of success exists, then maternal somatic support would be considered futile, and should not be permitted. It seems reasonable to consider prolongation of maternal somatic function to be futile if the pregnancy is of less than 16 weeks gestation at the time of maternal brain death, given the absence of reports of successful delivery of a live foetus in these pregnancies. This might be an appropriate cut-off point in this context. However, the fact that this is an arbitrary cut-off point must be emphasised.

Despite these difficulties, there remains an imperative to develop guidelines for healthcare providers in Ireland regarding how to resolve the issues raised by maternal brain death. It is likely that further similar cases will arise in this country in the future.

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A case of resistance to thyroid hormone without mutation in the thyroid hormone receptor beta

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ABSTRACT

Background Resistance to Thyroid Hormone (RTH) is a condition caused by tissue hyposensitivity to the effects of circulating thyroid hormone, and may be misdiagnosed as hyperthyroidism.

Aims We report the first case of RTH in an Irish patient highlighting the clinical features and the pathophysiological mechanism underlying the characteristic laboratory abnormalities found in the condition.

Methods We describe an isolated case of RTH initially misdiagnosed as hyperthyroidism, and detail the investigations which ultimately led to the correct diagnosis. Genetic screening of the thyroid hormone receptor beta gene was performed.

Results Thyroid function tests including T3 suppression test and TRH-stimulation test suggested a diagnosis of RTH. Genetic testing failed to demonstrate a mutation in the thyroid hormone receptor.

Conclusion RTH is a rare inherited condition that may be misdiagnosed as hyperthyroidism. The case we describe most likely results from a de novo mutation in an as yet undiscovered gene. RTH should be considered in patients with elevated thyroid hormone levels and normal TSH so that unnecessary and potentially harmful treatment can be avoided.

INTRODUCTION

Resistance to Thyroid Hormone (RTH) is a disorder of tissue hyposensitivity to the actions of thyroid hormone, and in many cases is initially misdiagnosed as hyperthyroidism. RTH is characterised by elevated thyroid hormone levels and unsuppressed thyroid stimulating hormone (TSH) levels, and a varying constellation of clinical findings. In the majority of cases, RTH is caused by an inherited mutation in the thyroid hormone receptor beta. We describe an isolated case of RTH without an identifiable mutation in the thyroid hormone receptor, the first reported such case in an Irish patient, and we review the condition with particular reference to non-thyroid receptor RTH.

CASE REPORT

A 21-year-old woman was referred for an endocrinology opinion because of abnormal thyroid function tests. She had attended her general practitioner complaining of fatigue. On questioning, she did not complain of symptoms suggestive of hyperthyroidism. She was on no medications and had no significant past medical history. There was no family history of thyroid dysfunction.

Physical examination revealed her pulse to be 80 beats per minute and regular. She weighed 52.6 kgs and had a goitre. There were no stigmata of hyperthyroidism on physical examination.

Thyroid function tests demonstrated a total thyroxine (TT4) of 217 nmol/L (69-141) and a TSH of 1.01 mU/L (0.4-4.0). Thyroid antimicrosomal and antithyroglobulin antibodies were negative.

A diagnosis of antibody-negative Graves' Disease was suspected and the patient was commenced on carbimazole 15 mg twice daily.

On review in November 1999, the patient complained of increased fatigue. The TT4 was 158 nmol/L but the TSH was now elevated at 11.8 mU/L. Two months later, following reduction in the dosage of carbimazole, the TT4 was 169 nmol/L but the TSH remained persistently elevated at 6.9 mU/L. The carbimazole was discontinued. Two months following cessation of therapy, the TT4 was 238 nmol/L, TSH 1.47 mU/L and total triiodothyronine (TT3) and free T4 were also elevated at 3.7 nmol/L (0.8-2.5) and 33 pmol/L (10.3-24.5) respectively. Levels of Sex-Hormone Binding Globulin, CPK, Serum Ferritin, and Alkaline Phosphatase were tested and were normal, apart from mildly elevated SHBG of 129 nmol/L (normal range 18.6-117).

Based on the pattern of thyroid function testing, the diagnoses of RTH or TSH-producing pituitary adenoma were considered. The family of the index case volunteered to have thyroid function testing performed. Neither parent nor either of the patient's two sisters demonstrated a similar abnormality in their thyroid function tests. Thyroid function tests were also measured at the University of Chicago (Figure 1). TRH stimulation testing performed in the index case demonstrated a normal TSH response to the administration of intravenous TRH (Table 1). Magnetic Resonance Imaging of the pituitary gland was normal (not shown). These results suggested that the most likely diagnosis was RTH. To confirm, a triiodothyronine (T_3) suppression test was performed. Oral T_3, at a dose of 50 microgrammes a day for three days, followed by 100 microgrammes a day for a further three days, was administered to the patient and to a control with no history of thyroid disease and normal thyroid function tests as baseline. On day seven, 200 microgrammes of TRH was given intravenously, and samples taken for measurement of FT4, TSH and prolactin at 0, 15, 30, 45, 60, 90 and 120 minutes. Results for the patient and the control are shown in Table 2 and Figure 2, and demonstrate, in contrast to the control in whom the TSH was fully suppressed, failure of complete suppression of TSH in the patient, and preservation of the response to TRH, despite the high doses of exogenous T_3.

These results are consistent with a diagnosis of RTH. DNA was isolated from peripheral blood and sent, together with a skin biopsy, to the University of Chicago for genetic analysis. The entire thyroid hormone receptor beta gene (both beta 1 and beta 2) was sequenced from genomic DNA and from cDNA reverse transcribed from fibroblast beta 1 mRNA. No mutations were found. A diagnosis of RTH without mutation in the thyroid hormone receptor beta was made.

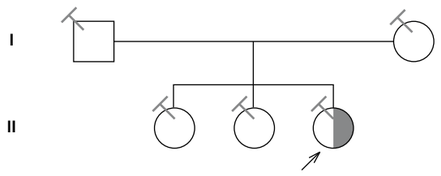
DISCUSSION

Resistance to thyroid hormone, an uncommon condition thought to occur in 1 in 50,000 births,[1] results from a defect in the normal signalling pathways that mediate the intracellular effects of thyroid hormone.[2,3] Four isoforms of the thyroid hormone receptor (TR) exist: TRα-1 and TRα-2, transcribed from a gene on chromosome 17, and TRβ-1 and TRβ-2, transcribed from chromosome 3. Of these only three function as receptors proper since TRα-2 does not bind thyroid hormone. TRs act as hormone-dependent transcription factors which bind to nuclear DNA at specific sites named thyroid response elements (TREs), located in the promoter regions of target genes, and thus positively or negatively regulate gene transcription. Binding of TRs to TREs occurs in the context of dimerization with a number of other members of the steroid thyroid hormone receptor superfamily such as the Retinoid X Receptors (RXRs). In the absence of thyroid hormone, unliganded TRs bind to TREs and *down*-regulate the expression of the target genes by associating with various proteins known as co-repressors (e.g. nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT)). When circulating TH binds to the thyroid hormone receptor, however, the co-repressors are replaced by various co-activator proteins (e.g. the steroid receptor coactivator (SRC) complex). These coactivators interact with the TR-TH complex to *up*-regulate gene expression to levels well above the baseline level in the absence of TRs.

Most cases of RTH result in a receptor with decreased affinity for circulating thyroid hormone, or impaired interaction with the aforementioned co-activators, so that higher levels of circulating thyroid hormone are required to mediate the desired intracellular effects. This results in the characteristic pattern of abnormal TFTs, where a higher than normal level of thyroid hormone is needed to suppress pituitary TSH release into the normal range. Most cases of RTH are inherited in an autosomal dominant manner and result from mutations in the TR gene, resulting in single amino acid substitutions in the ligand-binding domain. A rare autosomal recessive form of RTH, caused by a deletion in the TR gene, also exists and is characterised by deaf-mutism in association with the abnormal thyroid function tests.[4]

The clinical manifestations of RTH are quite variable.[5,6] Most patients are eumetabolic, with a normal basal metabolic rate and normal serum markers of metabolism, such as creatine kinase, sex-hormone binding globulin, ferritin or cholesterol. Thyroid enlargement is the most common physical finding

Family Mby (Nov 2000)



DOB	9.24.43	4.13.71	11.19.77	2.12.78	12.16.46	Normal Range
Sample #	R2305	R2060	R2206	R2203	R2204	
TT4 (µg/dl)	9.0	**121**	10.1	**18.5**	8.4	5.0-11.8
TT3 (ng/ml)	124	162	133	**213**	112	90-185 in children 100-205
TrT3 (ng/ml)	19.9	24.4	22.2	**71.6**	17.6	14.5-30.0
FT41	9.1	9.3	10.5	**20.0**	8.2	6.0-10.5
TSH (mU/L)	0.8	2.4	1.0	1.8	2.0	0.4-3.6
TG (µg/L)	5	27	8	3	4	1-25 in children up to 40
TPO/TG ab	**20/40**	**80**/-	-/-	-/-	-/-	Neg

Figure 1 — THYROID FUNCTION TESTING IN PATIENT (R2203, HALF SHADED) AND FAMILY. DATES OF BIRTH ARE BELOW THE SUBJECTS' SYMBOLS. ABNORMAL RESULTS ARE SHOWN IN RED. TRT3, TOTAL REVERSE T3; FT4I, FREE T4 INDEX; TG, THYROGLOBULIN; TPO, THYROPEROXIDASE; AB, ANTIBODY

Table 1
TRH TEST

TIME POST TRH (MINS.)	TSH LEVEL (MU/L)
0	1.35
15	12.0
30	16.6
45	13.0
60	9.77
90	6.31
120	4.11
180	2.38

Table 2
T3 SUPPRESSION TEST

DAY	DOSE LT3	TSH PATIENT (mU/L,NORMAL 0.4-4)	TSH CONTROL (mU/L, NORMAL 0.4-4)
1	50 µg		
2	50 µg		
3	50 µg		
4	100 µg		
5	100 µg		
6	100 µg	0.12	0.03

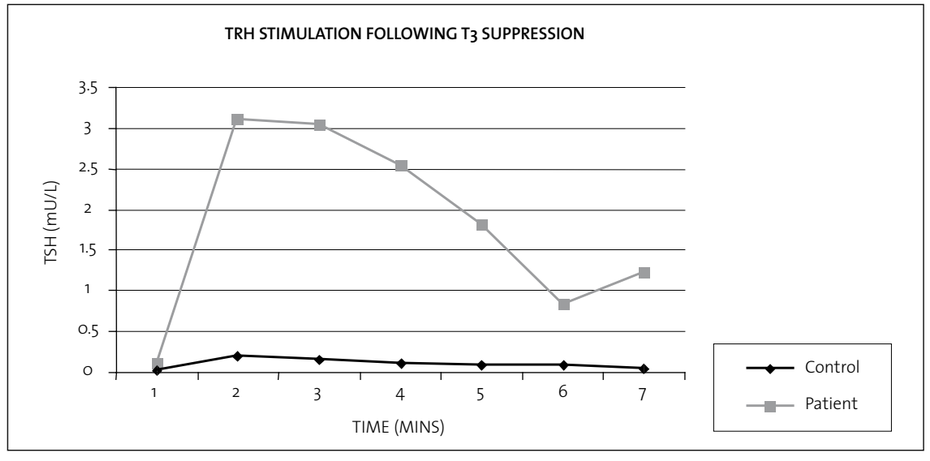


Figure 2 — TRH TEST POST T3 SUPPRESSION (DAY 7)

and up to 80% of patients have a sinus tachycardia. Other findings, such as hyperactivity, learning disability, short stature, and delayed bone age, occur less frequently. Considerable variation in phenotypic features is seen not only between families with different TR mutations but also between members of same family, who harbour the same mutation.[7] This within family variability may be explained by variable degrees of expression of the wild-type TR, differences in distribution of the various TR isoforms between different tissues or genetic variability in coactivators, corepressors, or dimerization molecules involved in thyroid hormone action.

The presentation of our patient was fairly typical of the condition. The non-specific complaint of fatigue was attributed to her abnormal thyroid function tests (despite her clinically euthyroid state and her normal TSH), and she was commenced on carbimazole. Unfortunately, many patients with RTH are mistakenly diagnosed with hyperthyroidism at initial presentation and are treated with anti-thyroid medications or subjected to thyroid surgery.[6,8]

The majority of patients with RTH have a first-degree relative with the condition.[2] When RTH is suspected, therefore, a sensible first step in the diagnostic evaluation is to test the first-degree relatives of the suspected case. A similar abnormality in thyroid function tests in a parent or sibling immediately makes RTH the likely diagnosis, and further investigations to exclude the main differential diagnosis, a TSH-secreting adenoma, assume less importance. In this respect, our patient was somewhat atypical, as her family members had normal thyroid function tests and, therefore, further testing was required to confirm the diagnosis of RTH. Such sporadic cases of RTH, likely due to *de novo* mutations, have been reported in 18% of families with the condition.[2]

The T3 suppression test [2] is a useful aid in the diagnosis of RTH, and also gives an insight into the underlying pathophysiological processes of the disease. Because of resistance to the action of T3 at the pituitary thyrotroph level, the normal feedback inhibitory effect of T3 on pituitary TSH release is diminished. Despite the high doses of exogenous T3 given to our patient, TSH was not suppressed to undetectable levels and retained responsiveness to TRH. The contrast with the control subject is obvious, and the failure of TSH suppression under these experimental conditions makes it easy to appreciate why TSH levels remain normal in the face of the often comparably minor elevations of T3 and T4 in RTH.

The T3-suppression test is not necessary if one can demonstrate a mutation in the thyroid hormone receptor. The patient reported here, however, had no mutation on genetic testing. Cases of RTH without a TRβ mutation (non-TR RTH) have been described in the past, but, to our knowledge, this is the first reported case of non-TR RTH in an Irish patient. In 1996, Weiss and colleagues[9] reported the first such case of non-TR RTH, in a female patient with the classical RTH phenotype who had no detectable mutation of the TRβ gene and also no linkage with the TRα gene. Subsequently, Pohlenz and colleagues,[8] from the same laboratory, described five further families with RTH and no detectable TR mutation, and concluded that non-TR RTH is present in approximately 10% of families with the RTH phenotype. Interestingly, four of the six families described appeared to have developed new mutations causing RTH (as in these families both parents of the index case had normal thyroid function), and a *de novo* mutation must also be present in the case we describe. Of note, in addition to sequencing of the TRβ gene, four of the six families in this series had sequencing of the TRα gene performed, and no mutation was detected. A TRα mutation is now considered to be a very unlikely cause of RTH, as no such mutation has ever been discovered in RTH patients, and mice deficient in TRα-[10] or with point mutations in the TRα- gene[11,12] do not exhibit the RTH phenotype. Our patient, therefore, was not tested for a TRα mutation.

So what is the cause of RTH in patients with no mutation in the thyroid hormone receptor? A defect in any of the steps involved in the signalling pathway described above could, conceivably, result in RTH, and a defect in one or more of the cofactors involved in thyroid receptor function is believed to be the most likely explanation. The discovery that mice with a deletion in the SRC-1 cofactor manifest the RTH phenotype gives credence to this belief, [13] and RXR-γ-deficient mice have also been found to have a mild form of RTH.[14] As yet, however, no specific cofactor dysfunction resulting in non-TR RTH has been described in humans, and linkage analysis performed in four of six families with the condition failed to demonstrate involvement of the SRC-1 cofactor, or the RXR coregulator, [15] in human disease. The search for the specific cause of non-TR RTH continues.

In summary, we report a case of RTH where an initially typical presentation led to the eventual diagnosis of RTH, after a period of treatment with anti-thyroid medications. Subsequent investigations confirmed the rare diagnosis of RTH without an identifiable mutation in the thyroid hormone receptor gene, the first reported case of its kind in an Irish patient. The normal thyroid function tests in the first-degree relatives of the patient suggest recessive inheritance or a *de novo* mutation. This case illustrates the point that a high index of suspicion for RTH in patients presenting with the characteristic pattern of abnormal thyroid function tests, could help avoid unnecessary and potentially harmful treatment for hyperthyroidism.

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Irish Neonatal Mortality Statistics 2002

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SM Gormally

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Dear Editor

The Neonatal Mortality Survey, conducted through the auspices of the Faculty of Paediatrics of Ireland, provides important data on the trends in deaths of all live born Irish (Republic of Ireland) infants who are greater than 500g birth weight and who die in the first 28 days of life.[1,2,3] The term Neonatal Mortality Rate (NMR) refers to the number of deaths expressed per 1,000 live births. Early Neonatal Mortality Rate (ENMR) specifically examines those deaths occurring within the first seven days of life. Corrected Neonatal Mortality Rate (CNMR) refers to those deaths that occur as a result of causes other than lethal congenital malformations.

Twenty five of the 26 Irish Neonatal/Paediatric centres, including all three Dublin maternity hospitals, responded to the 2002 Neonatal Mortality Questionnaire, giving a response rate of 96%. There were 60,521 live births in Ireland in 2002. One hundred and eighty seven neonatal deaths occurred during this period. The Neonatal Mortality Rate was 3.1/1000 live births with a Corrected Neonatal Mortality rate of 1.8/1000 live births. Early neonatal deaths accounted for 81% of the total neonatal mortality.

Post mortems were performed in 63 (34%) infants (Figure 1). Deaths were classified into (1) Congenital malformations, (2) Prematurity, (3) Asphyxia and (4)'other causes'.[3]

Congenital Malformations represented the greatest proportion of deaths (44.5%; n=83) followed by prematurity (36%; n=67). Fourteen deaths occurred as a result of asphyxia (7.5%), twelve occurring in term infants. Of the deaths due to Congenital Malformations, chromosomal abnormalities (n=16) and cardiac malformations (n=15) accounted for the greatest proportion. Ten deaths occurred as a result of renal anomalies with seven neonatal deaths secondary to a congenital diaphragmatic hernia. Neural tube defects and other central nervous system abnormalities accounted for 11 deaths during this period. Other congenital malformations included non-chromosomal syndromes (n=3), skeletal dysplasias(n=6) and primary pulmonary hypoplasias(n=4). Sixty-seven deaths were documented as being primarily due to Prematurity. Fifty (75%) of these occurred in the Extremely Low Birth Weight group. Intraventricular haemorrhage was cited as a principal cause of death in 13% of preterm deaths.

Causes of death other then the three main Wigglesworth categories[3] (n=23) included meningitis (n=3), sepsis (n=3), Sudden Infant Death Syndrome (n=3), necrotising enterocolitis (n=2) and hydrops fetalis (n=3).

The annual National Neonatal Mortality Survey serves as an important audit of Irish perinatal care. The response rate of 96% for 2002 has been the highest to date and is indicative of the dedication of Irish paediatricians and neonatologists to monitoring neonatal outcomes. Irish Neonatal Mortality and Corrected Neonatal Mortality Rates have shown a steady decline over the past 15 years (Figure 2).[1,2] In 1987, when this data were first examined, NMR and CNMR were 5.3 and 3.3/1000 live births respectively. This compares with rates of 3.1 and 1.8/1000 live births in 2002. These figures have reached a plateau

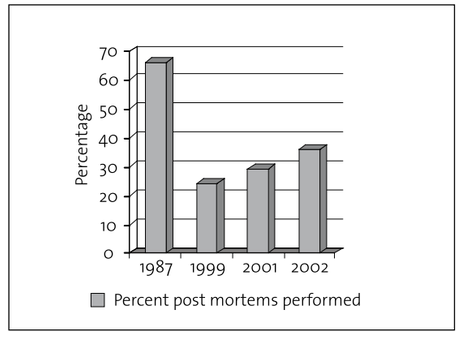

Figure 1 — TRENDS IN NEONATAL POST MORTEM RATES 1987 – 2002

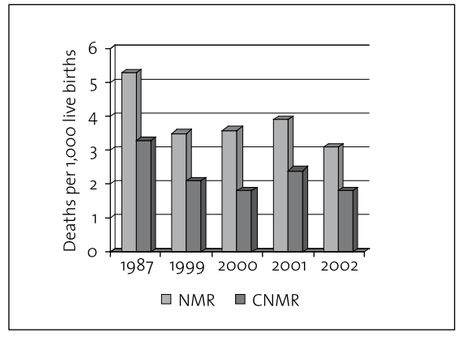

Figure 2 — TRENDS IN IRISH NEONATAL AND CORRECTED NEONATAL MORTALITY 1987 – 2002

since 2000. As with previous years, congenital malformations and prematurity account for the greatest proportion of neonatal deaths.[1,2,4] In 1987, asphyxial deaths accounted for 8% of neonatal mortality. This figure fell throughout the 1990s with the lowest level at 2.1% in 1999. However deaths attributable to asphyxia have risen in the past three years.[4] In 2002, 12 full term asphyxial deaths occurred. While this trend is disquieting, it may be a reflection of earlier withdrawal of intensive care in asphyxiated infants deemed to have a hopeless outcome, rather than being a reflection of poorer obstetric care. Also the increased asphyxial trend has occurred during a period when there has been a dramatic increase in the number of asylum seekers into Ireland, many of whom have had poor antenatal care. Further analysis of this type of trend is limited within the confines of the Irish Neonatal Mortality Survey in its present format. In an effort to encourage a meaningful response rate from Irish paediatricians, the amount of information that can be requested on the questionnaire is limited. To address this shortcoming, argument could be made for future development of a confidential, government-funded, enquiry into Stillbirths and Neonatal Deaths similar to the UK CESDI model.[5] Such an auditing system would provide a robust framework for the evaluation of current obstetric and neonatal practices and services in Ireland. It would also provide a basis on which to plan future developments in these areas.

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Using HIPE data as a research and planning tool

A reply to Miriam Wiley's response to paper *'Using HIPE data as a research and planning tool: limitations and opportunities'*, both published in Irish J Med Sci 2005;174(2)

Dear Editor

An important role for university based researchers and peer-reviewed journals is to continually progress the research agenda. This has begun by your recent publication of our article.[1] Notwithstanding the detailed defence of the operation of the system in your simultaneously published response,[2] it is clear that the operators of the system agree with at least some of our analysis and, as their response indicates, they have themselves been considering some of the issues we have raised. We reiterate our most important conclusions and invite the operators of the system to work with us and the wider research community in bringing them about. These are: extend the system to cover private hospitals, adopt routine small area and socio-economic coding and adopt unique, albeit confidential, personal identifiers.

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Correspondence in response to a book review published in Vol 174;2:70

Dear Editor

I am surprised to hear myself being called an egocentric in CS Breathnach's review of my biography of Dr Malachy Smyth, 'A Life in Medicine' in volume 174 of the Irish Journal of Medical Science. I would sincerely like to know where he draws that conclusion considering I haven't put any of myself into the book.

Could he also tell me where the chronology falls down? I would be intrigued to know this as none of the dozen or so reviews of the book that have appeared so far have noticed any discrepancy.

I think there were about four misprints, which is about average. He calls them 'scarlet'. Could he please explain? [Perhaps the book was found in his surgery and became inadvertently doused in blood!]

I have no knowledge of CS Breathnach's expertise in anatomy and physiology in UCD but he should familiarise himself better with literary terminology before he next launches his spleen. For his information, a 'ghosted' autobiography is a contradiction in terms.

Authorial ghosts, by definition, are behind the scenes. There are co-written autobiographies, to be sure, but this is not one such. It is written in the third person. That makes it a biography. Is CS Breathnach familiar with what a biography is? It is a life story of one person written by another. In this case, a biography of Dr Smyth by me. Where do ghosts come in? Where, for that matter, does autobiography come in?

This is one of the strangest 'reviews' I have ever read.

A Malone

Reply to Aubrey Malone

A misunderstanding: the autobiographer was Malachy, not Aubrey the ghost.

The fundamental trouble with A Life in Medicine is that Aubrey Malone relayed Malachy Smyth's account without reference to other medical authors, a norm in medical biography. The ghost in the machine is the uncritical acceptance of Dr Smyth's presentation of his work – undoubtedly valuable – on intervertebral discs. W J Mixted and J S Barr's paper in New England Journal of Medicine in 1935 (211: 210-215) is taken as the point of departure on 'rupture of intervertebral disc with involvement of the spinal cord'. By 1946 this explanation of sciatica was fully endorsed in Watson-Jones's Fractures and Joint Injuries a decade before Malachy's work in Leeds which was published in 1958. Anachronisms and misprints were euphemisms for this deeper malaise, and it would be futile to take part in a point to point refutation in a '20 yards hurdle' (p. 17 of the book), one of the strangest athletic contests ever run, even in College sports. Punning may be the lowest form of wit, but Hilaire Belloc's comment and hope that 'His sins were scarlet, but his books were read' did not catch the eye in the bloody field.

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Gerry's Real World Guide to Pharmacokinetics and Other Things

GM Woerlee
ISBN: 1-905237-16-2
Price: £9.95

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GM Woerlee introduces his most recent publication, *Gerry's Real World Guide to Pharmacokinetics and Other Things*, as "written for all those wishing to learn about basic principles of pharmacokinetics as applied to anaesthetic drugs. It is intended as an entertaining guide to these things with a maximum of practical common sense and a minimum of mathematical knowledge". Dr Woerlee's credentials to guide the reader on this pharmacological tour include 23 years teaching and anaesthesia practice in Leiden, the Netherlands following specialist training in Western Australia and England.

The 'Other Things' referred to in the title are comprised of humorous, if sometimes clichéd, observations of the human condition as it is played out in the operating theatre, philosophical musings and quotes from erudite sources ranging from the Koran to Nietzsche.

This small monograph is targeted toward all levels of trainees, consultants and nurses with a common interest: Clinical Anaesthesia. It reaches this audience through a range of illustrative operating room scenarios discussed in a conversational tone. Each chapter presents a new patient very much in a 'Problem Based Learning' format.

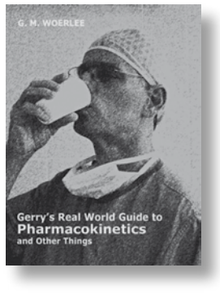
As in all simulated clinical scenarios, these story lines rely on the reader's suspension of reality. Throughout each clinical case, a senior consultant anaesthetist questions a registrar under his mentorship about the pharmacology of anaesthetic agents in the practical setting. Doctor Gerry is introduced as an 'experienced crusty older anaesthetist, intolerant of fools and a bit of a pharmacokinetic freak'. The hard working but often pharmcokinetically challenged registrar, Doctor Bob, approaches his first day 'with some trepidation'.

While the role-play is occasionally pithy the premise of this book works. The reader is drawn along as a silent observer of this educational foray. The buzz of the operating room accompanies Doctor Gerry's probing questions and comprehensive answers. Through practical examples, the reader is gently reacquainted with core pharmacokinetic concepts.

The ten chapters offer unambiguous explanations of principles such as plasma half-life, drug distribution and elimination. Relevant tables are included in the text while detailed tables are reserved for the appendices. The text could benefit from more diagrams (invaluable teaching tools in pharmacokinetics) but the author may have sacrificed these to preserve the informal style.

GM Woerlee is an anaesthetist's anaesthetist. I strongly suspect that he may share more than some character traits with Doctor Gerry though I believe GM Woerlee to be more pleasant and less patriarchal. He is known for his lecture at the European Sceptics Conference and publication 'Mortal Minds: A Biology of the Soul and the Dying Experience' which demystify the physical sensations reported in near death experiences.

Anaesthetists in any clinical practice will find the authenticity of this book's illustrative cases resonant which contributes to the realization of its objective - to make pharmacology clinically relevant. Its success ultimately results from short digestible chapters that approach an interactive educational style. This book is not a core textbook; a fact that makes it all the more enjoyable to read.



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1. Allen JM, Keenan AK, McHale NG et al. Lymphatic functions and cardiovascular disease. *N Engl J Med* 1999;123:10-14.
2. Davis GK, Mertt O. Transition metals in nutrition. In: Trace elements in nutrition (4th edition). Ed O Mertt. Academic Press, San Diego 1998:123-132.

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