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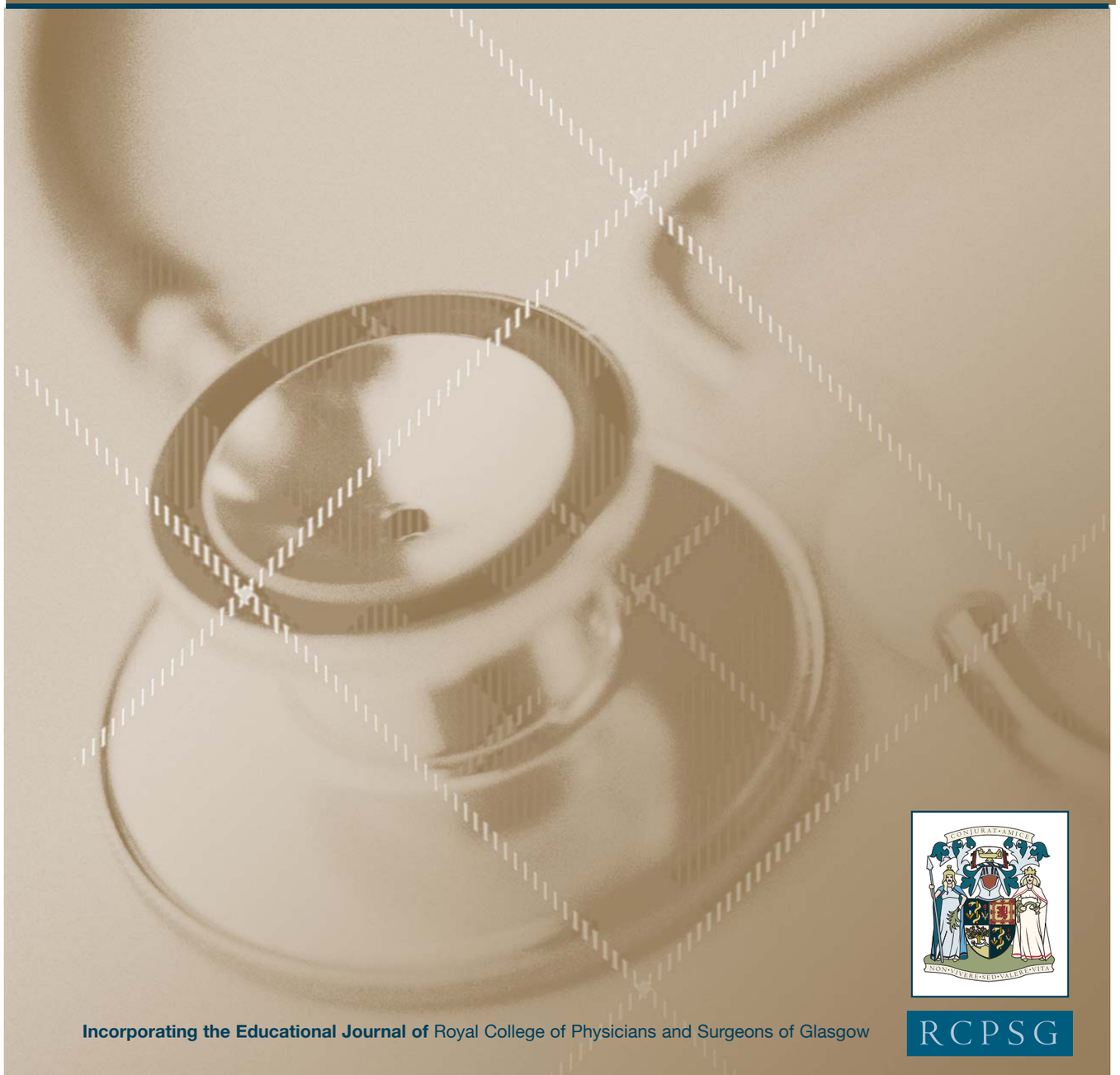

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CONTENT

ORIGINAL ARTICLES

Epidemiological Aspects of referral to TIA Clinics in Glasgow

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ABSTRACT

A retrospective cohort study was carried out of new referrals to TIA clinics in Glasgow. The aims of the study were to describe the profile of referrals and to assess the odds ratios for TIA, minor stroke or Amaurosis Fugax of both cardiovascular risk factors and clinical features.

In total, data were collected for 813 new referrals in a period of six months. Thirteen point eight percent of referrals were from other Health Boards. The overall referral rate in residents of Greater Glasgow NHS Board was 165.6 per 100,000 per year. About 20% of referrals were made by clinicians in secondary care. The specialties from which referrals were most commonly made were Accident and Emergency, General Medicine, Ophthalmology and Geriatric Assessment. The most common risk factors in patients referred were hypertension (52.9%), smoking (31.7%), ischaemic heart disease (22.7%) and former smokers (22.4%). The most common clinical features were hemiparesis (13.3%), weakness of an upper limb (8.7%), vertigo (7.9%) and dysphasia (7.3%). In 48.7% of cases, a non-cerebrovascular diagnosis was made.

Separate multivariate models were established for risk factors and clinical features. In the model for risk factors, five factors were significant for risk of TIA, stroke or amaurosis fugax. These were hyperlipidaemia, age over 64 years, hypertension, smoking and ex-smoking. In the model for clinical features, five factors were also significant. These were visual field defect, speech defect, facial weakness and hemiparesis and dysarthria.

Introduction

Stroke is an important problem in the public health of all western countries. Stroke accounts for more than a thousand deaths in Glasgow each year and is now the second most important single cause of death.[1] A Transient Ischaemic Attack (TIA) is defined as an episode of temporary and focal cerebral dysfunction of vascular (occlusive) origin that is rapid in onset and of variable duration, ordinarily lasting 2 to15 minutes but rarely as long as one day.[2] In some cases, a minor stroke may occur in which the clinical features disappear rapidly, but last more than 24 hours. In about fifteen percent of cases, a major ischaemic stroke is preceded by a TIA.[3]

The importance of recognising and treating TIA lies in the fact that the risk of a major ischaemic stroke is greatly increased in the aftermath of the more minor cerebrovascular event. In the Oxfordshire Stroke Study, the risk of stroke was estimated at 11% in the first year after a TIA and 5% in each succeeding year[4], but considerably greater levels of risk have been described in more recent studies. Estimates of risk at ninety days after a TIA have ranged from 10 to 17%.[5,6,7] In one of these studies, the incidence of stroke was found to be as high as 8% in the first seven days after a TIA.[6] These results underline the importance of rapid referral and assessment of patients who may have sustained a TIA.

Secondary prevention is an important component of a stroke service, and a range of effective interventions is currently available for the secondary prevention of stroke.[8] In addition, the requirement for secondary prevention has been recognised in the development of secondary prevention clinics, or TIA clinics[9], designed specifically for the rapid assessment and treatment of patients who may have sustained a TIA. Although TIA clinics have now been established in most acute general hospitals, there have been relatively few studies of activity or of the epidemiological characteristics of referrals.[10] For this reason, a study was undertaken to describe overall patterns of activity and to identify the risk for TIA or minor stroke associated with both the cardiovascular risk factors and clinical features.

Methods

Ascertainment

The study was a retrospective cohort study of new referrals to any of the TIA clinics in Glasgow between 1st January 2003 and 30th June 2003. Cases were identified from lists of patients who had been appointed to the clinics. These lists were obtained either from consultant physicians or from hospital medical records departments.

Data collection

Data were collected directly from case records and recorded in a specially designed collection form. Data were collected about demographic factors, referral, risk factors, clinical presentation, investigations and diagnosis.

Data preparation

The data were coded and keyed into a database in Microsoft Access. The ICD10 classification of disease[11] was used for coding both reasons for referral and diagnoses. Missing items of data were coded by allocating 'missing data' codes. The quality of the data was checked by manual comparison of each electronic record in Access with the corresponding data collection form. The final version of the dataset was later transferred to SPSS© for analysis.

Populations

The source of information about the population of Greater Glasgow NHS Board (GGNHSB) was the Registrar General's mid-year estimate of populations, derived from the decennial Census of 2001.[12] The Carstairs Index[13] was used as the indicator of material deprivation. The Carstairs index is derived from data collected in the Census, and has seven categories which range from 1 (most affluent) to 7 (most deprived). The code is applicable at the level of postcode sector.

Cases and controls

The univariate and multivariate analyses were carried out by defining case and control subjects. Cases were defined to be patients with a new diagnosis of TIA, stroke or amaurosis fugax, and controls were defined to be patients with all other diagnoses.

Statistical analysis

Standardisation of rates and calculation of univariate odds ratios were carried out in the Microsoft Excel package. Multivariate logistic regression was carried out in the SPSS package. Standardisation of referral rates was carried out by the indirect method. This allows calculation of a standardised referral ratio, which is analogous to the commonly-used standardised mortality ratio (SMR). The referral ratio allows the referral experience in different populations to be compared with that in the standard population, in this case, the population of Greater Glasgow NHS Health Board (GGNHSB). The referral ratio in Glasgow is, by definition, 100.

Results

Referrals

In total, 840 new referrals were made to TIA clinics in Glasgow in the first six months of 2003. Of these, 15 patients failed to attend and the notes were not available for 12 other patients. Case notes were available for 813 of the 825 patients who attended the clinic, an ascertainment rate of 98.5%. A correction factor of 1.033 was applied globally to calculate the absolute referral rates cited in the report.

Together, the age-groups 45-64 years and 65-84 years accounted for about 35.5% and 48.8% respectively of all referrals. In total, 13.8% of all referrals were from the populations of boards other than GGNHSB. The importance of this is that only referrals from the defined population of GGNHSB could be used to calculate referral rates. The overall referral rate was 165.6 referrals per 100,000 per year (Table 1). The referral rate was greatest, 610 per 100,000 per year, in the population aged 65 to 84 years.

Table I Referral Rate (per 100,000) to TIA Clinics

Age	Males	Females	Total
<25	0.0	7.6	3.8
25-44	41.5	51.0	46.5
45-64	260.0	248.1	253.9
65-84	701.4	548.6	610.1
>84	693.1	369.3	447.8
Total	**162.7**	**168.3**	**165.6**

The difference in level of referral between the more and less deprived areas of the population may be expressed as a ratio. The value of the ratio for the entire population would be 100. Referral ratios standardised for age and sex were calculated for the population of GGNHSB respectively in deprivation categories 1 to 4 and 5 to 7. The ratio for categories 1 to 4 was 83.1, and the confidence interval was (72.7, 93.5). The ratio for the three most deprived categories was 112.6, and the confidence interval was (102.2, 124.0).

Source of referral

Of the total number of attendances, 655 (81%) resulted from direct referral by a primary care physician. The remaining 158 attendances (19%) were the result of referral by doctors in hospital specialties The five specialties which accounted for most of the referrals from hospital were accident and emergency (28.5%), general medicine (24.1%) ophthalmology (20.9%), geriatric assessment (12%) and neurology (5.6%).

Risk Factors

The risk factor that was most prevalent in patients referred

to TIA clinics was history of hypertension. About 53% of all patients had a history of either treated or untreated hypertension. The four next most frequent risk factors were smoking (31.7%), hyperlipidaemia (17.2%), ischaemic heart disease (22.7%) and previous smoking history (22.4%). Other risk factors were history of previous stroke or TIA (20.7%), diabetes mellitus (11.7%), alcohol abuse (9.5%), atrial fibrillation (7.0%), peripheral vascular disease (6.0%) and history of other cardiac disease (4.4%).

Clinical presentation

Patients presented to TIA clinics with a wide range of clinical presentation. The commonest presentations were hemiparesis (13.3%), weakness of an upper limb (8.7%), vertigo (7.9%), dysphasia (7.3%) and hemiparaesthesia (4.7%).

Diagnosis

A diagnosis of TIA, stroke or amaurosis fugax was made in only 51.4% of referrals (Table 2). In almost half of the referrals, an alternative diagnosis was made. The most common alternative diagnoses included migraine, syncope, neuropathy, seizure and anxiety (Table 3).

Table II Diagnostic Categories by Health Board of Residence

Category	Health Board of Residence		
	GGNHSB	Other	Total
TIA	198	19	217 (26.8%)
Stroke	150	16	166 (20.5%)
Amaurosis fugax	28	5	33 (4.1%)
Other	324	71	395 (48.7%)
Total	**700**	**111**	**811 (100%)**

Univariate odds ratios

Both univariate and multivariate analyses were carried out by defining cerebrovascular cases as patients with a new diagnosis of TIA, stroke or amaurosis fugax. All others were defined as controls. The univariate odds ratios and associated confidence intervals for risk factors are shown in Table 4. The odds ratios were greater than one and significant for peripheral vascular disease, hyperlipidaemia, age, hypertension, atrial fibrillation, smoking, history of stroke or TIA, ex-smoking history and male sex. The risk factors for alcohol excess, diabetes and history of other cardiac disease were not significant.

Univariate odds ratios and associated 95% confidence intervals for clinical features are shown in Table 5. The odds ratios were greater than one and significant for speech defect, visual field defect, facial weakness and hemiparesis, and less than one and significant for blurred vision, vertigo and visual disturbance. The risk factors for hemiparaesthesia, diplopia and ataxia were not significant.

Table III Diagnostic Categories other than TIA, Stroke or Amaurosis Fugax

Diagnosis	No.	%
Migraine	35	8.9
Syncope	30	7.7
Peripheral neuropathy	17	4.3
Seizure	16	4.1
Postural hypotension	14	3.6
Cervical spondylosis	14	3.6
Anxiety	13	3.3
Dementia	11	2.8
Middle ear disease	11	2.8
Brain tumour	9	2.3
Transient global amnesia	8	2.0
Occluded retinal artery	7	1.8
Arrythmia	5	1.3
Sequelae previous stroke	4	1.0
Motor Neurone disease	3	0.8
Multiple sclerosis	3	0.8
Parkinson's disease	3	0.8
Asymptomatic stenosis of carotid artery	3	0.8
Benign paroxysmal positional vertigo	2	0.5
Epilepsy	2	0.5
Depression	1	0.3
Oversedation	1	0.3
Trigeminal neuralgia	1	0.3
Others	179	45.7
Total	**392**	**100.0**

Table IV Odds Ratios for Risk Factors (Univariate Analyses)

Risk factor	Point estimate and 95% Confidence interval
History of PVD	2.88 (1.51, 5.48)
Hyperlipidaemia	2.10 (1.54, 2.88)
Age over 64 years	2.03 (1.53, 2.69)
Hypertension	2.00 (1.51, 2.64)
Atrial fibrillation	1.85 (1.04, 3.41)
Smoking	1.66 (1.23, 2.25)
History of TIA or stroke	1.60 (1.13, 2.27)
Ex-smoker	1.47 (1.05, 2.05)
Male sex	1.42 (1.07, 1.88)
History of IHD	1.30 (0.93, 1.81)
Alcohol excess	1.17 (0.73, 1.89)
Diabetes	1.15 (0.74, 1.79)
History of other cardiac disease	0.90 (0.45, 1.79)

Multivariate regression

Separate multivariate logistic regression models were constructed for risk factors and clinical features respectively. Only the variables that had been found to be significant in the univariate analysis were included in multivariate models. The results of these models are shown in Tables 6 and 7. In the multivariate model for risk factors, five of the original variables were found to be

Table V Odds Ratios for Clinical Features (Univariate Analyses)

Clinical feature	Odds ratio (95% confidence interval)
Speech defect	4.15 (2.73, 6.33)
Visual field defect	3.96 (1.58, 9.90)
Facial weakness	3.33 (1.78, 6.22)
Hemiparesis	2.57 (1.68, 3.93)
Blurred vision	0.42 (0.19, 0.91)
Vertigo	0.36 (0.23, 0.57)
Visual disturbance	0.28 (0.13, 0.59)
Hemiparaesthesia	1.65 (0.95, 2.78)
Diplopia	0.52 (0.21, 1.32)
Ataxia	0.50 (0.17, 1.47)

Table VI Odds Ratios for Risk Factors (Multivariate Analyses)

Variables	Odds ratio (95% confidence interval)
Hyperlipidaemia	2.34 (1.67, 3.28)
Age over 64 years	2.37 (1.73, 3.24)
Hypertension	1.67 (1.24, 2.26)
Smoking	2.65 (1.86, 3.78)
Ex-smoking	2.08 (1.42, 3.05)

Table VII Odds Ratios for Clinical Features (Multivariate Analyses)

Variables	Odds ratio (95% confidence interval)
Visual Field Defect (VFD)	5.56 (2.05,15.05)
Speech defect	4.24 (2.70, 6.68)
Facial Weakness	3.38 (1.71, 6.69)
Hemiparesis	2.96 (1.89, 4.64)

significant. These were hyperlipidaemia, age over 64 years, hypertension, smoking and ex-smoking. In the multivariate model for clinical features, four of the original variables were also found to be significant. These were speech defect, visual field defect, facial weakness and hemiparesis.

Discussion

The case-records were available for 98.5% of the 825 patients who attended the clinic. In fifteen cases, the patient did not attend at all, although multiple appointments were offered. In general, non-attendance at clinics is often viewed as an administrative problem whose main consequence is waste of clinic time, but in regard to TIA clinics, non-attendance may have more serious implications. In one study,[5] about one half of the strokes that occurred within 90 days of a TIA were within the first three days. This underlines the need for rapid assessment and treatment after a TIA. Patients who fail to attend, or who fail to attend for the first appointment offered, may incur a greater risk of a disabling stroke.

Almost one half of the patients were aged 65 to 84 years and 35.5% were aged 45 to 64 years. This demographic profile reflects the fact that cerebrovascular disease is primarily a condition of the elderly population, and that age is one of the most important non-modifiable risk factors for stroke and TIA.[14]

Source of referral

About 80% of all new referrals were made by primary care physicians. This reflects the most common method of presentation, in which patients initially consult a primary care physician. In the remaining 20% of cases, the referral was made by a clinician in secondary care. The hospital specialties from which referrals were most commonly made reflect alternative modes of presentation and the diversity of clinical presentation associated with stroke or TIA. For example, a substantial number of patients attend an A&E department after a TIA, instead of making an appointment to see a primary care physician, and most of the referrals from ophthalmology reflect the frequency of amaurosis fugax and other ocular symptoms in presentations associated with TIA or stroke. These factors may result in circuitous pathways of referral, in which an initial referral to a hospital specialty is followed by a second referral to a TIA clinic. The delay in referral may be important in view of the risk of a second cerebrovascular event soon after an initial TIA.[5]

Clinical features

Patients presented to TIA clinics with a wide range of clinical features. These reflected not only the classical presentations of TIA and stroke but also the symptoms of a wide range of other pathology. Hemiparesis, weakness of the upper limb, vertigo, dysphasia and hemiparaesthesia were the commonest presenting features. Although these are among the classical presentations of stroke,[15] they are non-specific. Some patients presented with other clinical features that are uncommon features of TIA or stroke, including headache and loss of consciousness.

Diagnosis

A diagnosis of TIA, stroke or amaurosis fugax was made in only 51.4% of referrals. In almost half of the referrals, an alternative diagnosis was made. This reflects the range of pathology in the group of patients referred, a finding that has been reported in other studies of referrals to TIA clinics.[10] The pathology included relatively common conditions, for example, migraine, and also small numbers of cases of less common conditions, for example, motor neurone disease and multiple sclerosis. This underlines the

degree of clinical suspicion that is necessary for medical staff in TIA clinics to maintain.

Risk factors and clinical features

In this study, a case-control methodology was employed to calculate both univariate and multivariate odds ratios for TIA, stroke or amaurosis fugax for vascular risk factors and clinical features. The most serious methodological limitation of the case-control methodology is bias due to differential recall of information of possible prognostic importance by case and control subjects. This is unlikely to have been significant in the present study, either in respect of clinical features or risk factors, for a number of reasons. Most importantly, the period between the event and attendance at the clinic was relatively brief, usually not more that a few weeks, so that recall of clinical features was likely to have been accurate. Information about clinical features was also supplied by primary care physicians and other referring clinicians by whom patients were usually seen soon after the event. Lastly, most referrals were made because of neurological features of some kind. There was no reason to assume differential recall on the part of patients who subsequently fell into different diagnostic groups. It was considered that information about different risk factors was unlikely to be a source of bias, because information was available in the referral notes and case-records as well as from patients themselves.

The significance of the two types of analysis was different. The aim of the analysis in relation to risk factors was to define the epidemiological importance of each factor for the risk of TIA, stroke or amaurosis fugax. The aim of the analysis in relation to clinical features was to assess the degree of association of the features with the presence of a new lesion.

In the univariate analysis of risk factors, eight risk factors were found to significantly increase the risk of an ischaemic lesion, but only five remained significant in the multivariate analysis. These were hypertension, hyperlipidaemia, age over 64 years, smokers and former smokers. The results of the multivariate analysis were broadly similar to those of previous studies.[16, 17] For example, the estimates of odds ratio associated with hypertension in the current study and in the study by Whisnant et al were respectively 1.67 and 1.80. Differences in these estimates may reflect different methods of selection of cases and controls. In the current study, both cases and controls were represented by patients referred to a TIA clinic. In the Whisnant[16] study, cases and controls were selected from a population register so that both groups represented approximately a random sample from case and control subjects.

In the univariate analysis, seven clinical features were found to be significantly associated with a diagnosis of TIA, stroke or amaurosis fugax. Only four of these remained significant in the multivariate analysis. These were visual field defect, speech defect, facial weakness and hemiparesis. This appears to be the first study set in a TIA clinic in which odds ratios have been calculated for clinical features. The probability of a TIA-related diagnosis would be different in patients with different combinations of clinical features, so that groups could be defined in which the proportions of TIA-related diagnoses could be expected to be high, average or low.

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ORIGINAL ARTICLES

Birth Weight and Maternal Glycated Haemoglobin in Pregnancies Complicated by Type 1 Diabetes

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ABSTRACT

Aim
To re-examine the relationships between birth weight and maternal glycated haemoglobin (HbA1c) concentration at different time points in pregnancies complicated by pre-gestational Type1 diabetes.

Methods
A dataset was collected prospectively on all deliveries in Scotland to women with pre-gestational Type 1 diabetes occurring during two 12 month periods (01/04/98 to 31/03/99 and 01/04/03 to 31/03/04). Relationships between standardised measures of birth weight and HbA1c at each time point were examined using correlation analysis.

Results
Standardised birth weights (Z scores) were calculated for 338 singleton live born infants. HbA1c concentrations were available for: 204 women (pre-pregnancy), 297 women (1st trimester), 314 women (2nd trimester) and 303 women (3rd trimester). Standardised birth weight showed a unimodal distribution shifted to the right relative to a reference population (Mean, +1.62 S.D). There was a significant negative correlation between pre-pregnancy HbA1c and birth weight (Spearman's Rho -0.138; p=0.049).

Conclusions
Standardised birth weights of the infants of diabetic mothers are higher than those of a reference population. There is no simple relationship between maternal glycaemic control and birth weight, but the previously described paradoxical inverse relationship between pre-pregnancy glycaemic control and birth weight has been confirmed using a larger dataset.

Introduction

Pregnancies in women with Type 1 diabetes are more likely to be affected by a large for gestational age (LGA) infant (birth weight >95th centile for gestational age) than are pregnancies in non-diabetic women. An understanding of the pathophysiology behind this is important due to the increased risks of perinatal morbidity and mortality, and of delivery complications in these babies. Foetal growth and birth weight are determined by maternal, foetal, placental and environmental factors. Maternal glycaemic control (routinely measured using HbA1c assays) is potentially a remediable maternal factor in these pregnancies. However, it has proved difficult to establish a consistent relationship between maternal glycaemic control and fetal size.[1-8] We previously reported on the relationship between birth weight and maternal HbA1c in pregnancies complicated by Type 1 diabetes.[9] In this paper, we present findings based on a larger dataset which now includes 338 women with pre-gestational Type 1 diabetes.

Methods

The methods used are those which have been published previously.[9] During two 12 month audit periods (01/04/98 to 31/03/99 and 01/04/03 to 31/03/04), all pregnancies among women with pre-gestational, Type1 (insulin dependent) diabetes were identified prospectively by volunteer clinicians in each of Scotland's consultant-led maternity units. Data were collected in the context of a national audit. As advised by the multi-centre research ethics committee for Scotland, formal ethical approval was not required. Our methods of data collection and processing met the requirements of the Privacy Advisory Committee of Information Services of NHS Scotland. In line with these requirements, during the second audit period, explicit written consent was obtained from women to access their clinical records and those of their babies for the purpose of the study.

Data collected for each pregnancy included up to four recorded measurements of serum glycated haemoglobin (HbA1c) in each of four time periods: pre-pregnancy (in the six months prior to conception), first trimester, second trimester and third trimester. Where a woman had more than one measurement recorded in a given time period, the lowest value was used in the analysis.

As each unit used its own assay for HbA1c, we obtained information on each hospital's quoted reference range for HbA1c in pregnant diabetic women. To allow aggregation of data, each woman's lowest HbA1c value for each time period was expressed as a percentage difference from the quoted upper limit of normal for her own maternity unit.[9]

Standardised birth weight scores (Z scores) were calculated based on published birth weight standards for a Scottish (Aberdeen) population[10] which served to correct for gestational age, sex of baby, and parity of the mother. Only pregnancies progressing to delivery of a live born singleton infant at >32 weeks gestation were included in the analysis, due to limitations of the published birth weight standards.

Our previous report related to 203 pregnancies occurring in 1998/99.9 Three hundred and seventy two pregnancies were identified during the two audit periods. Thirty four pregnancies in the following categories were excluded from the analysis; 4 twin pregnancies, 9 perinatal deaths, 13 pregnancies ending <32 weeks, 3 pregnancies with birth weight or gestation missing preventing z scores from being calculated, and 5 second pregnancies of women featuring in both audit periods. Twelve pregnancies with major congenital anomalies were included in the final analysis in keeping with conventional reporting systems. Thus, the analysis presented in this paper relates to an updated series of 338 singleton, live born infants.

Relationships between standardised measures of birth weight and of HbA1c in different time periods were examined using correlation analysis.

Results

Among the 338 mothers, the mean age at delivery was 29 years, 171 women (50.6%) were primigravids, the median duration of diabetes was 13 years, 83 (24.6%) were current smokers, 85 (25.1%) took the optimal 4-5mg dose of folic acid periconceptually, 108 (32%) attended for formal pre-pregnancy counselling, and 182 (53.8%) of the pregnancies were documented as planned. Among the infants, the mean standardised birth weight score was 1.62 and 143 infants (42.3%) weighed greater than the reference popultion 95th centile for gestational age.

Women who had pre-pregnancy HbA1c values available were more likely to have planned pregnancies 126/204 (61.8%) vs 56/134 (41.8%) p=0.0004 and to have attended formal pre-pregnancy counselling 90/204 (44.1%) vs 18/134 (13.4%) p=<0.0001 compared to those women for whom no pre-pregnancy HbA1c values were available. They were also more likely to be taking the optimal 4-5mg dose of folic acid 58/204 (28.4%) vs 27/134 (20.1%) p=0.0964.

Table I Standardised HbA1c (Expressed as a Percentage Difference from Quoted Hospital 'Upper Limit of Normal') in Different Time Periods and Correlation with the Standardised Birth Weight Score

Time period	Number of cases	Percentage difference of HbA1c from hospital 'upper limit of normal'	Correlation co-efficient (Spearman's Rho)	Significance (two tailed p value)
Pre-pregnancy	204	26.9	-0.138	0.049
First Trimester	297	15.7	-0.075	0.199
Second trimester	314	1.7	0.009	0.880
Third trimester	303	4.6	0.059	0.309

Women who had pre-pregnancy HbA1c values available were less likely to have any degree of retinopathy. They were also less likely to be smokers 43/204 (21.1%) vs 40/134 (29.9%) p=0.07[17] but this difference was not statistically significant. There was no significant difference in the presence of nephropathy between the two groups.

Discussion

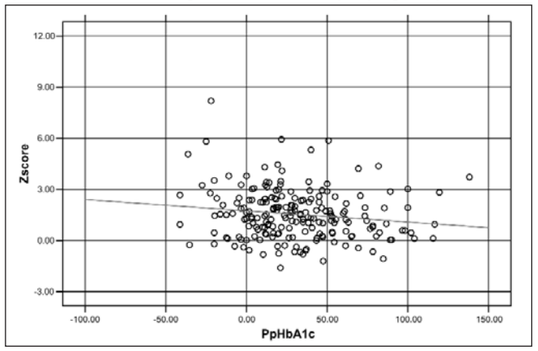
Using a larger dataset, we have confirmed our previous finding of a significant negative correlation between pre-pregnancy standardised HbA1c and standardised birth weight. However, this relationship is less strong than previously shown and again no significant correlations at other time points were seen.

Aggregating data on HbA1c levels from all centres in a country is problematic because of the different assay methods and different normal ranges used. We have attempted to overcome this difficulty by expressing each HbA1c level in terms of a percentage difference from the upper limit of normal quoted by the relevant centre. This approach was devised as a pragmatic solution to a methodological problem. We acknowledge that more rigorous statistical methods may have been applicable. However, approaches relating to the distribution of values obtained from each centre (for example, calculation of t-scores) were not feasible due to the small numbers of values available from some centres.

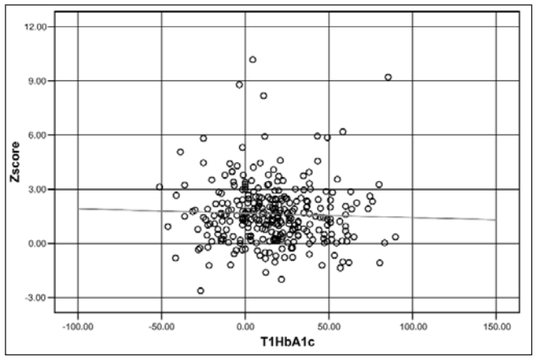
Many studies have combined data on gestational, Type 1, and Type 2 diabetes mellitus and include only small numbers of women. We have studied a large, population-based dataset of women with pre-gestational Type1 diabetes only. We acknowledge that our data on pre-pregnancy HbA1c are incomplete. Incomplete data may explain, at least in part, the correlation seen since, in some centres the pre-pregnancy records were not available to the audit teams. Those women who had pre-pregnancy HbA1c values available were more likely to have planned pregnancies and to have attended formal pre-pregnancy counselling compared to those women for whom no pre-pregnancy HbA1c levels were available. We are hypothesising that women with no pre-pregnancy HbA1c values available may have worse pre-pregnancy glycaemic control and if these results were available, and included in the analysis, the negative correlation would be more pronounced. This is supported by the fact that women with no pre-pregnancy HbA1c values available were more likely to be smokers and more likely to have microvascular disease both of which could adversely affect placental function and consequently fetal growth.

Figure 1 Scatterplots summarising the relationships between standardised HbA1c in different time periods

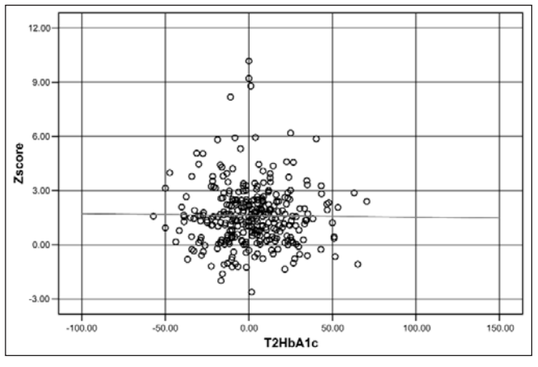
a) Standardised birth weight vs. standardised pre-pregnancy HbA1c



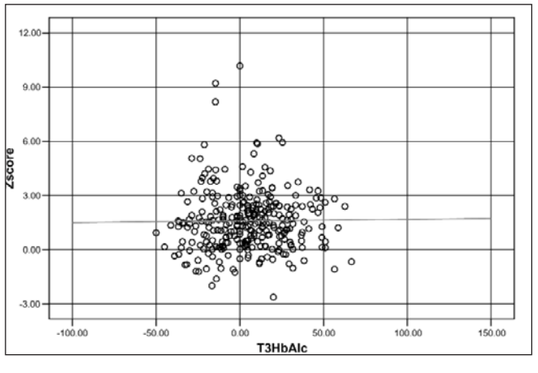
(b) Standardised birth weight vs. standardised first trimester HbA1c



(c) Standardised birth weight vs. standardised second trimester HbA1c



(d) Standardised birth weight vs. standardised third trimester HbA1c



Studies examining the relationship between birth weight and HbA1c vary, with some including and some excluding congenital anomalies. Infants with congenital anomalies tend to be smaller than structurally normal infants and this is most pronounced in infants with chromosomal anomalies. Therefore, a potential explanation for the negative correlation seen between birth weight and pre-pregnancy HbA1c is that inclusion of babies with congenital anomalies – as a result of poor peri-conceptual glycaemic control – has biased the results. However, as first trimester HbA1c, rather than pre-pregnancy HbA1c, more accurately reflects prei-conceptual control and as no negative correlation is seen between first trimester HbA1c and birthweight, this is unlikely to be the case.

Therefore, having a pre-pregnancy HbA1c value available, irrespective of the value, may be a surrogate marker for some other variable, or combination of variables, which influence fetal size.

Birth weights of babies born to mothers with diabetes are subject to the same influences as babies in the rest of the population but diabetic mothers have much more variable energy substrate levels e.g glucose. Therefore, a simplistic explanation for the marked difference in birth weight between the 'diabetic' and 'non-diabetic' populations would be that glycaemic control is the important variable. This theory is compatible with the generally accepted maternal hyperglycaemia- fetal hyperinsulinaemia hypothesis.

Most studies have shown a relationship between glycaemic control and foetal size;[1;3-8] but the relationship is inconsistent and most authors accept that it does not explain all of the variance seen between diabetic pregnancies and those of the general population.

Johnstone et al showed that glycated HbA1c at 27-33 weeks was the strongest explanatory variable, of those analysed, affecting foetal size.[4] Evers et al showed that despite good glycaemic control (as measured by HbA1c) the incidence of macrosomia remained high in their population.[2] One possible explanation is that intermittent hyperglycaemia is a more significant contributor to the development of macrosomia than chronic hyperglycaemia.[11] HbA1c reflects chronic hyperglycaemia, rather than the peaks and troughs of maternal glycaemic control. Therefore, it may be too imprecise a tool to predict or explain the relationship between glycaemic control and birth weight. Other measures of glycaemic control have been investigated. Persson et al examined the relationship between birthweight and both fasting and post-prandial glucose levels.[7] Although raised fasting glucose levels were associated with macrosomia, this relationship pertained only when glucose levels were raised between 27-32 weeks gestation. Sturrock et al also studied blood glucose in pre-gestational diabetes and found a positive correlation between birthweight and blood glucose measures in the second and third trimesters.[3] No similar relationship was seen for HbA1c levels in the same group of women.

Thus, the relationship between HbA1c and birth weight cannot be easily explained. Better understanding of the pathophysiology of macrosomia and alternative measures of glycaemic control are required.

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ORIGINAL ARTICLES

Lack of Knowledge of Osteoporosis: A Multi-Centre, Observational Study

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ABSTRACT

Background and Aim
Osteoporosis poses a significant health problem. As the population ages, its incidence increases. Effective prevention requires good awareness of the disease among the general public. The aim of this study was to assess the level and source of osteoporosis knowledge in a group of patients attending for Dual Emission X-ray Absorpitometry (DEXA) scanning.

Methods
A questionnaire was devised to assess knowledge of the osteoporosis risk factors, risk-reducing measures and signs/symptoms. Questionnaires were completed by 176 patients in two centres; Glasgow Royal Infirmary, UK (120 patients), and St. George's Radiology Department, Christchurch, New Zealand (56 patients).

Results
Overall knowledge of osteoporosis was poor. In terms of risk factors 31.8% (n=56/176) knew no risk factors at all, 19.3% (n=34/176) knew no risk reducing measures and 39.2% (n=69/176) knew no signs or symptoms of osteoporosis.

Conclusion
Knowledge of osteoporosis, despite this cohort being a group of patients attending for DEXA scanning, was poor. There is a need for the public to to be made more aware of osteoporosis, thereby enabling them to be more actively involved in preventive measures. National campaigns are required to increase awareness. Furthermore, increasing health professionals' awareness of the considerable limitations which exist in public knowledge of the disease, leading to a new realisation of the need for them to discuss osteoporosis with their patients, could provide a highly effective means of increasing awareness of the disease.

Background

By the age of 50, the estimated lifetime risk among Caucasian women of sustaining a fracture due to osteoporosis, is 40%. In the UK, the total number of fractures attributable to osteoporosis each year is estimated at 250,000,[1] with osteoporosis costing the National Health Service £1.7 billion per year.[2] Overall, the increase in life expectancy alone is predicted to at least double the number of hip fractures over the next 50 years.[1] Osteoporosis is therefore a large and expanding problem.

Osteoporosis is a silent disease. Often individuals are unaware they are at increased risk until they sustain a fracture, by which stage the opportunity for early preventive measures have been missed. To be actively involved in prevention, the public needs to be aware of the disease, its risk factors and recommended risk reducing measures. Therefore, it is relevant to ask, how much do the public actually know about osteoporosis and what are the most effective methods of increasing awareness?

Knowledge of the disease was assessed in a group of patients referred for Dual Emission X-ray Absorpitometry (DEXA) bone scanning for osteoporosis. For the purposes of this study, this provided a group which could be classed as potentially being at increased risk of osteoporosis.

Aim

The aim of the study is to assess the extent of knowledge of osteoporosis in patients attending for DEXA scanning, and to enquire as to their sources of knowledge about the disease.

Methods

An anonymous, voluntary questionnaire was designed and issued to 176 patients attending for DEXA bone scanning. Patients were asked to list as many as they could of the following; (1) "Risk factors (anything that might cause or increase the chance of developing osteoporosis)" (2) "Risk reducing measures (anything one can do or take to strengthen their bones)" (3) "Signs or symptoms, (anything that might make you think you or someone else has osteoporosis)". Respondents were also asked to indicate, from a list of options, what they felt were the sources of the their information about osteoporosis. They were also asked ifthey had ever had a previous discussion with any doctor about osteoporosis.

The risk factors and risk reducing measures listed in the Scottish Intercollegiate Guidelines Network Management of Osteoporosis (SIGN Guideline 71) were taken as the

correct responses to questions 1 and 23. With regard to coding questions 1 and 2, any response considered to relate to calcium was taken to be correct, examples included 1 "Not drinking milk", "Poor calcium intake", 2 "Cheese, yoghurt", "Calcium supplementation". Examples of inappropriate responses given to 1 included; "Overweight, allergies and over-exercising". Results were coded by an independent observer from the Glasgow Royal Infirmary audit department.

The questionnaire was issued in two centres, Glasgow Royal Infirmary, United Kingdom (120 patients) and St. Georges Radiology Centre, Christchurch, New Zealand (56 patients). The patients were referred for scanning from a number of sources including; general practice, fracture clinics, orthopaedic ward admissions, endocrinology and rheumatology.

Results

185 questionnaires were issued, 176 were completed fully, making a 95.1% response rate. 84.6% of respondents were female (n=149) and 14.7% were male (n=26). Gender data for one patient was missing. The age range was 22-85 years, with a mean age of 58.3 years.

(1) Risk factors

Patients were asked to list as many osteoporosis risk factors as possible. Analysis showed an average of 1.7 risk factors suggested per patient. This was achieved by dividing the total number of responses by the total number of respondents. The most commonly suggested risk factor was a lack of calcium, selected by 42.6% of patients (n=75). 32.4% (n=57) were unable to suggest any risk factors. Importantly only 7.3% (n=13) suggested a previous fracture as a risk factor, 6.8% (n=12) suggested advanced age and 1.7% (n=3) suggested being female.

(2) Risk-reducing measures

On average, patients knew 1.7 risk-reducing measures. The best-known risk reducing measure was an increase in calcium intake, which was suggested by 65.9% (n=116) patients. 19.3% (n=37) were unable to suggest any risk reducing measures.

(3) Signs/symptoms

On average, patients knew 1.07 signs/symptoms of osteoporosis. The most commonly suggested was sustaining a fracture, given by 43.2% (n=76). 39.2% (n=69) knew no signs or symptoms.

Table I Osteoporosis risk factors correctly suggested unprompted, (>4%)

OSTEOPOROSIS RISK FACTORS	Number of times suggested N/176	% total
Low intake of calcium	75	42.6
Lack of exercise	37	21.0
Family history of osteoporosis	37	21.0
Smoking	27	15.3
Early Menopause/post-menopausal	25	14.2
Use of steroid medication	18	10.2
High intake of alcohol	14	8.0
Previous fracture	13	7.4
Advanced age	12	6.8
Low body weight	9	5.1
None known	57	32.4

Table II Osteoporosis risk reducing measure correctly suggested unprompted, (>4%)

OSTEOPOROSIS RISK REDUCING MEASURES	N/176	% Total
Any calcium supplementation measure	116	65.9
Regular exercise	79	44.9
Healthy balanced diet	24	13.6
Taking hormone replacement therapy	24	13.6
"Medication/Drugs" not specified	8	4.5
Taking vitamin D supplements	7	4.0
None known	34	19.3

Table III Suggested osteoporosis signs/symptoms unprompted

OSTEOPOROSIS RISK REDUCING MEASURES	N/176	% Total
Any calcium supplementation measure	116	65.9
Regular exercise	79	44.9
Healthy balanced diet	24	13.6
Taking hormone replacement therapy	24	13.6
"Medication/Drugs" not specified	8	4.5
Taking vitamin D supplements	7	4.0
None known	34	19.3

Table IV Patient information sources for osteoporosis knowledge, (>4%)

OSTEOPOROSIS INFORMATION SOURCES	N/176	% Total
Medical doctor	71	40.3
Media Magazines	55	31.3
Media – TV	38	21.6
Relative/Friend other than mother	28	15.9
Medical pamphlets	27	15.3
Mother	15	8.5
Medical/Health books	14	8.0
Working in the medical field	11	6.3
None suggested	18	10.2

(4) Information sources

Patients were asked to record, from a list of options, the sources of their osteoporosis information. Patients could select more than one option.

The main source of information was from medical doctors, 40.3% (n=71)

(5) Previous discussion with a doctor

86/176 (48.9%) had previously had a conversation with a doctor about osteoporosis, 88/176 (50%) had not. These data for two patients was missing.

(6) Comparison between sub-groups Male vs Female and New Zealand vs Scotland

Comparisons were made of the knowledge displayed by males vs females and separately by patients from New Zealand vs Scotland. Females displayed a statistically significant increased level of knowledge of risk factors, risk reducing measures and signs/symptoms when compared to males ($p<0.007$) using non-parametric Mann-Whitney U testing. Interestingly, higher levels of knowledge were observed from the responses obtained in Christchurch, New Zealand when compared to Glasgow. These were statistically significant ($p < 0.001$) using Mann-Whitney U testing. It is important to note however that the participants in Christchurch, NZ live in a higher socio-economic area than those in the Glasgow Royal Infirmary's catchment area, thus making it unreliable to draw direct comparisons between the groups.

Discussion

Osteoporosis is a significant health problem, which with a growing ageing population is increasing in size. The keys to prevention are education and ensuring the the public is aware of the disease, its risk factors and recommended preventive behaviour.

This study found that knowledge of osteoporosis in patients attending for DEXA scanning was poor. 31.8% (n=56/176) of the patients in the group knew no risk factors, 19.3% (n=34/176) knew no risk reducing measures and 39.2% (n=69/176) no signs or symptoms of osteoporosis. Low calcium intake, despite being the best-known risk factor, was only suggested by 42.6% (n=75/176) of respondents. This was followed by lack of exercise and family history of the disease, both 21.0% (37/176). It is of concern that smoking, menopause and alcohol were only suggested by 15.3%, 14.2% and 8% of respondents respectively. Measures to increase calcium levels were the best-known preventive measures with 65.9% (116/176) of replies. Unfortunately only 44.9% (79/176) suggested the second best known measure, which is regular exercise. Only 4% (7/176) suggested avoiding smoking and 2.3% (4/176) suggested avoiding excess alcohol to reduce the risk. Only 43.2% (76/176) suggested that a fracture may be a sign of osteoporosis.

Notably, 50% (n=88) of the patients attending for DEXA scanning had not discussed osteoporosis with a doctor on any previous occasion. Therefore, health care workers should not assume that patients, such as the elderly or those who have been for a DEXA scan, would necessarily have had a discussion with a medical professional regarding osteoporosis.

It is accepted that some of the apparent of lack of knowledge could be due to questionnaire design, using open questions in 1-3 which may yield a lower response rate than closed equivalents. However in this study, unprompted questions were felt to provide a more accurate representation of knowledge, avoiding subjects being led to give a response they may not otherwise have given simply because it was on the list. Furthermore, the number of open questions used was limited with the aim of increasing the response rate.

It is not clear why osteoporosis knowledge is so poor. It may be that it has not received the same degree of publicity or is not perceived by the public to be as important, as other diseases. Kasper et al have shown that younger members of the public neither perceive themselves to be susceptible to the disease nor feel osteoporosis is as serious as other diseases they may be at risk of developing.4 It is also worthy of note that the patients in this study had been referred for further investigation, as they were considered to be at increased risk of osteoporosis. They may have actually had a higher level of knowledge about the disease than the general public. Knowledge among males was significantly lower than among females. This may reflect the traditional view that osteoporosis was considered a female problem and therefore health promotion has focused on females.5 This study shows that doctors and magazines are thought by patients to provide the best sources of osteoporosis knowledge. This perhaps reflects a situation where magazines aimed at a female readership are more likely to run articles on osteoporosis than magazines aimed at a male readership. "or that doctors are traditionally more

likely to discuss osteoporosis with their female patients. Furthermore, many males do not perceive themselves to be at risk of osteoporosis and therefore their poor knowledge may reflect a lack of interest in the disease because of this perceived lower risk.6

What is clear is that awareness of osteoporosis needs to be increased. These results show that all aspects of osteoporosis education require improvement. Of concern is the lack of knowledge that factors such as such as inadequate exercise, excess alcohol, smoking and the menopause have in the genesis of osteoporosis. It has been shown that osteoporosis education programmes can be effective.7,8,9,10 The respondents felt that doctors provided the best source of osteoporosis information 40.0% (n=71), followed by magazines 31.3% (n=55) then the television 21.6% (n=38). This would suggest that future educational campaigns would be more effective if they were relayed either via the media or through patients' own doctors. It is hoped that by highlighting the lack of knowledge that currently exists amongst the public, health care professionals will be more aware of the need to discuss osteoporosis with their patients. All ages should be targeted because of the importance of building and maintaining an adequate bone mass in early life.4,10 Attempts to address this problem have been successfully commenced in Glasgow with the Fracture Liaison Service, which via osteoporosis specialist nurses aims to identify, educate and treat at risk patients >50 years of age with fractures.11. Better still, increasing awareness of the disease amongst the public could in turn enable early preventive measures to be carried out before individuals sustain fractures.

Conclusion

Osteoporosis is a large and expanding disease, resulting in significant health issues and financial burden to the NHS. Its progression is often silent and it frequently presents, previously undiagnosed, following a fracture. This study has shown that knowledge of osteoporosis risk factors, preventive measures and signs or symptoms, despite the study cohort being a group of patients attending for DEXA scanning because of suspected osteoporosis, is poor. In order to address this issue, the public needs to be made more aware of osteoporosis, thereby allowing them to be actively involved in preventive measures from an early age.

National campaigns are required to increase the public's awareness of osteoporosis. Furthermore, making individual health care professionals more aware of the sizeable limitations that currently exist in public knowledge and therefore the need to discuss osteoporosis with their patients could provide a highly effective route of increasing awareness of the disease.

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ORIGINAL ARTICLES

"Do Unto Others as..." - Which Treatments do Psychiatrists Prefer?

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ABSTRACT

We undertook an independent national survey of psychiatrists' treatment preferences should they become mentally ill. The response rate was 59% from 921 individuals. For psychosis, atypical antipsychotics were generally favoured with risperidone receiving most votes. Psychotherapy and antidepressants were both endorsed as treatments for mild-to-moderate depression, and citalopram; fluoxetine; and venlafaxine were the three preferred antidepressants. ECT received the backing of a large majority of psychiatrists, particularly for severe mood disorder.

Introduction

The Mental Health (Care and Treatment) (Scotland) Act 2003 allows individuals suffering from mental disorder to specify their treatment preferences during future episodes of illness via an "advance statement".[1] An "advance statement" can only be drawn up by a capable adult, and implies that the individual concerned has some understanding of the risks and benefits of the treatments involved.

We sought to determine the treatment preferences of psychiatrists based in Scotland should they become mentally ill. We argue that this collective real world expert opinion is a powerful form of evidence, and that it complements the narrow rigour of the randomised controlled trials and meta-analytic data by synthesising that data through years of clinical experience.

Method

The UK Royal College of Psychiatrists (Scottish Division) mailing list of members and fellows who were either employed or participating in continuing professional development in Scotland contained 925 names. These individuals are all experienced psychiatrists, and either fully trained specialists (consultants) or senior trainees. All 925 psychiatrists were sent a standardised questionnaire. All responses were anonymous, but the respondent's age, gender, seniority, and place of work were recorded.

The questionnaire required the psychiatrist to specify which one antipsychotic medication they would take if they became psychotic; and whether they would prefer psychotherapy (eg cognitive behavioural or interpersonal therapy) or antidepressants (or both) should they suffer from a mild to moderate episode of depression, as well as which one antidepressant they would opt for if they required medication. In both scenarios the psychiatrist could indicate whether their choice of medication was due to the relative efficacy or the side effect profile, or both.

Additionally, psychiatrists were asked if they would consent to electro-convulsive therapy (ECT) and if so, for which clinical condition. Lastly the psychiatrists were asked if they would ever consent to neurosurgery for mental disorder (NMD).

Results

The response rate to the questionnaire was 59%, ie 544 psychiatrists replied from a possible total of 921 individuals, with a legal executor replying that one psychiatrist had died, whilst three retired psychiatrists felt unable to provide answers.

Sixyty nine percent of the psychiatrists who responded were consultants (fully trained specialists); with 51% of the total being male. There was an even distribution of age range, with 10% aged between 20-30; 34% between 31 and 40; 32% between 41 and 50; and 24% over 51 years old. Geographic distribution of responses followed staffing patterns across the country, with 50% of all responses being received from the main urban (Glasgow and Edinburgh) regions.

There was no dramatic difference in pattern of anti-psychotic choice between consultants and other grades of psychiatrist, or between men and women. As can be seen from Table I, most choices were based on relative side effect profile, rather than relative efficacy with only chlorpromazine, clozapine, and olanzapine having efficacy more frequently specified than side-effect profile.

Table I Antipsychotic Preferences, and Relative Reasons for Choice

Antipsychotic	*Psychiatrists' (n=544) choice (%)*	*Efficacy (%)*	*Side effects (%)*	*Both (%)*	*No response (%)*
Risperidone	29	12	33	51	4
Quetiapine	19	1	70	24	5
Olanzapine	14	34	21	44	1
Amisulpride	11	12	46	33	9
Aripiprazole	9	2	55	42	1
Clozapine	6	68	6	24	3
Chlorpromazine	4	77	7	16	0
Haloperidol	1	83	0	17	0
No choice made	7				

With regard to treatment for their own mild to moderate depression, 34% of psychiatrists preferred only psychotherapy as their treatment, 41% preferred only antidepressant medication, and 25% indicated they would prefer both.

Table II Antidepressant Preferences, and Relative Reasons for Choice

Antidepressant	*Psychiatrists' (n=544) choice (%)*	*Efficacy (%)*	*Side effects (%)*	*Both (%)*	*No response (%)*
Citalopram	27	10	64	19	7
Fluoxetine	21	32	29	36	2
Venlafaxine	21	66	6	33	4
Sertraline	11	10	52	38	0
Mirtazepine	6	29	24	47	0
Amitriptyline	3	65	5	20	10
Paroxetine	3	27	13	53	7
Lofepramine	2	46	15	39	0
Dothiepin	1	67	0	33	0
Moclobemide	0				
No choice made	5				

Where antidepressant medication had to be rated, neither gender nor seniority affected antidepressant choice. Of the favourite three antidepressants, citalopram was viewed as having best side effect profile; venlafaxine as the most efficacious; with fluoxetine having roughly equal votes for efficacy and side effects, as indicated in Table II.

Eighty five percent of all psychiatrists indicated they would accept ECT, with 15% of men and 13% of women stating that they would never consent to ECT. Treatment resistant depression and depressive psychosis were the two most preferred indications for ECT, and most (69%) female psychiatrists indicated they would consent to ECT for post-partum psychosis, whilst male respondents suggested this was not relevant.

The majority of psychiatrists who responded (60%) indicated they could not imagine any clinical scenario where they would consent to neurosurgery for mental disorder (NMD), with 4% not expressing a view.

Discussion

We have undertaken the first independent national survey of psychiatrists' preferred treatment choices, should they become mentally unwell. In this age of evidence based medicine, treatment choices are based not only on scientific data and expert guidelines, but also personal clinical experience, peer opinion, and marketing influence. We believe the data in this type of study offers a unique perspective on the real world practice of psychiatry, although the results only have a finite shelf life as new treatments emerge.

There are some limitations to this work. Although we have opinion from across a range of ages and localities, with a balance of gender and career grade, it is possible our results are not representative of Scotland or the UK generally. A response rate of 59% is however better than many postal surveys.[2] The brief standardised questionnaire forced the respondent into specific listed choices, and hence if an option was not listed but preferred this could have acted as a disincentive to completion. Numerous responses contained freehand comment regarding the survey, for example "..absence of a depot (antipsychotic) is a fatal flaw…"

Debate has continued over whether intra-class differences in efficacy exist between atypicals.[3,4] In this survey, the first atypical to be licensed in the UK, risperidone, was clearly the preferred antipsychotic. It is worth observing that aripiprazole was only launched some four months before the commencement of this survey. Our results demonstrate that atypicals as a whole command widespread confidence, perhaps reflecting NICE recommendations,[5] and although most choices were based on side effect profile important differences in both efficacy and side-effect profile were felt to exist. Interestingly in a survey of Scottish patients who had been treated in the mental health services (with 756 replies returned)[6] sulpiride was the preferred antipsychotic medication. Data on national prescription rates for Scotland in 2003-4, in both primary and secondary care,[7] revealed that only chlorpromazine, risperidone, and olanzapine were prescribed over 20% by volume. Thus there would appear to be differences between what the psychiatrists say and do, although the national data includes family physician or general practitioner prescriptions. Also interesting is that patients would appear to value a relatively non-sedative antipsychotic medication (sulpiride) which was not specifically included on our list although amisulpride is a similar compound.

With regard to the choice of treatment for mild to moderate depressive episode, there was a comparatively even split of opinion between psychotherapy and antidepressant medication, and perhaps surprisingly a minority of psychiatrists voted for a combination approach. One study suggested both generic counselling and antidepressants were effective in primary care for mild to moderate depression.[8]

Amongst the preferred antidepressants there appeared an inverse correlation between relatively benign side effects (citalopram) and the perception of added efficacy (venlafaxine). Fluoxetine appeared midway between these two poles, whereas sertraline scored in a similar pattern to citalopram. The Scottish patient survey listed trazodone as the patients' preferred antidepressant,[6] and the national prescription rate data showed that only amitriptyline, citalopram, and fluoxetine were prescribed at over 16% by volume in Scotland during 2003-4.[7] The patients' preferred antidepressant medication, trazodone, was not on our limited list of choices, and is often employed in part because it provides nocturnal sedation which of course may be desirable during a depressive episode. This may suggest that psychiatrists should consider asking patients specifically if they would prefer a medication which confers nocturnal sedation.

One of the most controversial treatments in psychiatry is ECT, but here an overwhelming majority of expert opinion was favour of its use, particularly for severe mood disorder and post-partum psychosis in women. No data on why it was rejected by 15% of all psychiatrists was available.

Scotland has a specialist centre for neurosurgery for mental disorder. Although it is perhaps difficult to foresee a clinical scenario where all other treatment options have been exhausted, it is possibly surprising that only a minority (36%) of psychiatrists felt they would consent to this low-frequency intervention.

In summary, psychiatrists in Scotland are clearly able to state their own treatment preferences, and genuine differences in both side effect profile and relative efficacy are felt to exist between amongst the listed antipsychotics, and amongst the listed antidepressant medications. Psychotherapy and ECT are both valued as treatment options in mood disorder.

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ORIGINAL ARTICLES

Acute Abdomen as a Cause of Death in Sudden, Unexpected Deaths in the Elderly

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ABSTRACT

Aims

This study profiles patients aged 70 years or above dying suddenly of an 'acute abdomen' and investigates the specific features associated with the conditions and their diagnoses.

Methods

A retrospective study using data obtained from autopsy and police reports held in the Forensic Medicine Section of the University of Edinburgh.

Results

From 1997 to 2000, out of 2121 autopsies of patients aged 70 or above, an 'acute abdomen' was considered as a primary cause of death in 111 cases. The number of cases increased over the period of study. Peptic ulcer disease was the commonest underlying cause of death. Twenty-nine (26.1%) cases were due to its complications, namely gastrointestinal haemorrhage and perforation. Sixty-nine (62.2%) patients were seen by a medical practitioner in circumstances arising from the onset of acute abdomen. In 27 (39.1%) cases a provisional diagnosis was recorded.

Conclusion

The 'acute abdomen' is still an appreciably frequent cause of death in sudden, unexpected deaths in the older age group. Some of the deaths may have been preventable with an early diagnosis. A high level of vigilance and early attention to an 'acute abdomen' by medical practitioners is therefore advocated.

Introduction

Acute abdominal pain is a common presenting complaint to the casualty department. In publications on three series of patients suffering from acute abdominal conditions, elderly people accounted for a significant proportion of such patients.[1-3] In the UK series, which included over 16,000 patients of all ages, the mortality escalated sharply with age: in patients younger than 60 years, the mortality was never higher than 1%; in contrast, the figure rose to 7% in patients aged 80 years and over.[3] In addition, the diagnostic accuracy on admission to hospital declined with increasing age: in patients aged 80 years or above, the initial diagnostic accuracy was only 29% compared to over 40% in younger patients.[3]

Studies of the acute abdomen in the aged have been carried out, which were mainly of patients presenting with acute abdominal complaints[4-8] or of patients admitted for emergency abdominal surgery.[9-12] However the 'acute abdomen' presenting as sudden, unexpected death was not a topic on which publication has appeared.

This study profiles patients aged 70 years or above dying suddenly of an 'acute abdomen' and investigates the specific features associated with the conditions and their diagnoses.

Methods

For the purpose of this study, an 'acute abdomen' is defined as a condition caused by an underlying intra-abdominal pathology, which would typically present with acute onset of abdominal pain and may be associated with features of peritonism on clinical examination. Ruptured abdominal aortic aneurysm was excluded from this study because the number of deaths would dominate the analysis.

The study was based on the post-mortem data relating to cases referred to the Forensic Medicine Section (FMS) by the Procurators Fiscal as part of their common-law duty to investigate all sudden and unexpected deaths in the Lothian and Borders regions of Scotland.

Autopsy reports of patients aged 70 years or above, from 1997 to 2000 were screened for all cases in which a condition associated with 'acute abdomen' was noted as a primary cause of death on the death certificate. The autopsy reports and the police (sudden death inquiry) reports of the identified cases were further reviewed. The police reports are based on an investigation conducted by a specially trained police officer, including an interview of the deceased's general practitioner (GP) and contain a summary of all potentially relevant medical history of the deceased and to outline the circumstances surrounding their death.

Results

During the four-year period from 1997 to 2000, a total of 2121 autopsies of patients aged 70 or above were carried out by forensic pathologists at the FMS of the University of Edinburgh acting on the instructions of Procurators Fiscal in Lothian and Borders. They comprised 1069 (50.4%) males and 1052 (49.6%) females.

'Acute abdomen' as a primary cause of sudden, unexpected deaths

There were 111 cases in which an 'acute abdomen' was certified as the primary cause of death, consisting of 47 (42.3%) male and 64 (57.7%) female. The number of cases increased over the period of study (Figure 1).

Figure 1 Cases of 'Acute Abdomen' from 1997-2000 Showing Distribution of Patients According to Sex

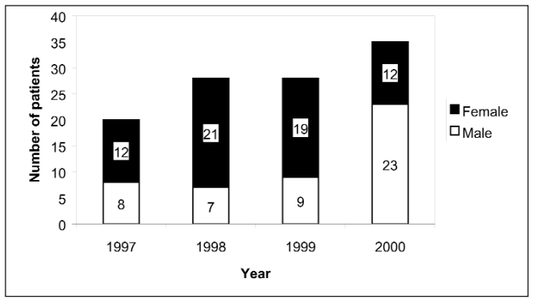

Table I Causes of 'Acute Abdomen'

Primary Cause of Death	Male	Female	Total (%)
Acute gastrointestinal haemorrhage	16	8	24 (21.6)
Peptic ulcer	10	4	14 (12.6)
Other causes[a]	6	4	10 (9.0)
Perforated colon	5	14	19 (17.1)
Diverticulum	4	9	13 (11.7)
Other causes[b]	1	5	6 (5.4)
Perforated peptic ulcer	5	10	15 (13.5)
Acute urinary tract infections	4	11	15 (13.5)
Intestinal obstruction	8	3	11 (9.9)
Mesenteric ischaemia	3	8	11 (9.9)
Acute pancreatitis	2	4	6 (5.4)
Carcinoma of pancreas	2	2	4 (3.6)
Acute cholecystitis	1	2	3 (2.7)
Others[c]	1	2	3 (2.7)
Total	47	64	111 (100)

a Due to adenocarcinoma of gall bladder, cholecysto-colonic fistula, mesenteric ischaemia, rectosigmoid infarction, ulcerated gastric adenocarcinoma, ruptured oesophageal varix, oesophago-gastric tear, acute oesophagitis & gastritis, aorto-jejunal fistula, acute erosive gastritis.

b Due to stercoral ulceration(3), carcinoma, ischaemia, acute enterocolitis.

c Due to ruptured appendix, acute gastroenteritis, pseudomembranous colitis.

Overall, the mean age of patients was 79.4 years (SD 6.3). The difference between the mean age for males [78.2 years (SD 5.7)] and females [80.2 years (SD 6.6)] was not statistically significant.

Peptic ulcer disease

Peptic ulcer disease was the commonest underlying cause of death in this series. Twenty-nine (26.1%) cases of 'acute abdomen' were due to the complications of peptic ulcer disease, namely gastrointestinal (GI) haemorrhage and perforation. There were more duodenal ulcers (20) than gastric ulcers (9). Two patients had a previous diagnosis of peptic ulcer; 6 were prescribed some non-steroidal anti-inflammatory drugs (NSAIDs) or steroids; three were taking either a H_2-receptor antagonist or a proton pump inhibitor. Twelve (41.4%) patients with peptic ulcer disease did not present to any health care service until death.

Intestinal obstruction

There were 9 cases of small intestinal obstructions due to peritoneal adhesions (4), volvulus (three), a caecal carcinoma and a diaphragmatic hernia. Two cases of large bowel obstructions, attributed to a rectal carcinoma and a sigmoid volvulus, were also identified.

Contributory cause of death

In addition to an 'acute abdomen', 68 (61.3%) patients had one or more conditions identified at post-mortem examination as a contributory cause of death. Cardiovascular diseases (mainly hypertension and atheroma) were the commonest and recorded in 43 (63.2%) of them.

Chronic alcohol misuse was recorded as a contributory cause of death in 5 patients.

Medication

The patient's history of prescribed medication was reported by the police in 49 (44.1%) cases. Thirty-one (63.3%) were taking some form of analgesic (ie. NSAIDs, dihydrocodeine) or corticosteroids.

Place of death (Table II) and interaction with the health care service

Table II Place of Death

Place of death	Male	Female	Total (%)
Found dead at home:			
Own residence	23	26	49 (44.1)
Nursing Home	7	8	15 (13.5)
Sheltered House	0	2	2 (1.8)
In hospital:			
A&E	4	9	13 (11.7)
Hospital (other wards)	13	19	32 (28.8)
Total	47	64	111 (100)

Sudden deaths at home

Sixty-six (59.5%) deaths occurred at home. Twenty-four patients had consulted their GPs with some symptoms. Twenty (83.3%) consultations were in the last 24 hours prior to death; two (8.3%) were three days previously; one (4.2%) was 4 days previously.

Thirty-nine (5 of whom were in the nursing home) patients did not come to the attention of any health care staff until found dead. Three patients were attended by paramedics but attempts at resuscitation were unsuccessful.

Sudden deaths in hospital

Forty-five (40.5%) deaths took place in hospital. Of those who died in the Accident and Emergency Department (A&E), 8 were self-referrals, 4 patients were referred by their GPs and one was apparently discovered dead at home by her daughter and son-in-law, then conveyed to A&E.

Among the 32 (28.8%) deaths, which occurred after admission into a hospital, 13 were self-referrals through the A&E, 10 were emergency GP referrals, 5 patients were admitted for apparently non-abdominal conditions, including three cases of fractured neck of femur due to a fall, an admission for physiotherapy and one for the treatment of CREST syndrome and ischaemic foot. Four other patients were transferred from another hospital (three from a psychiatric hospital and one from a cottage hospital).

Only one emergency exploratory laparotomy was carried out but the patient was deemed inoperable. Another two patients died before a laparatomy was commenced. Hence no surgical treatment was undertaken on any patient in this study.

Medical Contact

Sixty-nine (62.2%) patients in this series were seen by a medical practitioner in circumstances arising from the onset of acute abdomen. Thirty-eight (55.1%) patients consulted their GP, 14 (36.8%) of whom were referred to secondary care. Twenty-one (30.4%) self-referred to A&E and 9 (13.0%) were already under hospital care. The remaining patient apparently died at home but was taken to A&E by relatives (where life was pronounced extinct). Table III compares the presentation, provisional diagnosis and the autopsy findings of the 27 (39.1%) patients for whom this information was recorded by the police. In 4 (14.8%) cases the provisional diagnosis was accurate.

Table III Comparison of Provisional and Post-Mortem Diagnoses

Age	Sex	Presentation	Provisional Diagnosis	Post-mortem Diagnosis
70	F	Abdominal pains, diffuse abdominal tenderness, pale, hypotensive.	Aortic aneurysm	Acute GI haemorrhage due to mesenteric ischaemia
73	F	Haematemesis	Cardiac arrest; bleeding oesophageal varices	Acute GI haemorrhage due to aorto-jejunal fistula
70	M	Chest pains, anorexia	"Not heart related"	Acute GI haemorrhage due to peptic ulcer
81	M	Found collapsed, dehydrated, rigid abdomen	Infarcted bowel	Acute GI haemorrhage due to peptic ulcer
73	F	Abdominal pains, shocked, cold, confused	Peritonitis	Peptic ulcer-perforated
81	F	Nausea & abdominal discomfort; collapsed with hypotension and high pulse	Postoperative pulmonary embolism or a major cardiac event	Peptic ulcer-perforated
71	F	Vomited, feverish, abdominal discomfort, jaw pain, breathless, peripheral cyanosis, slight tenderness in abdomen	Pulmonary oedema	Colon-perforated diverticulum
74	M	Abdominal pains	Constipation	Colon-perforated diverticulum
75	F	Stomach pains; vaginal discharge	Vaginal fistula	Colon-perforated diverticulum
79	M	Urinary frequency, lower abdominal pain, distended bladder	Urinary retention	Colon-perforated diverticulum
79	F	Abdominal pains, constipation, nausea, distended, tender abdomen but no guarding	Constipation	Colon-perforated diverticulum
85	F	Abdominal pains, fullness in left side of abdomen, extremely unwell	Mesenteric Ischaemia	Colon-perforated diverticulum
79	F	Sudden onset of generalised abdominal pain, no motions but passing flatus, guarding, pyrexial	Peritonitis, septicaemia, cardiac failure	Perforated colon due to ischaemia
75	M	Weight loss, gaunt, listless	Diarrhoea due to antibiotics for an UTI; malnourished	Perforated colon due to carcinoma
83	F	Stomach pain, "very ill"	**Intra-abdominal perforation**	**Perforated colon due to stercoral ulceration**
89	F	Dizzy	UTI	Perforated colon due to stercoral ulceration
74	F	Poor colour, cold, clammy, nauseous, anorexia	Infection	Mesenteric Ischaemia
87	F	Unwell; shock	**Mesenteric infarction**	**Mesenteric ischaemia**
92	F	Sore stomach, sickness	Gastroenteritis	Mesenteric Ischaemia
76	M	Tonic clonic seizures; hypotensive, distended abdomen	Usual seizure for the patient (known chronic epileptic)	Acute intestinal obstruction due to diaphragmatic hernia
89	M	Abdominal pains, distended abdomen	Urinary retention	Acute intestinal obstruction due to ileal volvulus
83	M	Abdominal distention and vomiting	**Intestinal obstruction**	**Acute Intestinal obstruction due to caecal carcinoma**
73	F	Unwell, sickness, back pain	"Nothing wrong found, hence no treatment"	Acute UTI
92	F	Unresponsive, refused to drink; swollen legs; hypoglycaemia	Cerebrovascular accident Diabetes Mellitus	Acute UTI
77	F	"Chesty"	Exacerbation of COPD	Acute pancreatitis
87	F	Abdominal pains, vomited blood; drowsy, cold, peripherally shut down, tender abdomen, markedly raised amylase	**Pancreatitis**	**Acute pancreatitis**
76	F	Diarrhoea, anorexia, low urine output for days	Diarrhoea due to antibiotics	Pseudomembranous colitis

(Diagnoses in bold = diagnosis confirmed at autopsy)

Discussion

'Acute abdomen' in the elderly constitutes a heterogeneous clinical entity. This study provides a unique perspective as it examines cases of 'acute abdomen' in the aged, which had been largely unnoticed or undiagnosed until a post-mortem examination, to the extent that these had to be referred to the legal authorities as uncertified deaths.

The results from this study suggest that 'acute abdomen' is increasingly found as a cause of sudden, unexpected death in the elderly. The rising trend could possibly reflect the changing referral pattern to the Procurators Fiscal and the growing geriatric population in our society. There was a predominance of females in this study, which is consistent with the findings of other hospital series[5,6,8,9,11,12] examining acute abdominal diseases in the aged and the higher longevity of females.

The leading causes of 'acute abdomen' in this study, namely, acute gastrointestinal (GI) haemorrhage, intestinal perforations and obstructions all represent a surgical emergency. A retrospective study of 152 patients over the age of 65, who underwent emergency abdominal surgery in a general hospital in a neighbouring city (Glasgow), showed that intestinal obstructions and perforations and GI haemorrhage comprised 92 (60.5%) of all cases.[12] As was the case in our study, peptic ulcer disease was the commonest underlying aetiology, accounting for 40 of the 92 cases.[12]

In a retrospective review of 6962 autopsies in Germany to identify previously unknown peptic ulcer disease as the cause of sudden, unexpected death, 43 such cases were reported and the average age of these patients was 62.2 years.[13] In an older study of a group of 31 patients in whom perforated peptic ulcer was not diagnosed until autopsy, 24 (77%) were aged 60 or over.[14] These findings highlight the significance of the condition as a cause of sudden death in the elderly. Peptic ulcer disease may present in the elderly without pain in one-third of patients, but may result in GI haemorrhage, anaemia, nausea, vomiting or weight loss.[15] This may partly explain why there are still a number of clinically unnoticed or undiagnosed peptic ulcers.

Furthermore, frequent use by the elderly patients of NSAIDs and steroids for other concurrent illness obscures their pain perception and at the same time predispose them to developing peptic ulcers or to aggravating pre-existing ulcers.

Nearly one-third of the deaths studied had occurred after admission to hospital (ie. excluding those who died before leaving the A&E). A small number (5) of patients had been admitted for apparently non-abdominal conditions but later died of an 'acute abdomen' on the ward. This underlines the difficulties faced in the management of geriatric patients, which is often complicated by the co-morbidity present. At the same time, this underscores the importance of a holistic approach to the management of this group of patients.

Significant challenges are encountered in diagnosing acute abdominal conditions in the elderly patients. They often present with less pronounced clinical features. Their abdominal muscles frequently are thin, due to some degree of atrophy, making them react with less splinting, muscle guarding or spasm.[16] In a retrospective study of elderly patients with peritonitis, abdominal pain was reported in only 55% of the cases, and guarding and/or abdominal rigidity in only 34%.[17] These factors could well explain the non-specific presentation often reported in the patients in this study.

Thirty-four (30.6%) patients in this cohort, who lived in their own home, did not come to the attention of any health care staff until death. One possibility is their fear of being hospitalised with potential institutionalisation and the associated loss of independence. This may prevent many elderly patients from seeking medical attention in an early stage of their disease. There is some evidence from individual cases in this study, which supports such an observation. Moreover, many of the elderly self-diagnose constipation or indigestion and treat themselves accordingly before seeking medical help, thereby delaying the potentially life-saving intervention in the initial phase of their condition.

The comparison between provisional and post-mortem diagnoses illustrates the difficulty of achieving an accurate diagnosis of 'acute abdomen' based on the signs and symptoms extant at the initial presentation. If death had been certified on the basis of the provisional diagnosis, the medical cause of death would have been erroneous. Hence the data highlight the need for autopsy examination in these cases: to audit the provisional diagnosis and to ensure that the accurate cause of death is identified.

The 'acute abdomen' is still an appreciably frequent cause of death in sudden, unexpected deaths, particularly in the older age group. Some of the deaths discussed in the study may have been preventable with an early diagnosis. A high level of vigilance and early attention to an 'acute abdomen' either by primary care or hospital physicians is therefore advocated.

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ORIGINAL ARTICLES

Oxidase Activity of Ceruloplasim and Some Acute Phase Reactant and Trace Element Concentrations in Serum of Patients with Chronic Lymphocytic Leukemia

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ABSTRACT

In the present study, we aimed to investigate the parameters in serum of patients with Chronic Lymphocytic Leukaemia (CLL) and correlate with the cancer stage. The serum concentrations of ceruloplasmin, a-1-acid glycoprotein, albuminumin, transferrin, copper, zinc, manganese, and ceruloplasmin oxidase activity were measured, and compared with those from a healthy control group. The serum from 34 patients with CLL were extracted before chemotherapy. Serum transferrin, albuminumin and Zinc concentrations were lower in patients with CLL while serum a-1-acid glycoprotein, ceruloplasmin, copper concentrations, and ceruloplasmin oxidase activity were higher in CLL patients when compared with the control group. Although serum manganese concentration was lower in CLL groups than in the control group, the difference was not statistically significant. Serum transferrin concentration was lower in the early stage group compared with the advanced stage. Serum ceruloplasmin level positively correlated with serum ceruloplasmin oxidase activity in patients from the early stage group. Serum ceruloplasmin level positively correlated with serum ceruloplasmin oxidase activity in patients with advanced stage. In conclusion, increased serum ceruloplasmin oxidase activity, ceruloplasmin, a-1-acid glycoprotein, copper levels and decreased transferrin and albuminumin, unchanged manganese levels are associated with CLL and appear to be a consequence of the disease itself.

Introduction

Chronic lymphocytic leukemia (CLL) is a haematologic neoplasm characterised by the proliferation and accumulation of relatively mature appearing lymphocytes in the blood, bone marrow, lymph nodes, spleen, liver and other organs. The disease is seen rarely in those below the age of 30; most patients with CLL are over 60 years of age. CLL increases in incidence exponentially with age; by 80 the incidence rate is 20 cases per 100,000 persons per year. Asian countries such as Japan and China have an incidence of CLL only 10 per cent that in the United States and other Western countries.[1,2] The major causes are not known nor is there detailed understanding about how the elusive origin(s) may relate to clinical expression, basic biological mechanisms, or pathogenesis.[2,3]

The acute-phase proteins are a family of proteins synthesised by the liver whose levels change in response to infection, injury and neoplasia. In response to injury, the levels of some acute-phase proteins such as serum amyloid A, ferritin, and ceruloplasmin (Cp), increase. In contrast, levels of others, such as Albumin, prealbumin and transferrin (Trf), fall.[5]

Alpha-1-acid glycoprotein (AAG) is a 44 kDa plasma protein and its concentration in plasma increases approximately two to four fold following tissue injury. It has been speculated that AAG plays an important role in inflammation, and may be the best laboratory parameter for the pre-therapeutic prognostic evaluation of lung cancer patients.[6,7]

Albumin contains 17 disulphide bridges and has a single remaining cysteine residue and it is this residue that is responsible for the capacity of albumin to react with and neutralise peroxyl radicals. This property is important in view of the role that albumin plays in transporting free fatty acids in the blood. Albumin also has a single high-affinity copper binding site that transfers newly absorbed copper to the liver.[8,9]

A major contributor to the antioxidant defence system of human plasma is reported to be ceruloplasmin. Ceruloplasmin acts as an antioxidant by several mechanisms[10, 11, 12,13,14] inhibiting iron-dependent lipid peroxidation (LP) and HO formation from hydrogen peroxide (H_2O_2) via its ferroxidase activity, 12 reacting with and scavenging H_2O_2 and superoxide anion, and inhibiting copper-induced LP by binding copper ions.[10,12] Ceruloplasmin is a plasma glycoprotein that is primarily synthesised by the liver and secreted into the blood. It binds about 60% of plasma copper and is considered a copper transport protein. Ceruloplasmin permits the incorporation of iron into Trf without the formation of toxic iron (Fe) products.[14, 15,16]

Trace elements exist in very low concentrations in the body and consist of 0.01% of total body weight. It is well known that certain major and minor elements play an essential part in a number of biological processes.[16]

To our knowledge, there is no available data on serum AAG, Albumin, Trf, ceruloplasmin, copper, zinc, manganese concentrations and ceruloplasmin oxidase activity in patients with CLL. Therefore, in the present study, we aimed to investigate these parameters in serum of patients with CLL and correlate with the cancer stage.

Materials and Methods

Patients

Thirty-four patients (29 males) with CLL comprised the patient group, and 26 healthy subjects were taken as control group (23 males), with the age range being 39 - 78 years (mean ± SD; 60.1± 10.3) for the patients and 37 - 66 years (mean ± SD; 57.6 ± 11.9) for the controls. CLL patients were staged according to the Rai et al,17 classification: 5 were in stage I; 12 in stage II; 7 in stage III, and 10 in stage IV. CLL patients were divided into two groups as early stage (stage I and II) and advanced group (stage III and IV). The patients were taking no antileukaemic therapy and were newly diagnosed cases.

Blood Sampling

CLL patients and healthy control subjects were recruited into the study after obtaining their informed consent. Venous blood (8 ml) was taken from controls and patients. The blood samples were centrifuged and the serum samples obtained were stored at -80°C until analysis.

Biochemical Measurements

Serum ceruloplasmin, albumin, AAG and transferrin levels were determined by nephelometric method (Beckman Array 360 Protein System, Minnesota, Brea, USA). Serum transferrin, AAG, ceruloplamin and albumin were expressed as mg/dL, and g/dL respectively.

Serum ceruloplasmin oxidase activity was measured according to the method of Schosinski et al.[18] The method is based on the ability of ceruloplasmin to oxidise substrate such as o-dianizidine (3,3,-dimethoxybenzidine) yielding a yellow product. Briefly, 0.75 ml of 0.1 M acetate buffer, pH 5, in 2 tubes was mixed with 0.05 ml of serum sample and kept for 5 min at 30°C. To both tubes 0.2 ml of 0.25 % o-dianizidine dihydrohloride was added and one mixture was incubated at 30°C for 5 min, and the other for 15 min. The reaction was stopped by adding 2 ml of 9 M sulfuric acid. The optical density was determined at 540 nm using a spectrophotometer (CECIL CE 3041, Cambridge, UK). Ceruloplasmin oxidase activity was expressed as U/dL.

The ceruloplasmin oxidase activity was calculated as: Cp oxidase activity (U/l) = $(A_{540}{}^{15\ min}\text{-}A_{540}{}^{5min})$ x 625

For trace element assays, all of the materials (glass and plastic) used were thoroughly cleaned with hot solution of nitric acid (20%, v/v) for 48 hours and rinsed five times with deionized water. Serum samples were diluted with deionized, double distilled water for element measurements, when required. Zn, Cu, and Mn measurements were carried out with an atomic absorption spectrometer (Unicam 929, UK). Serum Cu, Zn and Mn were expressed as mg/dL and ng/dL, respectively.

Statistical Analysis

The findings were expressed as the mean ± SD. Statistical and correlation analyses were undertaken using the Mann-Whitney U-test and Spearman's rank correlation coefficient test, respectively. A p value < 0.05 was accepted statistically significant. Statistical analysis was performed with Statistical Package for the Social Sciences for Windows (SPSS, version 11.0, Chicago, IL, USA).

Results

The results from patients with CLL and control group are summarised in Table I. As seen from Table I, although serum Mn concentration was lower in CLL cancer groups

Table II Mean ± SD of Trf, AAG, Cp, Albumin, Cu, Zn, Mn Levels and Cp Oxidase Activity in Serum of Patients with Chronic Lymphocytic Leukemia and Control Group

	Control group	Early stage (I+II)	Advanced stage (III+IV)	Total patient group
Trf (mg/dL)	276.2 ± 36.0	181.4 ± 33.1[c]	227.6 ± 44.8[c,d]	204.5 ± 45.3[c]
AAG (mg/dL)	89.3 ± 16.0	120.1 ± 26.9[c]	141.2 ± 31.5[c]	130.7 ± 30.8[c]
Cp (mg/dL)	31.5 ± 5.8	62.7 ± 19.6[c]	78.9 ± 13.9[c]	70.8 ± 18.6[c]
Cp oxidase activity (U/dL)	16.7 ± 4.1	22.2 ± 7.3[b]	25.3 ± 5.5[c]	23.8 ± 6.5[c]
Albumin (g/dL)	4.3 ± 1.0	3.7 ± 0.46[c]	3.6 ± 0.43[c]	3.6 ± 0.44[c]
Cu (µg/dl.)	71.8 ± 14.0	91.3 ± 9.8[c]	98.8 ± 7.7[c]	95.0 ± 9.5[c]
Zn (µg/dL)	83.1 ± 5.2	66.1 ± 9.4[c]	61.9 ± 5.8[c]	64.0 ± 8.0[c]
Mn (ng/dL)	116.0 ± 17.4	115.1 ± 11.5	112.2 ± 7.6	113.7 ± 9.7

a: p<0.005, b: p<0.01, c: p<0.001, when compared to control group.

than in the control group; this difference was not statistically significant ($p>0.05$). Serum Trf, albumin and Zn concentrations were lower in patients with CLL while serum AAG, Cp, Cu concentrations, and Cp oxidase activity were higher when these patients compared with control group. Serum Trf concentration was lower in early stage group compared with advanced stage group. However, among all stages, no significant difference were found in the basis of above mentioned parameters. As seen from table, as the stage of the disease increased, higher concentrations of serum AAG, Cp, Cu and Cp oxidase activity, and lower concentrations of serum albumin and Zn were determined.

Serum Cp level positively correlated with serum Cp oxidase activity ($r = 0.81$, $p<0.001$) in patients with early stage group.

Serum Cp level positively correlated with serum Cp oxidase activity ($r = 0.74$, $p<0.001$) in patients with advanced stage. However, no other correlation could be found among the parameters in patients with CLL and healthy controls.

Discussion

Several factors such as serum acute phase reactants (APR) have been reported to be useful markers for staging the disease and predicting the prognosis in patients with cancer.[5,6,7] In this study, we aimed to investigate the importance of APR and some trace elements in patients with CLL.

The activity of antioxidant enzymes, mainly of cellular location, plays a crucial role in oxidant carcinogenesis. A contribution of Cp to antioxidant defense can be of great importance, in regard to its plasma location. Increased production of some of acute phase proteins, also Cp, that often accompanies neoplastic process, supposedly is caused by interleukin-1 (IL-1) and tumor necrosis factor (TNF) released by macrophages. In various carcinomas the oxidase activity and the concentration of Cp were reported to be elevated.[12]

Of the extracellular antioxidants, Cp permits the incorporation of Fe into Trf without the formation of toxic Fe products. Trf inhibits iron-ion dependent OH formation from H_2O_2. Iron-catalyzed reactions are limited by the presence of Trf in human plasma. Under physiologic conditions, Cp is also important in the control of membrane lipid oxidation, probably by direct oxidation of cations, thus preventing their catalysis of lipid peroxidation.[15,16] We found that increased serum Cp oxidase activity and Cp level in patients with CLL. This increase of Cp oxidase activity and Cp level in serum may be due to a compensatory mechanism. By keeping iron in Fe^{3+} state, Cp presents it from undergoing the redox cycles necessary to initiate toxic effects.[16]

In one study, Agroyannis et al,[19], decreased serum Trf and increased Cp levels were reported in patients with gastrointestinal cancer. Zowczak et al,[12] documented significantly increased Cp oxidase activity in various cancer patients. Taysi et al,[16] and Varela et al,[20] reported significantly increased Cp in serum of laryngeal cancer patients.

Our results for Cp oxidase activity, Cp, and Trf, levels in serum of patients with CLL are in agreement with those obtained by Zowczak et al,[12] Varela et al, [20] and Taysi et al's[16] studies.

AAG is one of positive acute phase proteins and its concentration in plasma increases approximately two to four fold following tissue injury. It has been speculated that AAG plays an important role in inflammation and cancer, but its exact biological function is still unclear.[21] Our results showed significant decrease in the mean albumin level and significant increase in the mean AAG level in the serum of patient groups comparison the control group. This latter result is in agreement with the results of other researchers.[7]

Recent studies draw attention to trace elements. Zn, and Mn are important elements in the preservation of immune resistance and both Zn and Cu are required for numerous biochemical functions and for optimal activity of the immune system. Zn is involved in the function of approximately 80 enzymes in body.[16]

Cu and Fe can catalyze the formation of the highly reactive hydroxyl radicals from H_2O_2 via the Haber-Weiss reaction and decompose of lipid peroxides to peroxyl and alkoxyl radicals, which favor the propagation of lipid oxidation. The competition of Zn for Fe binding sites is particularly relevant taking in account that Zn deficiency facilitates intracellular Fe accumulation.[22]

In this study, serum Cu level was found to be elevated while serum Zn level was found to be decreased. These data confirm the earlier studies.[16,23] Contrarily, unchanged serum Zn and Cu were determined gastrointestinal system and cervical cancer cases, respectively.[24, 25] As both metals, together with Mn, are the prosthetic group of Superoxide dismutases (SODs), any alterations in their levels may affect activities of the enzyme. The relationship between SOD activity and estimated trace elements remains to be enlightened. Nevertheless, this may cause oxidative stress or may further increase the existed stress.[16]

There are contradictory results on the alterations in serum or tissue trace elements and concentrations of serum antioxidant protein in various cancers. The mechanisms by which these alterations occur in certain cancers need to be enlightened. It is also obscure that whether these alterations are a cause or a consequence of the malignancy. As a conclusion, in our opinion, alterations in the level of trace elements and antioxidant proteins are important for many metabolic processes, in CLL may not be a reason for, but in fact a consequence of the disease itself. These parameters and other acute phase proteins might have important metabolic roles in cancer progression.

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ORIGINAL ARTICLES

Presence of Herpes Simplex Virus on the Oral Mucosa in Patients Undergoing Chemotherapy

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ABSTRACT

Background
The aim of this study was to confirm the presence of herpes simplex virus type 1 and 2 on the oral mucosa, in patients undergoing chemotherapy, by means of polymerase chain reaction - PCR.

Methods
The research was carried out on 40 patients receiving chemotherapy as treatment for different malignancies. The status of oral mucosa and viral presence were assessed in all patients at the initial examination (prior to chemotherapy), and at the control examination (two weeks after the initiation of the chemotherapeutic cycle).

Results
The presence of HSV-1 was detected in 28 patients (70%) prior to chemotherapy, of whom 7 (25%) manifested oral complications. The control examination showed the presence of HSV-1 in 35 patients (87.5%), of whom 23 (65.7%) presented oral mucosa changes. HSV-2 has not been detected in any of the patients.

Introduction

Patients receiving chemotherapy commonly develop pathological changes in the oral mucosa. Oral mucositis can occur as a result of direct cytotoxic effect of cytostatics on the oral tissue, but also as a result of underlying immunodeficiency. This immune dysfunction is an enhancing factor for opportunistic infections localised in the oral cavity, the agents being bacteria, fungi or viruses. Most frequently, oral mucosa damage consists of exanthemas, vesicles, erosions and ulcerations, usually followed by a subjective stinging and burning sensation and pain.[13,8] What is more important is that the mucosal damage is the port of entry for a great number of pathogens. [9,4] Infections caused by herpes simplex virus are very frequent in immunocompromised patients. However, due to a usually atypical clinical picture, they remain mostly unrecognised or misdiagnosed. Due to diminished resistance, herpes simplex virus can easily cause lesions of the oral mucosa, or worsen the already existing damages caused by the stomatotoxic effect of cancer therapy. There is also a possibility of its systemic dissemination followed by numerous changes in the visceral organs.

Therefore, sensitive laboratory methods aimed at detecting the presence of the virus in various biological specimens within the shortest possible time should be introduced as routine practice. [2,11]

Objective

The objective of this study was to confirm the presence of herpes simplex virus, type 1 and 2 (HSV-1, -2) by means of polymerase chain reaction (PCR), on the oral mucosa of patients suffering from various forms of malignancies and receiving chemotherapy.

Methods

The study consisted of 40 patients of both sexes and different age, all undergoing chemotherapy. (Table I).

Table I Classification of patients according to age, sex and type of malignancy

Age	Type of malignancy										
	Colorectal CA		Acute leukemia		Chronic leukemia		Breast CA		Head and neck CA		∑
	m	f	m	f	m	f	m	f	m	f	
19-29			3								3
30-39			2	5					1	1	9
40-49	1		3	3				3			10
50-59	2	1				2			1		6
60-69	5	2		3		1					11
70-79	1										1
∑	9	3	8	11		3		3	2	1	40

Clinical study

The initial clinical examination was done prior to chemotherapy, while the control examination was conducted two weeks after the initiation of the therapy cycle. Clinical tests were done at the Department of Haematology, Institute of Internal Diseases, Clinical Centre in Novi Sad, and at the Institute of Oncology in Sremska Kamenica, Serbia. The oral mucosa status was determined according to the mucositis severity criteria of WHO, which is as follows:

grade 0= None
grade 1= Soreness +/- erythema, no ulceration
grade 2= Ulcers, patient can swallow solid diet
grade 3= Ulcers, extensive erythema, patient cannot swallow solid diet
grade 4= oral mucositis to the extent that the patient cannot swallow

Laboratory analysis

This part of the research was carried out at the Department of Microbiology and Immunology of the School of Medicine in Belgrade, as well as in the Laboratory for Molecular Biology at the School of Dentistry in Belgrade. In order to establish the presence of HSV-1 and 2, swab samples of all patients were taken from soft tissues of the oral cavity, as well as from lesioned sites. The swab samples were sowed in test tubes containing transportation medium (MEM), then each sample was placed in a centrifuge vial, homogenised by vigorous vortex mixing and centrifuged for five minutes at 1200 rpm; the supernatant was poured into sterile test tubes and held at -70? until processing.

The extraction of potentially present viral DNA was performed by boiling the collected material at 100?C for ten minutes, after which PCR was applied aiming to confirm the presence of specific viral segments. Primers for HSV-1 (**forward 5' -ATA CCG ACG ATA TGC GAC CT** and **reverse 5' - TTA TTG CCG TCA TAG CGC GG**) are specific for the region which encodes a type-specific thymidine kinase. The size of the PCR product is 110-bp. HSV-2 specific primer pair for glycoprotein G (**forward 5' - TCA GCC CAT CCT CCT TCG GCA GTA** and **reverse 5' - GAT CTG GTA CTC GAA TGT CTC CG**) generated a 183-bp PCR product.3 The reaction mixture in a total volume of 25 □l comprised: 0.2 ?M "up-stream" and "down-stream" primers, 10xPCR buffer, 0.2mM deoxyribonucleotide triphosphate mix, 1 unit of *Taq* polymerase (Fermentas), 3 □l of sample. The number of amplification cycles was 35, performed in a thermal cycler (PCR Express, Hybaid). The PCR consisted of an initial denaturation of 3 minutes at 94? C followed by 35 cycles (denaturation at 94? C for 1 min, annealing at 52° C for 1 min, and extension for 3 min at 72? C) and a final extension of 7 minutes at 72° C.

PCR products were run on an 8% polyacrilamide gel, stained with ethidium bromide and visualized on a UV transilluminator (Power Station 300 plus, Labnet International, Inc.).

MANOVA and Roy's *t* test has been used for statistical analysis.

Results

At the initial examination, 9 out of 40 patients (22.5%) revealed changes in the oral mucosa. Six were suffering from acute leukemia. The severity of mucositis in 3 patients was marked as grade 1, in two patients as grade 2, and in one patient as grade 3. In one patient suffering from chronic leukaemia, pathological conditions of the oral mucosa were observed, and marked as grade 3. At the initial examination, oral mucositis marked as grade 1 was also observed in a female patient suffering from breast cancer, as well as in one patient suffering from head and neck cancer, graded 2 (Table II). The changes on the oral mucosa presented as paleness, petechial haemorrhage, vesicles and erosions.

Table II Mucositis severity at the initial clinical examination according to WHO criteria

	Mucositis severity					∑
	0	I	II	III	IV	
Acute leukemia	13	3	2	1		19
Chronic leukemia	2			1		3
Colorectal CA	12					12
Breast CA	2	1				3
Head and neck CA	2		1			3

However, contrary to the relatively infrequent manifestation of pathological changes in the oral mucosa, the presence of the HSV-1 genome in samples obtained from the oral cavity was revealed in a much greater number of patients. HSV-1 was detected in 28 patients (70%), versus 7 (17.5%) patients only, presenting oral complications (Table III).

Table III Presence of viral genome in samples obtained at the initial examination

	PCR +	PCR -	∑
Patients with oral complications	7	2	9
Patients without oral complications	21	10	31
∑	28	12	40

At control examination, the changes localized on the oral mucosa appeared to be more frequent. Their presence was detected in 26 patients (65%). The occurrence of oral mucositis was mostly found in patients suffering from acute and chronic leukaemia. 17 out of 22 leukaemia patients (77%) had oral mucosa damage at the control examination. The pathological conditions seen on the oral mucosa of these patients were not only more frequent, but they were also more severe than in patients with other malignancies. At the control examination, exanthema, vesicles and erosion of the oral mucosa, as well as ulcerations were observed, while one patient presented

necrosis of the oral mucosa. Oral mucositis marked as grade 2 or 3 was detected in 4 patients with colorectal cancer. In 2 female patients suffering from breast cancer, oral mucositis was scored as grade 1 and grade 2. Changes of grade 1 or 2 in the oral mucosa also appeared in 3 patients with head and neck cancer (Table IV).

Table IV Mucositis severity at control examination according to WHO criteria

	Mucositis severity					Σ
	0	I	II	III	IV	
Acute leukemia	5	5	5	3	1	19
Chronic leukemia			1	2		3
Colorectal CA	8	2	2			12
Breast CA	1	1	1			3
Head and neck CA		2	1			3

At control examination the presence of HSV-1 was detected in 35 cases (87.5%), 23 showing oral complications (57.5%). Five patients (12.5%) did not reveal the presence of virus (Table V). None of the samples was positive to HSV-2.

Table V Presence of viral genome in samples obtained at control examination

	PCR +	PCR -	Σ
Patients with oral complications	23	3	26
Patients without oral complications	12	2	14
Σ	35	5	40

The differences between the presence of viral genome on initial and control examination were not statistically significant.

Discussion

Until recently, no attention has been paid to viral infections in patients with malignancies because lesions of viral etiology present on the oral mucosa of these patients often have an atypical clinical picture, and are consequently misdiagnosed. [2,14,5] Thanks to new, sensitive and specific tests, it has been shown that oral infections of viral origin are frequent in patients suffering from malignancies, especially in patients with haematological malignancies.[11,10,6] Numerous studies point out to frequent infections of viral etiology (incidence ranging between 50% and 90%), mostly with Herpesviridae, localized in the oropharyngeal region. The studies have demonstrated that oral infections caused by these viruses can have a severe clinical picture.[5,16] The data obtained from available sources are in accordance with the results obtained in our study, which revealed a high incidence of cases positive to HSV-1, both on initial (70.0%) and control examination (87.5%). HSV-1 infection was found in patients with oral lesions but also without any change on the oral mucosa suggesting that asymptomatic viral shedding is very common among patients with malignancies.

It should be also emphasized that certain malignancies are more prone to viral infections than others. Some studies point to the fact that viral infections localized in the oral cavity are more frequent in patients with acute leukemia than in patients suffering from other forms of malignancies. Barrett et al estimate that 40% of patients with acute leukemia have a recurrent herpetic infection in the oral cavity during chemotherapy.[1] Epstein et al presented in their study an even higher percentage of herpetic infections.[7] With almost 80% of HSV-1 positive cases among patients suffering from leukaemia, the results of our research are in agreement with the data from other studies dealing with hematological malignancies. A high rate of HSV-1 detection in oral changes can be attributed by the application of sensitive PCR techniques.

The majority of authors agree on the fact that the greatest number of infections occur owing to reactivation of the latent virus in the host's body.[12,11] Primary herpetic infections in patients with malignancies are extremely rare, since they occur during the early years of life, regardless of the immune status.

Conclusion

Oral infections caused by herpes simplex viruses in patients undergoing chemotherapy have a much higher occurrence than previously estimated. Immune dysfunction, as a product of primary malignancy and application of chemotherapy, represents an enhancing factor for the reactivation of HSV infection. It can lead to a manifested herpetic infection that affects oral mucosa previously damaged by the cytotoxic action of chemotherapy, but it can also lead to asymptomatic shedding. Individuals with immunodeficiency, together with patients suffering from malignancies, are often at risk of virus dissemination in the body, which in some cases leads to lethal outcome. For that reason, the choice of sensitive, specific and rapid laboratory methods for virus detection is a crucial prerequisite for an adequate therapy administration. By using PCR methodology, minute quantities of viral genome can be confirmed in various types of biological specimens within a very short time, which can occasionally be of crucial importance to the course of the disease and survival of the patient.

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ORIGINAL ARTICLES

It's Getting Better: Progress in Medical SHO Training in Scotland

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ABSTRACT

Objectives
To identify factors which influence the quality of education and training for medical Senior House Officers (SHOs) in Scotland compared to a study in 1995.

Design
Postal questionnaire to collect both qualitative and quantitative data.

Participants
All 640 SHOs in hospital general medicine and medical specialty posts were identified; 395 (62%) responded.

Main outcome measures
Working patterns, experience of education and training, career choice, and an "attitudes to work" scale.

Results
Sixty seven percent of SHOs had been in post for 2 years or less. Seventy three percent work some form of shift pattern compared to 28% in 1995. There were improvements in on the job feedback (92% v 27%), and awareness of educational supervisors (96% v 48%). SHO specific teaching was only available to 49% and was rarely bleep-free. Sixty eight percent had made career decisions. There was a statistically significant improvement in 20/25 components of an attitudes to work scale.

Conclusions
Overall medical SHOs have more positive attitudes to their work in 2003 than in 1995, mirroring educational improvements in the work place and changes in working patterns. There remain challenges particularly in provision of formal educational activities.

Introduction

For many years there were concerns regarding the standard of training and education provided for the Senior House Officer (SHO) grade in hospital medicine. Problems identified by previous research include overwork, career indecision, lack of protected teaching time,[3,4] an inability to take study leave and insufficient practical experience.[5,6] In 1995 a Scotland-wide survey of medical SHOs reinforced many of those findings, and concluded that there were significant pressures on SHOs in relation to working hours and shift patterns, and tensions between service commitments and educational provision.[7,8] The present study was undertaken to revisit the quality of the educational climate for medical SHOs in Scotland in 2003 and to seek evidence of change since 1995.

Methods

A combined qualitative and quantitative approach was undertaken utilising a postal questionnaire including an attitude to work scale developed by Firth- Cozen (FCAWS) and used in the 1995 study. This scale comprises 25 statements reflecting a mix of positive and negative attitudes to work, rated on a 5-point scale ranging from strongly disagree, to strongly agree. At the start of the study, 2 focus groups and 12 one-to-one interviews provided insight into how SHOs perceive their current education and training and this qualitative approach was used to update the content of the 1995 questionnaire. Questions related to demographics, type of post, hours, workload, educational supervision, training experience and career plans. They were similar, but not identical to, the questions used in 1995. There was opportunity for free-text comments.

All SHOs in Scotland in general medicine and medical specialties, including those in posts forming part of a General Practice Vocational Training Scheme (GPVTS) were identified through Deanery, Royal College and hospital channels (640 posts). The questionnaire was posted and followed up with two reminders to maximise response.

Statistical analysis of data was undertaken using MiniTab to compare 1995 (T1) and 2003 (T2) data.

Results

hree hundred and ninety five replies were received, a response rate of 61.7%. This was similar across the four Deaneries. A slight majority of female respondents (55%) was compatible with the expected proportion in the target group and compared to 45% in 1995. Eighty one percent were UK graduates, 2% 'Other European' and 17% 'Non-European'. Eighty four percent were aged 30 years or younger. Almost two thirds had held an SHO post in the United Kingdom for up to two years and fewer than 5% for more than four years compared to 29% in 1995.

Thirty nine percent were on medical rotation schemes, 9% in GPVTS and 48% were in 6 to12 month stand-alone posts.

The Firth-Cozens[9] attitudes to work scale (FCAWS) showed that the 2003 SHOs were consistently more positive in their responses, and only 5 of the 25 comparisons did not achieve statistical significance

	T1	T2
'I am useful most of the time'	88%	93%
'The responsibilities of the job are overwhelming'	22%	17%
'I do not see myself continuing in medicine'	15%	13%
Experience of selection committee bias on grounds of gender	14%	12%
Experience of selection committee bias on grounds of race	14%	12%

The remaining questions in the scale cover a wide variety of topics and are reported in conjunction with the results of the detailed questionnaire.

Working Patterns

One in six of those responding to the question on contracted hours did not know their hours, and of those that responded 78% worked fewer than 56 hours per week compared to 6% in 2003. Table I shows the range of working patterns in the two studies. Sixty three percent of those giving an opinion preferred some form of shift-work. The most frequently cited from the 365 respondents were: social factors (55%), educational reasons (47%) and clinical service needs (37%).

Table I Working pattern in 1995 (T1) and 2003 (T2) and preferred working pattern in 2003 (T2)

	Declared working pattern		Preferred
	T1	T2	T2
	No (%)	No (%)	No (%)
On-call rota	180(72)	104(27)*	123(34)
Partial shift	35(14)	121(31)	104(29)
Full shift	13(6)	93(24)	87(22)
Mixed shift/hybrid rota	18(7)	60(15)*	36(9)
No response	NK	12(3)	38(10)

These results are mirrored in the Firth-Cozens scale where in response to the statement 'I have to work unreasonably long hours' there was a positive shift from 54% (T1) to 28% (T2) and 'I am able to enjoy my personal life' from 60% (T1) to 78% (T2), p = <0.001.

These results are mirrored in the Firth-Cozens scale where in response to the statement *'I have to work unreasonably long hours'* there was a positive shift from 54% (T1) to 28% (T2) and *'I am able to enjoy my personal life'* from 60% (T1) to 78% (T2), p = <0.001.

Clinical Work

Seventy three percent of respondents were in posts that involved acute receiving duties. There was considerable variation in numbers of patients admitted, ranging up to 60 per 24 hours, reflecting different sizes of hospitals. Two thirds felt that the balance of in-patient and out-patient work was educationally appropriate. This was mirrored in the FCAWS question: 'I am satisfied with the variety in my job' which increased from 63% at T1 to 73% at T2.

	T1	T2
'I have to work alone too often'	35%	22%*
'I am under great pressure at work	57%	42%*
'I am confident in my abilities'	68%	82%*
'I regularly feel I am working beyond my capabilities'	20%	13%**

* p = <0.001 ** p = <0.05

Agreement with the four statements below also showed an improvement in SHOs' responses to work:

Educational Environment

The biggest changes were observed in this area. In 1995 only 48% could identify their nominated educational supervisor but this had doubled to 96% in 2003. Eighty three percent of the present respondents understood the educational objectives of their current post and 66% had completed a personal learning plan.

There was also improvement in the frequency and perceived usefulness of feedback from seniors. In 2003 for both in-patient and out-patient work, more than 90% received helpful feedback and over 60% felt that it was adequate or extensive in amount. By comparison, in 1995, 27% reported that feedback on in-patient work was either non-existent or limited and not helpful.

These findings were confirmed by the FCAWS with 25% at T1 and 55% at T2 agreeing that 'senior doctors let me know how well I'm doing'.

	T1	T2
'I can discuss work problems with senior colleagues'	68%	79%*
'I can discuss personal problems with senior colleagues'	20%	34%**
'My need for a reference pressures me to conform'	41%	21%**
'I have on occasions been bullied by senior doctors'	36%	19%**

* p = <0.05 ** p = <0.001

Relationships with senior doctors also seemed better as agreement in these statements suggested:

Among the teaching opportunities described in 2003, almost all SHOs experienced regular teaching on wards, with spontaneous case discussion and questioning the most frequently used methods (95%); 19% had experienced teaching rounds led by consultants.

Formal education provision for SHOs is shown in Table II together with ability to attend and 'bleep-free' opportunities. Larger hospitals were more likely to provide SHO-specific and bleep-free teaching. Appreciation of teaching was evident in open-ended remarks, e.g. "teaching happens, regularly, on time, with good equipment, by specialists in those fields" and "current post is most educationally supportive with regular timetable specifically for SHOs."

Table II Provision of formal education reported by 395 respondents in 2003

	SHO Specific Tutorials	Relevant Hospital Meetings	Unit/ Specialty Meetings	Other formal teaching
	No (%)	No (%)	No (%)	No (%)
Regularly available	193(49)	238(60)	238(60)	70(18)
Usually able to attend	218(55)	260(66)	254(64)	111(28)
Generally bleep-free	85(22)	67(17)	71(18)	29(8)

Career Plans

Sixty eight percent had made a decision about their future career plan. Hospital medicine/medical specialties were the choice of 48%, general practice 24% and other hospital specialties - including accident and emergency, paediatrics and radiology - accounted for 22%. This compared to 51%, 23% and 16% of those who had decided in 1995. Factors potentially influencing the decision of current SHOs to continue or leave hospital medicine are shown in Table III.

Several questions in the FCAWS covered career interests and advancement and agreement with statements showed a difference between the two studies:

Table III Factors potentially influencing the decision to continue in Hospital Medicine. More than one response allowed.

	Encouraged by	Discouraged by
	No (%)	No (%)
Experience of jobs so far	268(69)	76(19)
Career/promotion prospects	204(52)	80(20)
Hours	100(6)	186(48)
Shift patterns	74(19)	186(48)
Advice from others	176(45)	64(16)
Eventual financial prospects	169(43)	55(14)
Personal satisfaction	279(71)	70(18)

	T1	T2
'I do not get adequate feedback for career purposes'	56%	33%*
'I am very satisfied with my choice of medicine as a career'	48%	69%*
'I am worried about career prospects in this specialty '	37%	28%*

* p = <0.001

Discussion

The responses to this survey came from a large group of SHOs working in Scotland in a variety of hospital settings including both large city conurbations as well as remote and rural hospitals. A uniformity of clinical experience is therefore unlikely although the educational climate should ideally be similar in all posts.

The most striking feature in this survey is the overall improvement in SHOs' attitudes to work between 1995 and 2003 evidenced by the improvement in rating scales in the Firth-Cozens' questionnaire. The more detailed questions developed from focus groups which mirrored the content in the original 1995 questionnaire also showed that the SHOs' perception of the educational environment and workplace support has improved greatly between the two studies.

A key finding of the 1995 study was that partial shifts are "detrimental to continuity of patient care, training, health and personal life". At that point, only 14% of SHOs in Scotland were working partial shifts. By 2003 this figure had risen to 58% including those working a hybrid of partial and full shifts. The negative attitudes have not persisted and indeed the reverse is now apparent in both the questionnaire and FCAWS scale.

Improvements in the educational environment were apparent. Comparison between the two studies shows a significant and encouraging improvement in perceived feedback from seniors, both for inpatient and out-patient work. There was a marked increase (from 48% to 96%) in SHOs who knew the identity of their educational supervisor. There was contemporaneous progress in the numbers aware of the educational objectives of their post and who had completed a personal learning plan. These results are very similar to the comparable South London trainee survey[10] and are congruent with the progress which has been tracked since 1996 by the continuous Educational Audit of SHO Posts in the North of Scotland Deanery.[11]

These improvements may be in part attributable to the higher priority given to SHO training in general by both NHS Education for Scotland (NES) and the Medical Royal Colleges with the development of documentation such as the Portfolio and Progressive Training Record (PPTR) by NES, and the complementary Federation of Royal Colleges of Physicians Core Curriculum and Record of Appraisal. This has led to an increased awareness of SHOs' educational needs, a more robust framework for appraisal and assessment and greater support and recognition of the educational supervisor's role.

Teaching was seen by the SHOs as a positive activity which supported and contributed to their confidence. As yet, SHO specific teaching is not fully developed and perhaps a central programme of topics produced by NES or the Royal Colleges might facilitate this.

Allowing for a significant proportion of SHOs as yet undecided, comparison with the previous study shows little change in career aspirations between hospital medicine and general practice. It is encouraging to note that for the vast majority, experience so far and personal satisfaction were perceived as influences to continue in hospital medicine. The reduction in numbers in SHO posts beyond 4 years would suggest career progression has improved since 1995.

Conclusions

Significant gains have been made over 8 years between the two surveys. This has occurred against a rapidly changing junior medical economy which has seen overall SHO post numbers rise by almost 50% and the 55% male preponderance reversed and a huge rise (6 to 78%) in those SHOs contracted to work fewer than 56 hours per week. It would appear that the educational improvements are substantially attributable to consultant staff embracing the standards and values promoted by educational organisations and the medical Royal Colleges. Thus feedback on the job, more overt senior support for acute receiving and more formal educational opportunities are now widespread.

Despite the many positive indicators, the responses also reveal that challenges remain. Ward duties appear to prevent almost half of SHOs from attending teaching sessions, and protected or bleep-free teaching time is still uncommon. Promotion of further change is pressing as the introduction of MMC will require ongoing high quality educational environments for training doctors for the future.

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EDUCATIONAL ARTICLE

What is New in Chronic Myeloid Leukemia?

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Abstract

Chronic myeloid leukaemia is a relatively rare condition, though it has stimulated widespread interest as a consequence of both the stem cell basis and the success of rationally designed therapies. This review will outline some of the issues involving the aetiology of the disease and how this relates to current and future therapies.

Introduction

Chronic myeloid leukemia (CML) is classified by the World Health Organisation as a myeloproliferative disorder (MPD), one member of a group of conditions including essential thrombocythaemia, polycythaemia vera and chronic idiopathic myelofibrosis. The MPD are all clonal disorders of the haemopoietic stem cell (HSC) characterised by abnormal myeloid (i.e. granulocyte, erythroid and megakaryocytic) proliferation. CML (also termed chronic myelogenous or granulocytic leukemia) is usually more appropriately considered as a distinct entity as a consequence of the now well characterised molecular biology of this disease. CML was first recognised in 1845[1, 2] with the initial description of the characteristic Philadelphia chromosome published in 1960.[3] Following this the causative *bcr-abl* oncogene with its protein product were described in the 1980s.[4, 5] This stimulated the search for rationally designed therapies of which imatinib (IM, Glivec®, STI571, Novartis Pharma), described in 1998, has achieved the most widespread use.

CML accounts for approximately one-tenth of all new leukemia diagnoses. The reported incidence in Scotland has varied little over the past decade at around 60 new cases per year, with a median age at diagnosis of 68 years.[6] This can be compared to the published estimates of incidence at 1-2 per 100000 population with a median age at diagnosis of 45-55 years.[7]

Pathogenesis

CML arises as a consequence of a reciprocal translocation between the long arms of chromosomes 9 and 22 (t (9; 22)) in an HSC. The shortened form of chromosome 22 is named the Philadelphia chromosome (Ph), after the city in which it was discovered. The only accepted causative insult from which this rare mutational event may occur is exposure to high levels of radiation, such as in survivors of the Hiroshima bomb and Chernobyl clean-up workers.[8,9] The majority of cases diagnosed worldwide are thought to arise spontaneously with no clear evidence for environmental triggers. The t(9;22) translocates the proto-oncogene *abl* from chromosome 9 to 22 forming a chimeric oncogene *bcr-abl*. This gene is responsible for the production of Bcr-Abl, an oncoprotein with constitutive tyrosine kinase activity. Bcr-Abl confers proliferative and anti-apoptotic properties to the cell and is responsible for the pathogenesis of the disease.[10]

The HSC carrying t(9;22) (Ph+HSC) is capable of performing the normal HSC functions of self renewal (allowing perpetuation of the haemopoiesis) and differentiation to committed progeny, seen as mature circulating cells – all of which carry the cytogenetic abnormality and fusion oncogene. In the normal HSC pool, the majority of cells are quiescent entering cell cycle only once every 1-3 months.[11] This is in contrast with the deregulated Ph+HSC population where the majority of cells are in cycle at any one time. However, a quiescent diseased population remains, constituting approximately 0.5% of the affected HSC population.[12,13] This represents a potential reservoir of disease in a cell group that by virtue of their inactivity may be less susceptible to conventional therapy

The stem cell basis of CML has become a paradigm for the mechanism of disease in a number of other malignancies. These include acute myeloid leukemia (AML), and non-haematological malignancies including tumours of the central nervous system and breast - all of which may arise of a consequence of deregulated stem cell activity.[14] However, CML is the only malignancy for which a specific causative cytogenetic abnormality has been identified.

Table I The definitions of accelerated phase and blast crisis as defined by major trials [20,35,36,51]. The diagnosis of chronic phase assumes the absence of any of the above criteria. *other than liver or spleen involvement † additional chromosomal abnormalities in Ph+ cells excluding variant Ph chromosome, loss of Y or constitutional abnormalities.

Accelerated Phase	Blast Crisis
Blast cells in blood or marrow 15-29%	Blast cells in blood or marrow ≥30%
Blast cells + promyelocytes in blood or marrow >30% (blasts <30%) Basophils in blood ≥20%	Extramedullary disease*
platelets <100 or >800x10^9/L (unrelated to therapy) clonal evolution†	

Clinical Features

The majority of patients diagnosed with CML are asymptomatic, with the diagnosis an unexpected outcome of a routine full blood count. The disease is divided into 3 recognised phases - chronic phase (CP), accelerated phase (AP) and blast crisis (BC) (Table I). At diagnosis patients are commonly in CP, a state characterised by leucocytosis and hepatosplenomegaly arising as a consequence of increased granulopoeisis and leukaemic infiltration. It has been shown that the presence of Bcr-Abl not only confers survival benefit, but influences the cell-stromal interactions within the bone marrow environment, leading to the release of more primitive cells into the circulation.[7] This is reflected in the characteristic blood film of a patient with CML as an elevated white cell count, with a shift in the myeloid line from mature to immature precursors ('left shift'). There are also typically an increased number of basophils and eosinophils. The bone marrow appearance is also typical with hypercellularity, a reversal of the normal ratio of erythroid to myeloid cells and a predominance of less mature forms. Untreated, CP will last a number of years and so it is suggested that the survival advantage of the leukaemic line is subtle relative to more aggressive diseases such as AML. The disease will then progress to BC, either directly or through an intermediate AP. Advanced stages (AP and BC) are characterised by a failure of maturation of the leukaemic precursors with the consequent disease resembling acute myeloid or lymphoblastic leukemia. With modern therapy the progression of CML appears to be significantly slowed, however when advanced disease does occur it responds poorly to chemotherapy with the median survival measured in months.

Initial assessment for the patient newly diagnosed with CML includes a medical history and clinical examination to assess performance status, spleen size and the presence or absence of extramedullary disease. We would recommend as baseline investigations peripheral blood including full blood count with an accurate white cell differential and Bcr-Abl levels, by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). A bone marrow aspirate is necessary, confirming disease phase by assessment of morphology and allowing cytogenetic examination to quantify the percentage presence of the Ph+ clone (at least 20 metaphases should be examined). A small number of patients with CML may be Ph-, with the formation of *bcr-abl* arising as a result of more complex chromosomal translocations. The diseased cells may have abnormalities in addition to Ph+, including deletions of the derivative chromosome 9 (del(der)9). This finding has been associated with a poorer prognosis, though with newer therapies may be of less significance.[15,16] The baseline investigations serve to enable the clinician to determine the patient's prognostic category. There are 2 scoring systems accepted for use, both of which require information from time of diagnosis: the Sokal score, utilising spleen size in centimetres below the costal margin, the blast cell % (from a white cell differential count) and the platelet count; and the Hasford score using the same information but adding the basophil and eosinophil %. The scoring systems allow assignment of the patient into one of high, intermediate and poor prognostic groups.

The presence of the *bcr-abl* fusion gene transcript provides a mechanism for diagnosis and monitoring of minimal residual disease in CML. Initially this was done qualitatively using polymerase chain reaction (PCR) to detect only the presence or absence of transcripts. The evolution of the technology now allows quantitative monitoring of Bcr-Abl levels by real time PCR (RT-PCR). Results are expressed as a ratio of Bcr-Abl/Abl transcripts. The *abl* control gene data will provide an assessment of the quality and quantity of RNA being examined, providing an experimental sensitivity for each sample.[17,18] It has been demonstrated that the fall in levels with therapy reflects a reduction in disease burden. A major molecular response (MMolR) is defined as a greater than 3 log reduction in Bcr-Abl levels from baseline (or <0.1% Bcr-Abl level if the level at diagnosis is 100%).[18] The test is however not standarised between laboratories and efforts are been made to correct this by use of an international standard, enabling patient groups to be compared more reliably when assessing therapeutic responses.[18] Classification of responses can be made based on the full blood count, Bcr-Abl ratio and bone marrow cytogenetics as seen in Table II.

Table II Definition of responses. % Ph+ is % of cells containing the Philadelphia chromosome on cytogenetic analysis of at least 20 bone marrow metaphases [18]. A major cytogenetic response includes those with both a partial and complete cytogenetic response.

Response	Criteria
Haematological response	
Complete	Platelets <450x10^9/L White cell count <10x10^9/L Normal white cell differential Absence of splenomegaly
Cytogenetic response	
Complete	0% Ph+
Partial	1-35% Ph+
Major*	≤35% Ph+
Minor	36-65% Ph+
Minimal	66-95%Ph+
None	>95% Ph+
Molecular response	
Complete	Undetectable transcript
Major	≤0.1 Bcr/Abl control gene ratio

The current recommendation is that patients on therapy are monitored by Bcr-Abl measurements from taken peripheral blood every 3 months. A bone marrow aspirate is required to assess for cytogenetic responses, though the frequency of routine testing in the absence of evidence of altered disease activity is the subject of some debate. Standard guidelines recommend cytogenetic testing every 6 months until a complete cytogenetic response (CCyR) is achieved and hence annually.[19] There is no evidence that Bcr-Abl testing on marrow aspirate offers any more information than results derived from peripheral blood and the low levels of variation may lead to confusion in interpreting results.[20] We would recommend that a consistent approach to testing is adopted, allowing more reliable comparison of sequential results. There is prognostic significance in the serial monitoring of patient responses to therapy, in particular the response to IM.

Disease Therapy

IMATINIB (IM)

The recommended standard first line therapy for patients with CML in CP is IM. This drug was shown to be superior to interferon-alpha (IFN-A) and cytosine arabinoside in the randomised prospective IRIS trial with initial data published in 2003. When adopted as initial therapy for those newly diagnosed with CP CML, IM led to a major improvement in outcome, as assessed by haematological, cytogenetic, molecular responses, progression free survival, side effects and quality of life.[21] Recent updated long term data generated from this trial reveals that 82% of patients achieve a CCyR with some late responses occurring in patients after 18 months treatment.[22] Early cytogenetic responses to IM are associated with improved outcome and can predict later response. Those with a partial cytogenetic response (PCyR) at 3, 6 or 12 months have a 90%, 80% or 50% chance respectively of achieving a complete cytogenetic response (CCyR) at 2 years. The benefit of achieving a major cytogenetic response (CCyR or PCyR) by 12 months is illustrated by recent data showing a 96% freedom from progression to advanced stages in this group, as compared to 81% in those with less than a partial response.[22]

Despite the impressive responses seen with IM there are some concerns about the long term efficacy. These have basis in the phenomena of disease persistence and IM resistance. It is accepted that despite the marked fall in Bcr-Abl measurements in those treated with IM therapy, with the majority of patients demonstrating a MMolR, few patients (<4%) will achieve a complete molecular response (i.e. undetectable Bcr-Abl).[23] Various groups, including our team in Glasgow, have focused on the Ph+HSC as the source of this minimal residual disease. We have shown that the quiescent Ph+HSC is not susceptible to the apoptotic effects of IM, even at concentrations greater than would be found within a treated patient. We have also demonstrated an accumulation of these quiescent cells with IM exposure of bone marrow samples taken from patients at diagnosis of CML.[24] This work is complemented by that of Bhatia *et al* who have shown that patients who have confirmed CCyR on IM maintain a population of functional Bcr-Abl+ HSC.[25] It is possible to reverse the quiescent state of these Ph+HSC and reconstitute disease, shown by experiments where selected non-cycling diseased cells are transplanted into immunocompromised host mice, which then develop transplanted leukemia.[12] This disease recrudescence is modeled in patients who discontinue IM therapy having achieved apparent disease control. The majority of patients rapidly relapse, though usually respond again to IM therapy.[26, 27, 28]

Resistance to IM is now a well recognised phenomenon. This may be primary, the failure of a patient to achieve a significant haematological or cytogenetic response, or secondary, manifest as reemergence of disease following an initial response. Resistance may occur in all phases of CML though is more common in AP and BC, where it may reflect the presence of additional cytogenetic abnormalities characteristic of advanced disease. Resistance may stem from: Bcr-Abl dependent mechanisms, such as point mutations in Bcr-Abl affecting IM binding, or amplification of the *bcr-abl* oncogene; and Bcr-Abl independent mechanisms, such as altered influx or export of drug from the cell or sequestration of IM by plasma proteins.[29]

IM binds to the inactive form of the Abl kinase and once bound maintains the enzyme in an inert state by blocking phosphorylation, a prerequisite for activation.[30] The most common mechanism of resistance identified in patients treated with IM develops from mutations occurring within the Abl kinase domain of Bcr-Abl.[29] Cells will then no longer be susceptible to the antiproliferative and proapoptotic effects of the drug. This will enable the resistant clone to multiply under selective pressure, which may be reflected in disease recrudescence after a period of apparent control, with rising Bcr-Abl levels.

Altered drug export from cells is another well described mechanism of resistance to therapy in both solid organ and haematological malignancies. This forms the basis of the multidrug resistance (MDR) phenotype. MDR is the simultaneous development of resistance to more than one therapeutic agent and since it is not specific to the drug target, can concurrently affect drugs with different mechanisms of action. The gene MDR1 (also known as ABCB1) encodes P-glycoprotein (Pgp) a protein serving as a drug efflux pump. IM is a substrate of this transporter and it has been shown in cell lines that increased expression of Pgp correlates with IM-resistance.[31] It has also been seen using CML samples from patients resistant to IM, that IM-sensitivity may be restored with use of Pgp inhibitors *in vitro*.[32] This demonstrates the importance of identifying such transporters, as inhibition of their activity may act as a mechanism to overcome resistance and enhance effective intracellular drug concentration. Other transporters which may be involved in IM transport include ABCG2 (a drug exporter)[33,34] and Oct1 (involved in drug uptake).[17]

Newer Tyrosine Kinase Inhibitors

The qualified success of IM has stimulated the search for more effective tyrosine kinase inhibitors. Nilotinib (AMN107, Novartis) has been designed based on the molecular framework of IM, though with adjustments to the molecular structure which allow a better topographical fit with the target Bcr-Abl molecule. Initial *in vitro* work has demonstrated the increased potency of this drug for inhibiting proliferation of Bcr-Abl+ cells.[35] This has been carried forward into phase 1 trials where Nilotinib has been shown to be effective in those intolerant of, or resistant to IM. Responses were gained in patients with all phases of CML, though as with IM, significant responses were achieved more commonly in those with CP CML.[36] Dasatinib (BMS-354825, Bristol-Meyer Squibb) is dual Src- and Abl- kinase inhibitor which has also been shown *in vitro* to have potent effects on Bcr-Abl+ cell lines. Phase 1 trial data, published concurrently with that of nilotinib, demonstrates the effectiveness of this drug in the IM-resistant or intolerant population of CML patients in all phases of the disease. Again responses are more frequently seen in those with CP disease.[37] Despite this promising data, as with IM the problem of disease resistance and persistence may remain. Data produced from cell line studies and phase 1 trials show that neither nilotinib nor dasatinib has activity against the T315I mutation of Bcr-Abl. We have also shown that dasatinib, which demonstrates potent antiproliferative activity with enhanced cell kill in dividing Bcr-Abl+ cells, does not appear to eradicate the quiescent Ph+HSC population.[34] Similar data has been produced using nilotinib.[38]

It is hoped that both these drugs will obtain licenses for UK use in the near future. They will be useful additions to the treatment options available for patients, though it is not thought that initially they will replace IM as first line therapy. There will also be a small group of patients with the T315I mutation who will not respond to either therapy. The answer for these patients may be in the future development of drugs aimed at other targets in the CML cell such as farnesyl transferase inhibitors, proteasome inhibitors, heat shock protein 90 inhibitors and histone deacetylase inhibitors all of which are under investigations either as single agent or combination therapies.[38, 39, 40, 41, 42, 43] Of particular interest is research using an aurora kinase inhibitor with *in vitro* activity against cells expressing the T315I mutation.[44] The potential of future targeted therapies may ultimately be dependent on their ability to eliminate the Ph+HSC. A phase 1 trial which has completed recruitment in Glasgow is the granulocyte colony stimulating factor (G-CSF) and IM intermittently (GIMI) trial. This trial was designed following *in vitro* work using CD34+ selected populations derived from the bone marrow of patients newly diagnosed with CML. Exposure of these cells to pulses of G-CSF with during times of IM interruption appeared to significantly reduce the frequency of quiescent Ph+HSC detected. An explanation for this may be that the quiescent cells were stimulated by G-CSF to proliferate and so were rendered susceptible to the effects of IM.[38]

Bone Marrow Transplant

Haemopoietic stem cell transplantation (HSCT) is currently considered the only cure for CML. However it is limited in application by donor availability and the toxicity of conditioning regimes. The use of HSCT in CML has declined recently and a likely explanation for this is the advent of IM.[19] Despite the morbidity and mortality associated with standard myeloablative HSCT, it remains an important treatment option for those with IM intolerance or resistance.[19] HSCT with reduced intensity conditioning (RI-HSCT) is now an established treatment modality for a variety of different haematological malignancies. The procedure differs from standard myeloablative HSCT in the chemotherapy received by the recipient prior to transplantation. The regimes used are significantly less toxic and are therefore appropriate for a broader patient age range and performance status. Published data confirms that patients have shorter in patient stays, and engraft sooner with reduced transplant-related mortality.[45]

Relapse of CML post transplant is a recognised problem thought to occur in between 16 and 33% of patients.[45, 46] Donor lymphocyte infusion (DLI) has been shown to be particularly effective in eradicating CML post transplant with responses seen in 70-80% of patients.[47, 48] DLI may be given as a response to high or rising Bcr-Abl measurements or the presence of donor/host chimerism (indicating the likely presence of residual diseased host cells). DLI is associated with a risk of graft versus host disease (GvHD), a potentially significant accompaniment to the desired graft versus leukemia (GvL) effect and marrow aplasia. The estimation of risk varies and may be minimised by the use of regimes involving a stepwise increase in cell dose given at set intervals.

There is also some controversy surrounding the use of IM in association with HSCT. IM use prior to transplant appears to be safe and does not appear to adversely affect outcome,[49] however the need for IM following transplant is less clear. IM is effective in the context of controlling relapsed disease of all phases,[50, 51, 52] though it is not known if it is routinely necessary. It is our view that the graft versus leukemia effect of the RI-HSCT and subsequent DLI will enable disease eradication, however some would claim that maximal control with minimal risk of disease progression requires the sustained use of IM. This dilemma will hopefully be addressed following publication of trials currently in progress.

Conclusions

CML is a rare disease but one which has become a paradigm for the stem cell basis of a number of malignancies. The treatment of IM has also been a major success in rational drug design. Despite recent advances, there are a number of dilemmas remaining for the clinician treating and monitoring patients with CML.

IM remains the standard first line therapy for CML in CP, with many patients in the advanced stages of disease also responding to this treatment. The problems of IM-resistance and minimal residual disease remain. This contributes to the sustained risk of disease progression and prevents safe interruption of therapy. The mechanism of resistance may result in a disease that is also insensitive to the more potent therapies currently in trial, as seen with the T315I mutant. The options for such patients are limited. For this reason efforts continue to eradicate persistent disease. This may be with the use of next generation tyrosine kinase inhibitors, novel compounds with alternative targets or by the use of combinations of existing therapies.

Despite the decline in popularity of HSCT in CML it remains a valuable option. Those intolerant or failing to respond to IM require HSCT to enable long term disease control or cure. The role for RI-SCT is not yet clearly defined. It may be that patients with a matched donor who demonstrate features carrying risk of disease progression should be offered transplant. Should RI-SCT be offered up front to all patients with matched donors? This could cure their disease without the need for lifelong therapy with IM. The morbidity and mortality of the procedure with the likely subsequent need for DLI and the long term relapse risk require consideration and so this is currently considered an option for selected patients in experienced centres only.

CML is a paradigm for stem cell based disease and IM a successful example of rational drug design. The unique molecular basis of this disease will undoubtedly fuel further research with the aim of achieving a cure without the need for lifelong therapy.

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EDUCATIONAL ARTICLE QUESTIONS

What is New in Chronic Myeloid Leukemia?

Select the most appropriate answer(s) from the following:

A. Consider the following statements referring to chronic myeloid leukemia (CML) progression:

1. CML may progress to acute myeloid leukemia
2. CML may progress to acute lymphoblastic leukemia
3. CML blast crisis (BC) may develop in patients with stable chronic phase disease
4. Clonal evolution alone is a feature of accelerated phase (AP)
5. Hepatosplenomegaly is a feature of AP or BC disease only

B. The following are well recognised chromosomal rearrangements found in chronic myeloid leukemia (CML):

1. t(2;5)
2. t(9;22)
3. t(1,19)
4. del(der)9
5. t(15;17)

C. Regarding response to treatment with IMATINIB (IM)

1. the majority of patients achieve a complete haematological response
2. the majority of patients achieve a complete cytogenetic response
3. the majority of patients achieve a complete molecular response
4. resistance to IM occurs only following exposure to drug
5. Nilotinib is effective in vitro against all IM-resistant Bcr-Abl mutations

D. Regarding the role of haemopoietic stem cell transplant (HSCT) in CML

1. HSCT is considered the only cure for CML
2. The Hasford score is designed for risk assessment prior to transplant
3. Reduced intensity stem cell transplant (RI-SCT) involves the less intensive conditioning chemotherapy and the infusion of fewer donor stem cells
4. Donor lymphocyte infusions (DLI) are usually required for disease control post RI-SCT transplant
5. DLI are sourced from pooled HLA-matched volunteer donors

To view the correct answers to the questions, go to Page 54.

HISTORICAL ARTICLE

Nineteenth Century Medical Education for Tomorrow's Doctors

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ABSTRACT
Many of the ideas contained within the GMC's 'Tomorrow's Doctors' could be considered as old ideas reworked for modern medical education. Sir John Struthers, a pioneer in the field of medical education, touched on many of the issues in 'Tomorrow's Doctors' in his writings published over one hundred years ago. The study of the history of medicine, often neglected by members of our profession in the search for new ideas, is not only of interest, but is valuable to current and future medical education. History illustrates the mistakes of the past, but also helps highlight the successes and insights that remain applicable and relevant today.

Introduction

'Tomorrow's Doctors', published by the General Medical Council (GMC) in 1993[1], and revised in 2003[2], heralded a transformation in undergraduate medical education. It sought to establish a consistent framework for curricula between medical schools[3], with a core curriculum that emphasised key knowledge, skills and attitudes for medical graduates, and a style that encouraged student learning through self-direction, problem solving, and critical evaluation of evidence.[1] The perceived information overload of the traditional curriculum was targeted, and traditional 'pre-clinical' teaching significantly reduced in many centres.

Prior to the implementation of *'Tomorrow's Doctors'*, the layout of the medical curriculum was largely unchanged from that introduced by the GMC in 1890 in an effort to establish the five-year curriculum and formalise clinical teaching.[4] Following the changes of 1890, medical students started with a general scientific education then graduated to clinical medicine in later years. Before 1890, a four-year course was standard, with a somewhat variable clinical element.[4] The chairman of the GMC education committee, archetypal in the development of the five-year course, was Professor John Struthers, Regius Professor of Anatomy at the University of Aberdeen from 1863 to 1889, and President of the Royal College of Surgeons of Edinburgh from 1895 to 1897[5] (Figure 1). Foremost a comparative anatomist, Struthers also wrote extensively about his views on medical education,[4,6,7,8,9] and should

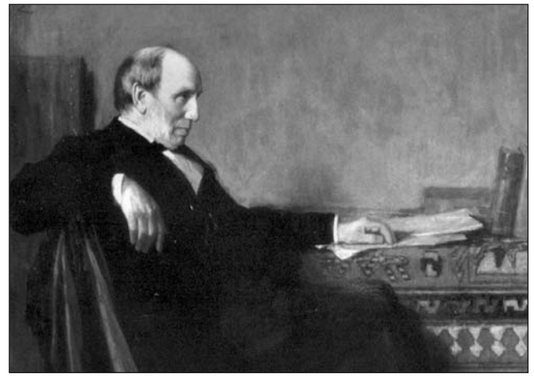

Figure 1 Sir John Struthers. From a painting by Sir George Reid RSA, by permission, University of Aberdeen

be considered a pioneer in this field that is now a rapidly emerging specialty in its own right. Many of the themes found in Struthers' educational work are reflected in the most recent edition of *'Tomorrow's Doctors'*.[2]

John Struthers had a distinguished career from medical school onwards.[10] After graduation, he became a successful lecturer in the extramural anatomy schools of Edinburgh before moving to Aberdeen as Professor of Anatomy. Struthers was a convinced Darwinian,[11, 12] and attempted to educate the traditionally sceptical public of North East Scotland about such theories, often to his ridicule.[11] (Figure 2) Evolution was also reflected in his teaching and research, with one of his other great passions being the

Figure 2 Professor Struthers the Rag-and-Bone Man. From Bon Accord II, 13 November 1886. Struthers was the object of some derision for his support of Darwinism, and his comparative anatomy collections. By permission, University of Aberdeen

study of the rudimentary structures of the whales occasionally found washed up along the east coast of Scotland.[11, 13]

Professor Struthers was involved with the GMC from 1883 until 1891. He retired from his chair at Aberdeen in 1889, but continued his GMC involvement. He was never idle in retirement, and from 1895 to 1897, he was President of the Royal College of Surgeons of Edinburgh. A knighthood was bestowed in 1898, just a year before his death.[5]

Tomorrow's Doctors' 2003

In this article, we aim to look at some of the key recommendations of the new edition of *'Tomorrow's Doctors'*[2], and consider what Professor Struthers said about similar subjects over one hundred years before the publication of this benchmark document. The study of the history of medicine, often neglected amongst the medical profession,[14] is not only of interest, but is valuable to those involved in current and future medical education.[15] Historical study may illustrate the mistakes of the past, but also help highlight the successes and insights that remain applicable and relevant today.

Guidance from *'Tomorrow's Doctors'* 2003[2] comes under five general headings and a series of main recommendations. We will review some of these recommendations, and also look at themes from 'Curricular outcomes', 'Curricular content, structure and delivery', and 'Putting the recommendations into practice'.

'Tomorrow's Doctors' - The Main Recommendations

'The core curriculum must be the responsibility of clinicians, basic scientists and medical educationalists working together to integrate their contributions and achieve a common purpose'.

Struthers recognised the importance of integration when teaching medical students. He wrote, about lectures in Anatomy: *"the lecture is rendered doubly interesting and useful when…both scientific and surgical anatomy are combined…so as to render attractive, simple and impressive, what, when otherwise treated, have been, and with sure truth might be called the dry details of Anatomy"*.[9] Current anatomical teaching is very much based on the details of anatomy deemed to be 'clinically relevant'. Courses incorporate not only basic anatomy, but also imaging, practical procedures, and clinical scenarios to illustrate and reinforce the points being made. Many centres have surgeons and other clinicians contributing significantly to the teaching of anatomy.[16]

"Factual information must be kept to the essential minimum that students need at this stage of medical education".

Struthers was keen that medical students should not be excessively burdened with subjects irrelevant to them. He wrote: *"Hardly anything could be conceived more likely to give a beginner an aversion to Anatomy than to be wearied with the details of the origins of muscles and the attachments of ligaments. He could not and ought not to try to follow such teaching…it must be on a course specially adapted for him"*.[4] Since the implementation of 'Tomorrows Doctors', many preclinical courses have been extensively revised to ensure that what is taught is largely relevant to future clinicians, and this has no doubt been enhanced by an increasing proportion of practising clinicians teaching the basic science elements of the course.[16]

"Learning opportunities must help students explore knowledge, and evaluate and integrate (bring together) evidence critically. The curriculum must motivate students and help them develop the skills for self-directed learning".

Struthers wrote extensively about teaching and learning. In his 1856 article "Hints to Students on the Prosecution of their Studies"[7], he said, regarding an introductory course on Osteology: *"The student, new to all such study, sees everything, handles everything, acquires the habit of observing for himself, instead of the schoolboy habit of committing to memory the words of the teacher, or of the book. He acquires the critical spirit, the spirit that demands to see and be satisfied of everything, and with such a beginning he is likely to carry these habits into his subsequent studies"*. Further, in a clear reference to self-directed learning and critical thinking, he says: *"You must not content yourselves with learning what books or teachers say, but use your own observation; use your own eyes, ears, hands and thoughts; be active, not passive agents in your own education"*.[7]

Curricular Outcomes

'Tomorrow's Doctors' - Good clinical care
"Doctors must practice good standards of clinical care, practice within the limits of their competence, and make sure that patients are not put at unnecessary risk".

"Doctors must know about, understand and be able to apply and integrate the clinical, basic, behavioural and social sciences on which medical practice is based".

Struthers advised his students *"not to affect more knowledge than you possess, or qualities which you have not"*.[7] This is clearly a reflection of probity. He encouraged students to learn the principles of a subject first, as *"the true practical man is not the man who despises Anatomy, Physiology… – or who neglects everything which does not concern his patient; but who has the foundation and the principles, and then adds the practical"*.[7]

Tomorrow's Doctors' - Maintaining good medical practice
"Doctors must keep up to date with developments in their field and maintain their skills".

"Doctors must be able to gain, assess, apply and integrate new knowledge and have the ability to adapt to changing circumstances throughout their professional life".

"Doctors must be willing to respond constructively to the outcome of appraisal, performance review and assessment".

Struthers told his students that the development of a work ethic as a student, would be of lifelong benefit: *"In the habit of industry* [studying], *he has gained not only a store of knowledge, but a means of keeping it up and adding to it. The habit of the student lives on in the man"*.[7] He advocated appraisal and audit of one's practice, writing: *"Let us never be alarmed when our opinions are called into question, but rather invite discussion of them, never afraid of the truth, being assured that it must benefit us either way; either on the one hand by ridding us of error, or on the other giving us greater security to our belief, by assuring us better of the foundation on which it rests"*.[7]

Curricular Content, Structure and Delivery

'Tomorrow's Doctors' - The scientific basis of practice
"Graduates must have a knowledge and understanding of the clinical and basic sciences. They must also understand relevant parts of the behavioural and social sciences, and be able to integrate and critically evaluate evidence from all these sources to provide a firm foundation for medical practice".

"They must know about and understand normal and abnormal structure and function, including the natural history of human diseases, the body's defence mechanisms, disease presentation and responses to illness. This will include an understanding of the genetic, social and environmental factors that determine disease and the response to treatment".

"Graduates must know about biological variation, and have an understanding of scientific methods, including both the technical and ethical principles used when designing experiments".

'Tomorrow's Doctors' - Treatment
"Graduates must know about and understand the principles of treatment including the following":
- "How to evaluate effectiveness against evidence".

'Tomorrow's Doctors' - General skills
"Graduates must be able to do the following":

"Use research skills to develop greater understanding and to influence their practice".

"Solve problems".

"Analyse and use numerical data".

Struthers tried to encourage the scientific spark in his students from the start, and stressed an experimental ethos in all work: *"the true spirit in which all study and investigation should be conducted – the desire for truth and reality prevailing over all others. To be partisans of no teacher or school, to have no blind attachment to any system or theory, to have our minds perfectly free and open to new facts and evidence, to weigh them carefully and importantly, and be ready to acknowledge when we are wrong"*.[7]

As an anatomist, he obviously had a personal interest in the place of the 'preclinical' sciences in medicine, and was clear at what stage of the curriculum he thought they should be taught: *"Unless you are well informed in the foundation sciences and principles, you may practise your profession, but you will never understand disease and its treatment; your practice will be routine, the unintelligent application of the dogmas and directions of your textbook or teacher"*.[7]

Professor Struthers would almost certainly be dismayed at the effect the implementation of *'Tomorrow's Doctors'*[1,2] is perceived to have had on the teaching and knowledge base of many preclinical disciplines. He stressed the importance of understanding 'foundation sciences' to his students, and discouraged their desire to be exposed to clinical medicine at an earlier stage: *"The young medical man, who has as yet only this knowledge* [basic medical science], *is in every way more hopefully situated than the other who has neglected it in the endeavour to grasp prematurely at a knowledge of the living phenomena and treatment of disease"*.[7] Medical students are now often exposed early to patients and families to encourage the development of skills and attitudes necessary for a profession that requires the trust of the public. Professor Struthers would likely have been pleased by attempts to vertically integrate preclinical sciences throughout the medical curriculum. This approach should ensure that students have a sound grasp of basic 'principles' appropriate for their stage of training. However, this has perhaps been harder to implement than anticipated. There is little space later in the curriculum for further 'preclinical' teaching unless at the expense of other subjects.

Struthers was an early advocate of increased clinical and practical teaching, which received sparse attention prior to the changes of 1890. The number of lectures was felt to be excessive, and their content often irrelevant.[9] In the early years he felt that a student's time was better spent training the eye and the mind in the dissecting room or bone laboratory, followed by a more formal clinical training: *"It requires, I think, no prophet to foretell that ere many years have passed, the clinical element will enter more largely into medical education than it has hitherto done"*.[7] He strongly

'Tomorrow's Doctors' - Teaching and learning
"The clinical and basic sciences should be taught in an integrated way throughout the curriculum".

"Students must have different teaching and learning opportunities that combine an appropriate balance of teaching in large groups with small groups, practical classes and opportunities for self-directed learning. Medical schools should explore and, where appropriate, provide opportunities for students to work and learn with other health and social care professionals. This will help students understand the importance of teamwork in providing care".

"Students must be properly prepared for their first day as a pre-registration house officer (PRHO). As well as the induction provided for PRHOs, students should have opportunities to shadow the PRHO in the post that they will take up when they graduate. Such attachments allow students to become familiar with the facilities available, the working environment and to get to know their colleagues. They also provide an opportunity to develop working relationships with the clinical and educational supervisors they will work with in the future".

"Modern educational theory and research must influence teaching and learning. Medical schools should take advantage of new technologies to deliver teaching".

encouraged students to spend time involved on the wards: *"The student must not merely present himself at the hospital as a clinical observer. He must take a concern in the cases, and get connected with them in some capacity, as a dresser or clerk"*.[7]

Struthers recognised the concepts of surface and deep learning, as proposed by Marton & Säljö[17] in 1976, and encouraged his students, via a careful process of study and observation, to adopt a deep approach: *"There are two kinds or parts of education; one is from without, put into us by the teacher or book, we commit it to memory and as long as we recollect it, we are able to repeat it as though we knew it. The other is what we work out for ourselves. They are quite distinct in principle"*.[7] Medical curricula were at risk of encouraging students to adopt a surface approach to learning, as a result of syllabus overload, and examination styles that often required factual recall only.[18] Syllabus overload is an ongoing problem, but problem-based learning and modern assessment techniques attempt to promote a deep approach and hence understanding rather than just a memory exercise.

Putting the recommendations into practice

'Tomorrow's Doctors' - The responsibilities of students
"Students must accept responsibility for their own learning, including achieving the curricular outcomes in this guidance".

Although Struthers was a strong advocate of clinical and practical teaching, he made sure his students understood the importance of studying outside the classroom: *"You may go about hospitals and dissecting rooms as much as you like, and attend lectures without number, but you will never get on without regular evening study"*.[7] He was renowned for quizzing students in lectures to ensure that they were paying attention, and that they had done their 'homework'.[11] He greatly disliked students taking excessive notes in lectures: *"Follow lectures attentively and thoughtfully, with occasional note-taking. Thus when the lecture is finished, the benefit is already secured. The essence of it is assimilated; while the systematic note taker, like the reporter, carries it away only in his pocket, in place of his head; the indifferent student, it may be added, having it in neither"*.[7] Students attempting to copy down lectures verbatim was apparently as much of a problem in the mid-nineteenth century as it is today![19]

Discussion

'Tomorrow's Doctors' has certainly revolutionised the undergraduate medical curriculum of today. Major changes in postgraduate medical education are still to be fully implemented under legislation such as the *European Working Time Directive* and *Modernising Medical Careers*. Looking at how the medical curriculum has developed over the years since Professor Struthers wrote his many articles on the subject of medical education, it becomes apparent that many of the 'modern' ideas may not be so new after all. Medical education appears to be like the world of fashion. Styles and ideas come and go, but certain things always 'come around again' – the recent introduction of a four-year medical course being a good example. There may be accusations of 'reinventing the wheel' from some quarters, but perhaps it is more accurate to say that soundly based educational principles remain sound, even if they were first penned over one hundred years ago, and to some extent forgotten, ignored, or simply not emphasised as important in the intervening years.

Professor Struthers may have been somewhat surprised by the effect that the interpretation of some of his theories has had, particularly with regard to the position of basic medical sciences. Remember his statement *"the true practical man is not the man who despises Anatomy, Physiology… – or who neglects everything which does not concern his patient; but who has the foundation and the principles, and then adds the practical"*.[7] Since the implementation of *''Tomorrow's Doctors''*, there has been a significant reduction in teaching time for subjects such as anatomy,[20] in order to make room for new curricular components and earlier clinical exposure. The likely detrimental nature of this approach has recently been recognised by the current chairman of the GMC.[21]

There are many anecdotal reports, but little objective evidence to suggest that current students and recent graduates are significantly lacking in areas such as anatomical knowledge. This deficiency may in part be due to a failure of the anticipated vertical integration of such subjects throughout the undergraduate curriculum. However, many senior clinicians now feel that the level of anatomical knowledge is insufficient for safe medical practice.[22] Most, if not all of these clinicians will have been educated under the pre-Tomorrows Doctors system, and may expect that students will have been taught anatomy and physiology to the same level as they were, rather than building on the basics that today's students will have. As new courses become more established and their graduates start to permeate throughout the postgraduate structure, perhaps this will change, but it seems likely that the importance of the basic medical science subjects will have to be re-emphasised.

Communication skills, plus moral and ethical responsibilities are some of the central themes of *'Tomorrow's Doctors'*. Perhaps unsurprisingly, this is not an area touched on by Struthers in his writings. However, he did stress the need for openness and honesty in teaching, research, and professional life, and given his desire for increased clinical exposure of students, it seems likely that he may have accepted the need to put doctors more in touch with the people they are treating. He would have almost certainly disapproved if this were at the expense of basic science teaching.

Professor John Struthers was integral in the establishment of the pre-*'Tomorrow's Doctors'* medical curriculum. From the study of his writings, it seems apparent that he would recognise that many of the educational principles he advocated during the nineteenth century are still central to medical training in the twenty-first century. He would no doubt wish to remind us though that: *"Unless you are well informed in the foundation sciences and principles, you may practise your profession, but you will never understand disease and its treatment"*.[7]

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ABSTRACT OF SOCIETIES

Scottish Intensive Care Society

Oral presentations

References for all articles can be found online at www.smj.org.uk

Teamwork in the Scottish ICU

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Studies of patient safety have indicated the importance of having effective teamwork within the intensive care unit (ICU). In particular, lapses in team communication between ICU nurses and doctors have been found to be an important factor in the occurrence of preventable medical errors.[1,2] Pronovost et al. [3] have also cited the importance of open communication between nurses and doctors, in order to create an environment where it is safe for all individuals to participate and speak up when necessary. This is consistent with many high-risk industries, where teamwork, and the processes of teamwork (e.g. communication), are recognised as being crucial.[4] Due to the role of communication in medical errors, it would appear important to measure the perceptions of nurses and doctors with regards to factors influencing the quality of communication in the ICU. To date, relatively little research has been done in the UK ICU environment.

The current study reports on the perceptions of ICU nurses and doctors with respect to communication in the ICU. Employing a questionnaire tool used previously within the US, the study examines perceptions of teamwork in a number of Scottish ICUs. The questionnaire has been used across the US, with associations between interdisciplinary communication, patient length of stays, and risk-adjusted mortality rates being found.[5,6] The questionnaire contains items that measure the quality of communication in the ICU between disciplines (i.e. nurses and doctors), and within disciplines (i.e. senior and junior doctors). Also measured by the questionnaire are perceptions of leadership, satisfaction with communication, understanding patient care goals, and perceived unit effectiveness. The preliminary results show that, overall, staff in ICUs have generally high perceptions of teamwork, similar to the US norm data. However, significant differences in perceptions of interdisciplinary communication openness were found between nurses and doctors. Also, there were significant associations between the leadership and communication scales, and between quality of unit communication and reported understanding of patient care goals.

The funding for this project comes from a PhD studentship awarded by the College of Life Sciences and Medicines, University of Aberdeen.

Recovery from the anaemia of critical illness is associated with resolution of the inflammatory state despite a depressed erythropoietin response

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Background: Anaemia is present in 80-90% of all patients at intensive care unit (ICU) discharge and persist for long periods in many patients.[1] In chronic conditions such as renal failure, anaemia is associated with impaired quality of life and significant morbidity, which can be improved by treatment.[2] We

investigated the factors contributing to the persistence of anaemia after critical illness. We present data relating anaemia recovery to erythropoietin response and persistent inflammation. **Methods:** Patients who received >24 hours of invasive ventilation and/or >2 organ support were screened for the presence of anaemia at discharge from the medico-surgical ICU of the Royal Infirmary of Edinburgh. Exclusions included ongoing requirement for renal replacement therapy, immunosuppresion or known chronic haematological condition. 19 of 30 enrolled patients completed followed up at 1, 3, 6, 9, 13 and 26 weeks post ICU discharge either in hospital or their homes. Blood samples were taken at each visit to measure haemoglobin concentration (Hb), reticulocyte count (*retics*), C-reactive protein (CRP) and serum erythropoietin (EPO) concentration. For analysis, patients were assigned to 2 groups depending upon whether or not Hb levels had normalised by 13 weeks following ICU discharge (7 'responders' and 12 'non-responders'). We compared measured parameters at 3 weeks post-ICU discharge to explore associations with poor recovery in Hb **Results:** CRP was higher and reticulocyte count lower among non-responders, but there was no difference in erythropoietin concentrations, which were inappropriately low in both groups (Figure 1 and Table I can be found at www.smj.org.uk). **Conclusion:** Among anaemic patients discharged from ICU erythropoietin response is inappropriately low. Slow/non-recovery of anaemia is associated with persistent inflammation in the post-ICU period and a hypo-responsive bone marrow.

Neurones Express Macrophage Inflammatory Protein-2 Following Traumatic Brain Injury in the Rat

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The expression of inflammatory mediators and the recruitment of leucocytes into the acutely injured brain are implicated in the pathogenesis of secondary brain injury.[1] However the inflammatory response to brain injury, its control and modulation remain incompletely described. The neutrophil chemotactic cytokine macrophage inflammatory protein-2 (MIP-2) is expressed *invitro* by glial and cerebral vascular endothelial cells. The *invivo* expression of MIP-2 in response to traumatic brain injury has been described previously. The production of this chemokine by glia has been implied but not demonstrated.[2]

We have investigated the cellular localisation of MIP-2 in the lateral fluid percussion model of focal brain injury. In accordance with the Animals (Scientific Procedures) Act 1986 and after review by the animal procedures committee, anaesthetised male Sprague Dawley rats received a moderate (1.7-2.0 atm) lateral fluid percussion injury. At 0, 4, 8, 12 & 24h after injury brains were harvested and dissected into anatomical regions. MIP-2 levels in the cortex were analysed by ELISA.

After injury MIP-2 was significantly increased in the injured cortex, peaking at 4 h after injury and declining rapidly to baseline by 12 h. Imminohistochemical staining of coronal sections from 4 h after recovery with an anti-MIP-2 antibody and the neuronal marker anti-NeuN localised MIP-2 expression to the cytoplasm of shrunken necrotic neurones.

Invitro chemokines are expressed by glial in response to pro-inflammatory cytokines. We have localised MIP-2 expression following focal brain injury to necrotic neurones. Our *invivo* results suggest that chemokine release may also be a fundamental primary response to tissue damage in the brain, initiating neutrophil chemotaxis.

Implementation of Structured Daily Goals within an Intensive Care Unit

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The United Kingdom Safer Patient Initiative, a collaborative between the Institute for Healthcare Improvement & the Health Foundation, aims to improve patient care by ensuring the consistent delivery of best practice. It has been shown that changes in process can lead to changes in outcome. Measurement of the process rather than outcome results in rapid and meaningful data with feedback. One initiative is utilisation of daily goals to improve interdisciplinary communication and provide clear targets that are patient centered. When this model was implemented in one intensive care unit (ICU) there was a fall in length of stay from 2.2 days to 1.1 days.[1] We developed and implemented a 5 element daily goal chart for our unit.

Compliance in use of goals was confirmed in a previous audit at 95.4% in our unit (unpublished data). We have now looked in more detail at the content and success of each goal which were categorised. It was expected for all goals, with the exception of parameters, that a time should be set to meet the goal. The attainment or not of each goal was recorded. Data collection was carried out by a member of staff not connected to the setting of the daily goals.

Data was collected for 133 patient days out of a potential 142 potential patient days (93.6%) over 4 weeks. 540 goals set with 496 (92%) being met. Only 48.9% of appropriate goals were time targeted. 34 goals were not met and in a further 10 the outcome was unknown. When categorised 65.6% were tasks 95.7% with completed: 18.9% were communications with 88.2% completed: 12.6% were parameters with 76.4% completed: 2.2% were miscellaneous with 100% completed: 0.7% were hardware removal with 75% completed.
The setting of daily goals should be multidisciplinary; this was not the case with most goals being medically orientated. The setting of more parameters would perhaps allow the multidisciplinary team to use their unique skills in patient care rather than using a medical model communication is always an area of concern in dealing with the patient, their relatives and others, as it is usually failings in communication that lead to dissatisfaction with hospital care 18.9% of all goals focused on this with 88.2% of these goals being met. We are not yet appropriately completing goals within a time limit.

It is too soon yet to see if this intervention has led to decreased length of stay. The development process is still ongoing but it has become evident that both the methodology and the monitoring of process are powerful tools in the provision of care for an ICU patient.

Mortality in Patients with Alcoholic Liver Disease Admitted to Intensive Care: Assessment of a New Scoring System

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Mortality is high in patients with alcoholic liver disease (ALD) who require intensive care (ICU) admission. Several scoring systems have previously been assessed to attempt to predict mortality in this group. Using these scoring systems in clinical practice has been difficult either because of complexity (e.g. APACHE II) or because of lack of objectivity (e.g. Child-Pugh). The Glasgow Alcoholic Hepatitis scoring system (GAHS)[1] is a new, objective scoring system which has been developed and validated for predicting mortality in patients with alcoholic hepatitis. It assigns scores for age, white cell count, urea, prothrombin ratio and bilirubin to give a total score between 5 and 12. This system has not previously been assessed for predicting mortality in patients with ALD admitted to ICU.

We carried out a search of the Ward-Watcher computer database in our ICU. We identified all patients with ALD admitted to ICU from January 2000 to June 2005. Case notes / laboratory databases were checked to confirm the diagnosis of ALD and to get details of the admission. The GAHS was calculated. As in Forrest's study patients were divided into two groups (scores of 5-8 or 9-12). We also calculated a total score for the Cardiovascular (CVS) and Renal sections of the Sepsis-related Organ Failure Assessment (SOFA) score. Likelihood ratios were calculated for each group.

63 patients were identified. Overall ICU mortality was 63% (hospital mortality 74%) consistent with previous studies. ICU mortality in the GAHS 5-8 group was 53% (38/63) compared with 80% in the 9-12 group (25/63). Corresponding likelihood ratios (95% Confidence Intervals) for ICU death were 0.6 (0.4-0.9) and 2.3 (1.0-5.3). The total score for the CVS and Renal sections of the SOFA score combined with GAHS gave ICU mortalities (see table at www.smj.org.uk)

Patients with alcoholic liver disease who are admitted to ICU have a high mortality. Reversibility of the acute critical illness is often controversial for patients with ALD. GAHS is a simple to use, objective method for predicting those sub-groups who are more likely to survive and would benefit from aggressive ICU support, particularly when combined with the CVS and Renal section of the SOFA score.

Management of Sepsis and Septic Shock in Critically Ill Patients Transferred by a Dedicated Transport Team in the West of Scotland

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Over 500 critically ill patients are transferred by a dedicated critical care transport team each year in the West of Scotland. With the advent of international guidelines for the management of severe sepsis and septic shock there are now criteria by which the management of these conditions can be assessed.[1] We undertook a prospective audit over a three month period to determine what proportion of the patients transferred have these conditions and to determine how management conforms to the guidelines.

Patients were deemed to have sepsis if they had suspicion of infection and two or more of the following: Temp. >38°C or <36 °C; WCC <4 or >12 x10^3 mm^{-3}; HR >90min^{-1}; RR >20min^{-1}; SBP <90mmHg or MAP <65mmHg or needing a vasopressor. We adapted sepsis resuscitation bundles derived from the guidelines and devised a data collection form with relation to the following: serum lactate measurement; blood cultures prior to antibiotics; antibiotics given within 3hrs for A&E <1hr for non-A&E referrals; MAP <65mmHg and management with a minimum 20$mlkg^{-1}$ fluid challenge, vasopressors, and CVP monitoring; achievement of MAP ≥65mmHg; measurement of central venous oxygen saturation ($ScvO_2$)[2]. Data were collected for every patient transferred during June, July, and August 2005.

90 patients were transferred from a total of 19 different hospitals during the audit period. Data was available for 82 (91%). 45 patients (55% 95% CI 44-66%) met criteria for sepsis. Of these 8 patients had blood cultures prior to antibiotics (18% 95% CI 8-32%), and in 23 (51% 95% CI 35-66%) this information was not available or unclear. Similarly, 24 patients (53% 95% CI 28-68%) had antibiotics within the time window, and in 17 (38% 95% CI 24-54%) this was unclear. 28 (62% 95% CI 47-76%) patients had circulatory failure with 19 of these (68% 95% CI 48-84%) requiring more than a fluid challenge alone. MAP ≥65mmHg was achieved in 43 patients (96% 95% CI 85-100%). Two patients with sepsis had serum lactate measured (4% 95% CI 0.5-15%). 1 patient of the 19 who had not responded to a fluid challenge had $ScvO_2$ measurement (5% 95% CI 0-26%).

A significant number of critically ill patients with sepsis and septic shock are transferred each year in the West of Scotland. Many have circulatory failure and this is managed consistently with fluids, vasopressor and CVP targeting. Documentation and communication of blood culture withdrawal and antibiotic therapy appears to be poor. Serum lactate and $ScvO_2$ measurement did not appear to be part of the routine management of patients with sepsis referred for transport. The former may be due to the lack of availability of access to the assay. However, as the use of $ScvO_2$ measurement and targeting merely requires access to a blood gas analyser, the latter finding may suggest that there is a reluctance to apply some aspects of the recommendations in this group of patients.

Non-Invasive Assessment of Central Aortic Haemodynamics and Endothelial Function in Critical Care

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Non-invasive pulse wave analysis (PWA) methods can generate the ascending aortic pressure wave from the radial/brachial pressure wave.[1] In cardiovascular disease, measurements derived from central aortic pressure waveform analysis have been reported to be strong independent predictors of cardiovascular mortality. Moreover, PWA combined with endothelium-dependent $ß_2$-adrenergic vasodilation has been shown to be a simple, repeatable, non-invasive means of assessing endothelial function in vivo.[2] The use of PWA in critical care has not previously been reported. We present pilot data from 13 patients admitted to our intensive care unit (ICU) and 10 age-controls.

PWA measurements were performed using the SphygmoCor™ *Mx* system. The following central aortic haemodynamic variables were determined: the aortic augmentation index (AIx – measure of systemic arterial stiffness), the time to wave reflection (Tr – measure of aortic stiffness), and the Buckberg subendocardial viability ratio (SEVR – measure of subendocardial perfusion). Data are mean ± SD.

Compared with the control subjects, in the ICU patients there was a significant reduction in Tr (155.5 ± 12.2ms vs 126.2 ± 13.3ms, $p<0.01$) and SEVR (171.2 ± 20.1 vs 114.5 ± 27.2, $p<0.01$), despite both groups having similar peripheral blood pressures. When the ICU patients were subdivided into septic (n=5) and non-septic (n=8), the septic patients had a greatly reduced AIx (-5.4 ± 17.0% vs 28.8 ± 11.9%, $p<0.01$) and a severely impaired response to endothelium-dependent $ß_2$-adrenergic vasodilation (Figure 1 see www.smj.org.uk).
As well as providing additional haemodynamic information useful in monitoring the critically ill, data derived from PWA may inform prognosis in the critically ill. Further research is warranted to determine the usefulness of these variables in critical illness. Of particular interest, PWA may be a useful non-invasive means by which to assess arterial endothelial dysfunction in sepsis.

Anonymous Incident Monitoring in Critical Aare

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Intensive care units are complex patient management environments in which critical incidents occur frequently.[1] The design of this project is based on the previous experience of the Australian Incident Monitoring Study in Intensive Care Units, a well established system, which has proven to be successful.[2] By recording and analysing incidents, we aim to identify patterns and system based failures amenable to change, thus improving patient safety.

The project was undertaken in a 17 bedded ICU / 8 bedded HDU critical care facility over 5 months (May-October 2005). A database, specifically designed for the anonymous collection of incident data, relevant to an intensive care environment, was installed in the unit. The database was designed to be user friendly, to maintain patient and staff anonymity and to prevent access to the data by anyone other than the local coordinators at a later date. An incident was defined as "any event that led to, or could have led to, patient harm if it had been allowed to proceed. It may, or may not, have been preventable and it may, or may not, have involved error." Details were requested on various aspects of the incident and contributing factors, as well as outcome. The system complemented the formal hospital incident report system.

Seventy-five incidents were reported over the 5-month project period. The majority of incidents involved airway management issues (39%), followed by procedures and lines (27%), drug errors (17%), unit management (15%) and environmental problems (3%). Medical staff precipitated 29% of incidents and nursing staff 48%. Most incidents were detected by nursing staff (80%). Incidents were detected within 1hour of their onset in 63% of cases. Reported incidents resulted in either no, or only a minor, physiological change in the patient's condition in the majority of cases (74%). During the pilot project there were 19 incidents reported through the existing hospital critical incident reporting system.

The anonymous incident reporting scheme has been well adopted by staff. As a result of this project, change has been implemented to reduce further adverse events, and a decision to continue using the database has been made. The system gives staff more direct feedback regarding incidents and staff members appear to be more comfortable using an anonymous system, reflected by the increased numbers reported. The Northern Ireland Incident Monitoring Study will prospectively audit adverse events in several intensive care units in the province.

Outcomes of Patients Treated with Activated Protein C for Severe Sepsis

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Severe sepsis has a mortality of 21.2-47.3%.[1] Activated Protein C (APC), a mediator of the inflammatory and coagulation systems, reduced hospital mortality of severely septic patients from 34.6% to 29.4% in a randomised controlled trial.[2,3] This therapeutic benefit outweighed the risk of bleeding complications in septic patients with multiple organ failure or an APACHE ≥25.[3]

This study assessed the outcomes of patients treated with APC in terms of mortality and organ failure through retrospective analysis of medical records. Expected mortality data was calculated 24 hours after admission to Intensive Care using the APACHE II score. Organ failure was assessed one day before, the four days during, and one day after treatment with APC using the Sequential Organ Failure Assessment (SOFA) score, without the neurological aspect – this was impossible to assess retrospectively.

APC was administered to 48 patients, who on the day of administration had 3-5 failing organ systems. The hospital mortality for the group was 33.3%. Predicted hospital mortality using the APACHE II score and diagnosis was 54.2% (48.2-60.2% CI). This gave an SMR of 0.61.

The figure (refer to www.smj.org.uk) illustrates daily SOFA scores of 40 patients with complete data. Mean SOFA scores rose in the day before treatment with APC and then fell. The fall in mean SOFA score reached statistical significance, at $p<0.05$, on day 4 onwards. (The paired t-test was used after confirmation of normal distribution. For non-parametric data, Wilcoxon's test was used)

By day 5, four patients had died and one transferred to another hospital. Four

cases of non-fatal bleeding were reported.

Our patients with severe sepsis who received APC had a lower than expected hospital mortality using the APACHE II prediction model. Their hospital mortality was between those of the treatment and control arms of the PROWESS study. Bleeding complications were not a major problem. There was a significant improvement in organ failure after infusion of APC.

Cervical Spine Clearance in the Multiply Injured, Unconscious Patient: Current Practice in the West of Scotland

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In the conscious trauma patient, clinical examination of the cervical spine (C-spine) offers the most sensitive, specific and cost effective method of excluding injury. Unfortunately in the unconscious or multiply injured population presenting to Intensive Care such clinical clearance is rarely possible. Most (90 - 95%) of these patients do not have a C-spine injury and keeping them immobilised unnecessarily for long periods is associated with a number of potentially life-threatening complications. Recently several groups have attempted to outline an optimal imaging strategy to identify those patients in whom it is safe to discontinue spinal immobilisation[1], with most suggesting a combination of plain radiographs and CT of the entire C-spine within 72 hours of admission as a reasonable standard.

Our unit receives unconscious trauma victims from all over the West of Scotland and we are regularly faced with the problem of "clearing" the C-spine radiologically. There is wide variation between different referring units in the type of C-spine imaging performed. To clarify this issue further we conducted a telephone survey of eleven hospitals in the West of Scotland. We contacted the consultants on-call for both radiology and intensive care and asked them about their current practice in imaging the C-spine in unconscious trauma patients.

Seven hospitals would perform three standard plain radiographs in this situation while three would perform only a lateral C-spine view. All centres would readily progress to CT scanning: eight would scan the entire C-spine while three performed limited scans. All CT scanners were able to complete adequately detailed scans within minutes and a formal report from a consultant radiologist would be available within 24 hours of the scan taking place. If imaging was normal two units would "clear" the cervical spine while the patient remained unconscious: four hospitals awaited return of consciousness irrespective of imaging. The remaining five units would "sometimes" clear the neck in this patient group after discussion with orthopaedic surgeons and radiologists, but admitted this was "very operator dependent". Four hospitals had a protocol for this scenario, although each protocol suggested a different management strategy. One clinician felt that protocols were best avoided in this area.

Little consensus in the management of this patient group was found despite several recent high profile publications. Most hospitals performed and reported the investigations listed above within the suggested time frame, however only two were prepared to act on this and discontinue spinal immobilisation if imaging was normal. Six units did not have a protocol for this issue and felt there should be one.

Ventilator-Associated Pneumonia – One Year's Surveillance

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Ventilator-associated pneumonia (VAP) is a complication affecting 8-28% of ventilated patients. VAP has an average device-associated incidence of 7 per 1000 ventilator patient days (range 1-20). It carries a crude mortality rate of 24-76%. VAP is also associated with prolonged lengths of stay in intensive care and the hospital.[1] VAP is preventable[2] and to audit the effect of preventative measures, it is necessary to have a robust surveillance programme.

We present data of one year's surveillance of VAP in our 18-bedded critical care unit, from 1 December 2004 - 30 November 2005. This is part of the ongoing programme of HELICS[3] (Hospitals in Europe Link for Infection Control through Surveillance). A dedicated research nurse prospectively collected data on patients staying more than 2 days. VAP was defined according to the HELICS protocol. A statistical process control chart has been used to track the incidence of VAP on a monthly basis.

1027 patients were admitted with 559 staying more than 2 days. Of these, 442 were ventilated for a total of 4095 days. 46 episodes of VAP occurred in 42 patients. Therefore 9.5% of patients ventilated for more than 2 days developed VAP. The device-associated rate of VAP was 11.2 cases per 1000 ventilator days. 21 VAP cases were caused by Gram positive bacteria, 35 by Gram negative bacteria and fungi responsible for 5 cases. One viral infection was identified. Mixed organisms were found in 9 episodes.

The incidence of VAP in our unit, its morbidity and mortality is in keeping with published series. We are able to produce statistical process control charts to facilitate surveillance and control of this important acquired infection.

ABSTRACT OF SOCIETIES

Scottish Society for Rheumatology

Oral presentations held on 2nd June 2006

References for all articles can be found online at www.smj.org.uk

Assessing risk of tuberculosis (tb) in patients on anti-tumour necrosis factor a (tnf-a) therapies: impact of the British Thoracic Society (BTS) guidelines

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Background: Patients embarking on anti TNF-a therapies are at risk of reactivation of TB. Changes to current screening practices for TB are necessary following publication of the BTS Guidelines[1] and withdrawal of Heaf strength Tuberculin PPD. **Aim:** To review screening results from our current practice and assess the impact of changing to follow BTS Guidelines. **Methods:** We reviewed records for all our patients treated with anti-TNF-a therapy since 2004. Current practice is to screen all patients with history, examination, chest X-ray (CXR) and Heaf test. Patients identified with latent TB are treated according to Centers for Disease Control Guidelines.[2] Patient records were reassessed according to the BTS Guidelines, and discrepancies identified. **Results:** 22 patients commenced therapy, predominantly for Rheumatoid arthritis (n=18). 18 (82%) are female, median age 60 years (range 20 – 74). All patients are white, 21 born in UK. 19 patients (86%) were on immunosuppressives. No patient had a history of TB. 2 patients had abnormal CXRs, both showing calcified granulomata. 19 patients underwent tuberculin tests. 3 patients were not tested (1 refused, 1 no reagent available, 1 no test advised). 5 patients (1 abnormal CXR, 1 abnormal CXR & positive Heaf test, 3 positive Heaf tests) were treated with anti-TB therapy. All commenced Etanercept after 1 month of therapy and none has evidence of active TB at median follow-up 8 months (range 5-12). Utilising BTS Guidelines, 2 patients with abnormal CXRs would have had anti-TB therapy, completed in full prior to anti-TNF-a therapy. 19 patients would be unsuitable for tuberculin testing, including 3 of those with positive Heaf tests. These 3 patients would have been under observation only. 3 of our 22 patients would have required a tuberculin test. **Discussion:** We have identified a high incidence of latent TB (23%) in this small West of Scotland series. We are concerned about the applicability of the BTS Guidelines to our patient population. Tuberculin testing may still be appropriate despite the use of immunosuppressive drugs. Future alternatives include using interferon-gamma immunological tests for TB. **Conclusions:** Changing practice to implement BTS Guidelines will only identify a minority of patients with latent TB. It is important to ensure BTS Guidelines are appropriate, to reduce the risks of clinical TB in our patients on anti-TNF-a therapy.

Psoriatic arthritis – Documentation of PUVA Exposure must be Accurately Recorded

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Background Psoriatic arthritis (PsA) is the second most common peripheral inflammatory arthropathy in Rheumatology clinics. Recent advances have seen new agents licensed for treatment for PsA including biological agents. **Methods** Consecutive patients attending a rheumatology unit over a four week period were identified. Using the BSR guidelines on anti-TNF therapy in PsA, we sought to identify which patients fulfilled the criteria. Data was collected on demographics, pattern of disease, previous and current treatment and contraindications to anti-TNF treatment. **Results** 50 patients age 15-78ys (median 48yrs) were identified. 50% were male, 94% Caucasian and 60% had erosive disease. Median PsA duration was 9 years. Pattern of arthritis (Moll & Wright): 62% had asymmetrical polyarthritis, 30% seronegative RA and 60% patients had ≥ 3 tender and swollen joints. All patients received NSAIDs before DMARDs. At time of study, 16% were on NSAIDs only and 38% had received ≥2 DMARDs. 9.5% had received ≥5 DMARDs, 5 patients on Etanercept. Commonest 1st DMARD was Sulphasalazine (76%) followed by Methotrexate (19%). The most frequent reason for DMARD failure was toxicity (29/42). In 34%, anti-TNF was contraindicated due to unknown quantities of PUVA treatment but in 64% there was no contraindication. Overall, 3/50 satisfied the BSR guidelines but were not receiving such therapy. 3 others would qualify if gold were recognised in the guidelines. **Conclusions** In our cohort, 16% of patients would be eligible for anti- TNF treatment of whom 10% are receiving this therapy. Although 60% met the required number of tender and swollen joints, previous PUVA would be a contraindication in more than a third due to lack of documentation. PUVA is therefore an important potential contraindication and documentation of total doses administered is important.

Angiotensin II receptor blockers as potential anti-inflammatory agents

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1Centre for Rheumatic Diseases, Glasgow Royal Infirmary, 2Department of Rheumatology, Gartnavel General Hospital, Glasgow, Scotland, UK, 3School of Engineering & Science, University of Paisley, Scotland, UK

Objective Angiotensin II (AngII) plays an important role in regulating blood pressure via the renin-angiotensin-aldosterone system. Subsequently, it was found to have pro-inflammatory properties and long-term effects on tissue structure. Studies on angiotensin converting enzyme inhibitors (ACEi) and AngII receptor blockers (ARB) have suggested that their therapeutic effects are mediated by inhibiting AngII. In theory, ACEi and ARB could be used as anti-inflammatory agents. Captopril is already established as having anti-inflammatory properties, mediated by the thiol moiety unique to the drug. The purpose of this study was to establish in an animal model of arthritis whether ARBs have anti-inflammatory effects and in a retrospective audit to establish the anti-inflammatory effects of ARB by comparing inflammatory markers of rheumatoid arthritis patients who were on ACEi (ramipril or lisinopril), or ARB or neither. **Study Method** Adjuvant monoarthritis was induced under anaesthesia in the rat knee joint (n=6) treated with vehicle or the selective AT_1 receptor antagonist losartan (15mg/kg s.c. alternate days), these being administered both prophylactically and therapeutically. Joint swelling was monitored as an indicator of inflammation. Patients were identified from 2 centres – Glasgow Royal Infirmary (GRI) and Gartnavel General Hospital (GGH). Data were collected by patient questionnaire at GRI and by computer database at GGH. Data included disease modifying anti-rheumatic drug (DMARD) therapy, ACEi (ramipril and lisinopril) and ARB use, and corresponding C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values. Results of CRP and ESR values of all patients were consolidated and statistical analysis performed. **Results** Rat joint swelling was significantly ($P<0.0001$) reduced (≥50%) by losartan treatment, both with prophylactic and therapeutic (day 12) intervention. Mean (± SD) ESR from RA patients on ARB (n=42), was lower (25.1±22.5) than that from patients on ACEi 30.8±29.2, n=58) or those on no angiotensin inhibition therapy (control group: 40.1±29.4, n=38), and these differed significantly ($P=0.02$, 1-way ANOVA, $\log_{10}$ transformed). *Post-hoc* testing (Bonferroni) revealed only the ARB-treated group differed significantly ($P=0.021$) from the control group. Although a similar trend between groups was apparent for CRP, this was not significant using non-parametric statistics (data set not normalised by $\log_{10}$ transformation). Adjusting for statin use, the difference in ESR between groups remained significant ($P=0.036$, 1-way ANCOVA). **Conclusions** Inhibiting AngII has anti-inflammatory potential and ARB may be more effective than ACEi.

Dietary n-3 fatty acids as non-steroidal anti-inflammatory drug sparing agents in rheumatoid arthritis

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Background: Non-steroidal anti-inflammatory drugs (NSAID) are frequently used in the management of patients with rheumatoid arthritis (RA). Dose dependant gastrointestinal and cardiovascular side effects are common, limiting their use. N-3 essential fatty acids have previously demonstrated some anti-inflammatory and NSAID sparing properties. The objective of this study was to determine whether fish oil supplementation reduces the daily NSAID requirement of patients with RA. **Methods:** This was a dual centre, double blind placebo controlled, randomised study of 9 months duration. Ninety-seven patients with RA were randomised to take either 10g of marine oil (Seven Seas Ltd) containing 2.2g of n-3 essential fatty acids (32% docosahexaenoic acid, 68% eicosapentaenoic acid) a day or air filled identical placebo capsules. NSAID daily requirement, clinical and laboratory parameters of RA disease activity and safety checks were done at 0, 4, 12, 24 and 36 weeks. At 12 weeks patients were instructed to gradually reduce and if possible stop their NSAID intake. Reduction of NSAID intake by at least 30% without an associated flare in disease activity was the primary endpoint.
Results: Both groups were matched for baseline characteristics. 29/49 patients who received marine oil and 23/48 of the placebo treated patients completed the study. 17 out of 29 (59%) patients in the active group and 5 out of 23 (22%) patients in the placebo group were able to reduce their daily NSAID requirement by more than 30%. ($p= 0.08$ Chi-squared test). There was a significant improvement in the visual analogue scale of pain in the active group ($p=0.032$ Mann-Whitney test), but no differences between the groups were observed in the remaining clinical parameters of RA disease activity or in the type or number of side effects observed. Plasma measurements of eicosapentanoic acid and returned tablet counts suggested good compliance. **Conclusions:** More than half of the patients who took marine oil supplements for 9 months were able to reduce NSAI therapy without any change in disease activity. This study confirms that fish oil supplements containing N-3 fatty acids can be NSAID sparing agents in RA patients.

Audit of feasibility and implementation of the Scottish Early Warning Scoring on a rheumatology ward

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Purpose There is often documented deterioration of physiological parameters before patients become critically ill. The Scottish Early Warning Scoring (SEWS) chart is a colour-coded chart for documenting patient physiological parameters including pulse, respiratory rate, oxygen saturation, temperature and blood pressure. SEWS dictates the frequency of observations and the threshold for prompting medical review. A 1-month audit was used to assess the feasibility of implementing SEWS routinely in rheumatology in-patients at the Edinburgh Western General Hospital (WGH). A 6-month prospective study was used to record patient outcome and to assess whether patients at risk of deterioration are identified for early interventions that might prevent catastrophic deterioration or admission to critical care units. **Methods** The rheumatology nursing team was trained in the use of SEWS. Rheumatology in-patients at WGH during September 2004 had observations documented using SEWS charts. The charts were examined retrospectively to assess the rate of complete documentation of physiological parameters. Questionnaires were used to assess staff satisfaction. During the 6-month study, SEWS was used to guide the frequency of measuring observations and the threshold for prompting medical review. SEWS charts and clinical notes of rheumatology in-patients at WGH from November 2004 to May 2005 were examined. **Results** During the 1-month audit, 84.2% of patients (n=19) had complete documentation of physiological parameters using SEWS. 85% of the nursing team agreed that a tool is required to identify sick patients; 100% agreed that the SEWS score was easy to calculate; 77% agreed that SEWS was helpful in identifying sick patients and 85% agreed that SEWS prompted earlier intervention. Data was collected from 117 patients during the 6-month prospective study. Eighty-eight patients had a maximum SEWS score of 2 or less; 8 patients with a score of 3; 2 with a score of 4; 2 with a score of 5 and 1 with a score of 6 (see Figure 1). All the patients with SEWS score of 3 or more were identified and reviewed by medical staff. Seven of these patients required additional intervention. There was no mortality and no transfers to critical care units. **Conclusions** SEWS charts were feasible to use on the Rheumatology ward. There was a high rate of full documentation of physiological parameters after the introduction of SEWS. SEWS charts were an easy-to-use bedside tool for alerting nursing and medical teams that patients are at risk of deteriorating. Patients with high SEWS scores were reviewed, and additional treatment was initiated when appropriate. Early identification of ill patients and intervention was achieved.

ABSTRACT OF SOCIETIES

SPCERH

Oral presentations held on 21st September 2006

References for all articles can be found online at www.smj.org.uk

Postnatal thromboprophylaxis

B Singhania, S Bollapragada, F MacKenzie, P Owen
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Objective: To assess the compliance of a large maternity unit in administering appropriate postnatal thromboprophylaxis. **Methods**: All deliveries for the month of December 2005 (n=373) were reviewed for the risk of venous thromboembolism and the use of thromboprophylaxis. The unit's protocol on postnatal thromboprophylaxis provided the audit standard. The results were discussed at the labour ward meeting in February 2006 and a memo was circulated to all the relevant health professionals to improve performance. The audit cycle was closed with further data collection for all the deliveries in June 2006 (n=348). **Results**: 1. Overall 38.3% (143 of 373) women were assessed to be medium or high risk by the auditing team and required thromboprophylaxis in the first audit as compared to 32.7% (114 of 348) in the re-audit. 2. The correct documented risk assessment was noted in only 19.3% (72 of 373) in the first audit as compared to 34.2 % (119 of 348) in re-audit. The risk factors most commonly overlooked were obesity and maternal age in the first audit as compared with obesity and long labour (>12hours) in the re-audit. 3. Of those requiring thromboprophylaxis, only 24.5% (35 of 143) were documented to have received adequate thromboprophylaxis in the first audit as compared to 44.7% (51 of 114) receiving adequate thromboprophylaxis in the re-audit. 4. 75% (75 of 100) of women in the high risk group did not receive thromboembolic deterrent stockings the first audit as compared to 59.5% (47 of 79) in the re-audit. 5. The correct dose, duration and timing of first dose of LMWH was given in only 50.3% (72 of 143) of women in the medium or high risk group in Dec 2005 as compared to 64% (73 of 114) in June 2006. **Conclusions**: There was a significant failure to implement the correct thromboprophylaxis measures in the first audit. While the performance in the re-audit did improve as compared to the first audit there were still significant failures. Continuing education of health care professionals is important and alternative measures such as introduction of a proforma for assessing the risk of VTE may be required.

Antepartum Anti-D Prophylaxis Anti-D Prophylaxis! How well is it Received?

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Forth Park Hospital, Kirkcaldy, KY2 5RA

Objectives: Antepartum anti-D prophylaxis has been introduced recently into clinical practice and we wanted to see how this concept is received by the antenatal women. **Materials and Methods**: This is a retrospective study conducted at Forth Park Hospital, Kirkcaldy during the period between April 2004 and April 2005 and one hundred and seventy cases were studied. **Results**: During the analysis we found that 11% of women had antepartum sensitising events (bleeding, amniocentesis, antepartum haemorrhage, abdominal trauma) and when women were offered anti-D prophylaxis all were happy to receive the same (100%). 3% of women who had sensitising events (bleeding 1st /2nd trimester, abdominal trauma) were not offered anti-D by the staff. Routine antepartum anti-D prophylaxis were offered to all women between 28 and 34 weeks (100% coverage) and to our surprise we found that only 86% of the women were willing to receive anti-D and the rest 24% had declined the same. Of the women who had declined 57% were multiparous and the reason was that they had not received it in their previous pregnancies and were unwilling to accept this new concept. 7% of primiparous women had declined and the reason was that none of their friends/relatives had received this earlier. 36% of the women had declined because their partners were rhesus negative. 24% of the women who received antepartum prophylaxis did not require it in the postpartum period. **Conclusion**: Overall in our study we found that antepartum anti-D prophylaxis was well received by most of the women. But to make this programme an outstanding success further awareness and education of all the staff and antenatal women are essential.

Management of 3rd and 4th degree perineal tears

R Panigrahy, F MacKenzie, J Welsh, P Owen on behalf of the Perinatal Effectiveness Committee (PEC)

Setting: Princess Royal Maternity Hospital, Southern General Hospital, and the Queen Mothers Hospital, Glasgow. **Introduction**: 3rd & 4th degree tears have considerable influence on a woman's future continence with 20-50% experiencing faecal incontinence following sphincter disruption. A sphincter repair performed under optimal conditions is associated with improved outcome. **Aims**: To audit the management of women identified with 3rd & 4th degree tears in the Glasgow maternity units and evaluate the findings against the recommendations of the relevant RCOG guideline (no.29). **Method:** Data were collected prospectively over a six-month period using a specifically designed data collection form. A report was published and widely disseminated. An operative proforma was also designed and introduced. The audit cycle was closed with data collection over a further 6 month period. **Results:** 98 women were identified in the re-audit, with an incidence of 3rd/4th degree tears of 2.5%. This compared with 66 women and an incidence of 1.6% in the initial audit. 88% of the repairs were carried out by middle grade obstetricians with Consultant presence in 58%. This compared with 75% and 67% respectively for the first audit. 98% of the repairs took place in theatre compared with 92% in the initial audit. 99% were carried out under regional anaesthesia in the re-audit compared with 92% in the initial audit. None of the repairs in re-audit were performed under local anaesthetic compared to 6% in initial audit. 91% were documented to have an overlap technique repair and 8% had end to end repair in the re-audit. This compared with 62% and 24% respectively in the initial audit. There was no documentation of method of repair in 14% in the initial audit and this reduced to 1% in the re-audit. In all the repairs in the re-audit a monofilament suture was used compared with 89% in the first audit. The use of intra-operative antibiotics improved from 59% in the initial audit to 91% for the re-audit. All women received post-operative antibiotics and laxatives in both audit cycles. In the initial audit 89% had their 6 week follow-up appointment arranged with the obstetric clinic, 6% with a colorectal surgeon and 5% with their GP. In the re-audit, 99% of women had a follow up in the obstetric clinic. 17% compared with 5% in the first audit were documented as having a six-month follow-up appointment with a colorectal surgeon. Use of the operative proforma in the re-audit was associated with higher compliance. **Conclusions**: The results of the re-audit highlight improvements in practice in all areas. The increase in the incidence of 3rd and 4th degree perineal tears suggests that more tears are being correctly identified at the time of delivery. The interval between audits broadly coincided with the availability of a local, one day training course in the repair of these tears. In addition, the introduction of the operative proforma has contributed to the improvement in the compliance with the RCOG guideline and we encourage its continued and more widespread use.

Audit of intrapartum Group-B Streptococcal(GBS) Prophylaxis (01/09/05 – 30/09/05)

L Hermis and P Owen
Department of Obstetrics & Gynaecology, Princess Royal Maternity Hospital, Glasgow

Objectives: To establish the adequacy of intrapartum antibiotic prophylaxis in women with GBS risk factors in routine clinical practice. To identify areas where adequate prophylaxis could not be achieved. **Introduction**: Group B streptococcus is the most frequent cause of severe early onset infection in newborn infants. Our department at PRMH employs a protocol which recommends that all women with GBS risk factors should receive intrapartum antibiotic prophylaxis >2hrs prior to delivery to prevent early onset neonatal GBS disease. **Method:** Audit against established protocol. Case notes of consecutive deliveries over a prospective 4 week period were reviewed retrospectively for the presence of GBS risk factors & the adequacy of intrapartum prophylaxis. **Results**: 452 deliveries occurred during the 4 week audit period, 61 of these women (13.5%) were eligible for intrapartum antibiotic prophylaxis. 74% of the eligible women received adequate prophylaxis in labour. The remaining 16 women (26%) received inadequate or no prophylaxis. **Conclusion**: The majority of women received adequate intrapartum prophylaxis. This re-inforces and confirms previously published audit data demonstrating a rise in compliance from 40% to >70% when the time interval for adequacy is shortened. **Recommendations**: Certain areas in our routine clinical practice could be improved to maximise the number of infants benefiting from intrapartum antibiotic prophylaxis.

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CASE REPORTS

Jill Murie

The full version of each case report can be found at **www.smj.org.uk**

1. Multiple pulmonary emboli despite the presence of a caval filter - a literature review
BB McGuire and C Kelly

2. Shedding Light on a dark case
EW Paterson, AD Chapman, OJ Dempsey

3. Massive scrotal oedema - an unusual primary presentation of Chronic Lymphocytic Leukemia
DA Ashdown, M Saxby

4. Acute thermal injury associated with cerebral protection in the surgical management of aortic dissection
K Hussey and R Jeffrey

5. Pneumomediastinum associated with Hyperemesis gravidarum
K Sivanesan, J Tierney

6. Primary Cerebral Lymphoma presenting with Parkinsonism
J Foy, WR Primrose, JM Mackenzie

7. Metastatic Glucagonoma transforming to Insulinoma following Chemotherapy
N Iqbal, A Byard, BM Singh, HN Buch

8. Pseudo-aneurysms in injecting drug abusers: a diagnosis not to be missed. - J Milburn and J Brittenden

RCPSG DIARY OF EVENTS

February 2007 - May 2007

01.02.07	Paediatric Supper Colloquium at Reid Macewen Conference Centre, Erskine
01.02.07 & 02.02.07	Hot topics in Endocrinology & Metabolism and the Finlayson & Fleming Lectures
21.02.07	Surgical Anastomosis Techniques
05.03.07 & 06.03.07	IMPACT Course
14.03.07	Spring Ophthalmology Symposium
16.03.07	The 2nd Glasgow International Cardiology Symposium
22.03.07	Joint Symposium with the Faculty of General Dental Practitioners (UK), West of Scotland Division"Don't bite off more than you can chew: Occlusion for Clinicians"
23.03.07	1st Annual Symposium on Podiatric Medicine
28.03.07 - 30.03.07	Basic Surgical Skills Course
30.03.07	ENT Symposium - Dilemmas in Thyroid Cancer Management
17.04.07 & 18.04.07	IMPACT Course
19.04.07	"The Many Guises of Oral Pathology: Reflections & the Future"Symposium in honour of Professor D.Gordon MacDonald
20.04.07	High Dependency for the Less Intense (Medical Update symposium)

BOOK REVIEWS

Religions, Culture and Healthcare: A Practical Handbook for Use in Healthcare Environments.

Susan Hollins

Oxford: Radcliffe Publishing, 2006 ISBN: 1857757556

Review by Rev Carol Campbell, Healthcare Chaplain Yorkhill RHSC Glasgow

Hollins (working as one of the four lead chaplains appointed by the NHS to take forward the modernisation agenda for spiritual healthcare) brings together a wealth of 'scattered information'. She questions how often our own narrow thinking, lack of cultural understanding and prejudices lead to poor healthcare. She suggests that 'by engaging in a journey of discovery about other cultures, we will become more tolerant and understanding of others' which will 'deepen our pastoral care as well as our clinical care.' An important area, which she comments on, is the belief system that illness is related to judgement. Hindu people, for example, believe that 'illness is thought to be punishment for wrong behaviour in a former life' For Islam, 'illness and suffering are regarded as a means of purification and as a punishment for wrongdoing' and for some Pagans, illness is 'a trial set by their Gods on their road to enlightenment.' Hollins therefore draws out the importance of education for healthcare workers on belief systems and culture, and cites this as the reason for her book.

Religion however is not Hollins' only concern. She speaks of 'spirituality' being important to those who do not adhere to a traditional belief system. The importance of 'relationships', 'emotions' and 'work' may indeed have an impact on an individual's healthcare journey, and may require 'spiritual care'. Hollins lists a number of elements to understanding pastoral care of an individual including 'feelings and any beliefs or philosophical framework for living' and 'search for and discovery of meaning'. She therefore concludes that to define spirituality too narrowly would be wrong. Referring to the chaplaincy/spiritual healthcare, she positively notes the coming together of the different faith communities to be in ongoing debate with regard to best spiritual care. She also notes the importance of patient and public involvement ensuring that a wider audience can be heard. However, although there are differing views with regard to the damaging/beneficial possibilities of religion in healthcare, Hollins suggests that the main religions should not be 'ignored as being irrelevant to the age in which we live.'

Much of the book is centred on looking at the culture and beliefs of many religions. Each chapter is dedicated to drawing out the central beliefs of the faith followed by very clear guidelines on how culture, belief and healthcare come together. To give some examples, Hollins notes:

The Islamic Faith - men are believed to be the protectors of women and should be consulted about any treatment for their wives or sisters.

The Buddhist Faith - death is a very important time and relatives may wish the body to remain where it is until a priest is able to attend.

The Christian Faith - it is important for many to have their baby baptised/christened.

The Hindu Faith - a woman may experience tremendous guilt following miscarriage or stillbirth as the Hindu emphasis is on a woman's fertility and ability to bear children.

The Jewish Faith - an Orthodox husband will not touch his wife during childbirth, as it is believed that blood loss makes her unclean.

The Sikh Faith - 'Accommodation in single-sex wards is essential.'

This book would make an excellent resource for medical, nursing and indeed any healthcare worker. I believe it meets its purpose in providing a clear understanding of religions and culture, and how this relates to healthcare, which would only enhance the religious and spiritual care of all people.

BOOK REVIEW

Master Pass: EMQs in Obstetrics and Gynaecology

Andrea Akkad, Marwan Habiba and Justin Konje

Oxford: Radcliffe Publishing, 2006. ISBN: 1-84619-031-2

Dr Lena Macara, Consultant Obstetrician Queen Mothers Maternity Hospital Glasgow

Undergraduate medical education in the UK has moved away from mass ritual lectures to topic and themed based self directed learning. While this encourages the student to learn independently it frequently proves difficult for them to assess if they have covered the topic adequately and fully understood the principles. The Extended Matched Question (EMQ) is an educational tool that has been developed to evaluate both of these concerns and is now being introduced for student assessment.

A team of clinicians actively involved in undergraduate and postgraduate education has written "EMQs in Obstetrics and Gynaecology". The aim of the book is "to help medical students prepare for in-course assessment in obstetrics and gynaecology and final exams". The sixteen chapters of questions, six in Obstetrics and ten in Gynaecology, cover a broad range of topics. The authors have chosen their chapter topics well, focusing on the commonly encountered aspects of the specialty. The obstetric chapters deal with maternal and fetal problems comprehensively, with importance placed on normal pregnancy physiology in addition to complications of pregnancy such as hypertension and the mother who is ill. The gynaecological chapters are extensive, with problems such as menstrual disorders, infertility, screening and family planning highlighted in particular. The lead-in questions for each topic are clear in their instruction and the patient vignettes are varied and clinically relevant, testing both the student's factual knowledge and their ability to apply that knowledge to clinical scenarios. While the clinical scenarios at times are almost too "text-book" in their presentation, they ensure that there is little dubiety regarding the correct answer. The answer section for each chapter gives a brief but pertinent explanation for each solution offered, directing the student to explore the area in more depth if they so wish.

As a test of factual knowledge and understanding in the common areas of obstetrics and gynaecology this book certainly achieves its goal and it to be commended. However, from the recent experience of undergraduate students in our own unit the breadth of knowledge tested in this book far exceeds the level achieved by most of our current students. Hopefully this book, if used during clinical attachments, will direct students in their studies and ensure they have achieved a competent level of knowledge in the specialty.

GUIDELINES FOR SUBMISSION

The Scottish Medical Journal is published four times per year - in February, May, August and November - and is devoted to the publication of original investigations in all branches of medicine, review articles, historical subjects of medical interest, and clinical memoranda. Papers are accepted for publication on condition that they are offered to this journal alone and that they become the property of the *Scottish Medical Journal*.

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Papers should be written in clear concise English language and spelling. Manuscripts should be typed, double spaced including title page, abstract, text, acknowledgements, references, figures, tables and legends. Number pages consecutively beginning with the title page. Total word count should not exceed 2500 words.

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The second page should carry an abstract of not more than 200 words. Abstracts should be sub-divided under the following headings: Introduction, Methods, Results and Discussion). Below the abstract include three to five key words or short phrases for indexing.

The description of methods and results should be in sufficient detail to allow repetition by others. Data should not be repeated unnecessarily in text, tables and figures. The discussion should simply repeat the results, but should present their interpretation against the background of existing knowledge.

References
References should be numbered consecutively in the order in which they appear in the text. Identify references in text, tables and legends by arabic numerals in superscript e.g. 3 or 2-4. Use the style of references adopted by Index Medicus. The titles of journals should be abbreviated and when there are more than six authors, it should be abbreviated to three authors followed by *et al*. The title of article, abbreviated name of journal, year, volume, first and last page numbers. 'Personal communications' and 'unpublished observations' (including information from manuscripts submitted but not yet accepted) should be so identified in parenthesis in the text and not included as references. Reference to books should include surname and initials of author(s), title of chapter, editor(s), title of book, place of publication, name of publisher, year, volume and page numbers.

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Figures should be numbered in arabic numerals. Image files should be supplied **IN ADDITION** to the manuscript as high resolution (300dpi) JPEG, TIFF or as EPS vector files. They should be technically excellent. If image files are not supplied, the quality of images may deteriorate when extracted from Word. Please indicate clearly in the copy where figures should be inserted. Each figure should be submitted on a separate sheet with a short legend as a heading with explanatory matter in footnotes. The name(s) of the author(s) should be written on the reverse side of the paper copy.

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These will be summarised in the Journal and full text will be available on the Journal website. The authors should not include names, initials or hospital numbers of patients, which might lead to their recognition. A patient must not be recognisable in any photograph unless written consent has been obtained.

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EDUCATION ARTICLE ANSWERS

What is New in Chronic Myeloid Leukemia?

The correct answers are as follows:

Question A
1T, 2T, 3T, 4T, 5F

Question B
1F, 2T, 3F, 4T, 5F

Question C
1T, 2T, 3F, 4F, 5F

Question D
1T, 2F, 3F, 4T, 5F