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Editorial

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Antiviral treatment of Hepatitis C Virus Carriers with normal ALT levels: actual utility or unnecessary expense?

Claudio Puoti

Many subjects with chronic Hepatitis C Virus (HCV) infection show persistently normal alanine aminotransferase (ALT) levels (PNALT),[1-4] and thus formerly defined as 'healthy' or 'asymptomatic' HCV carriers.[1] However, it is now clear that only a minority of these people show normal liver (15-20%).[5-7] Therefore, 'normal ALT' does not always mean 'healthy liver.'[4]

It is known that during the course of HCV infection ALT levels could fluctuate widely, with long periods of biochemical remission.[1-4]Thus, at least two different subsets of HCV-PNALT carriers exist: patients with temporal ALT fluctuations, that could be within the normal range for several months, and true 'biochemically silent' carriers showing persistently normal ALT values.[4]It means that the observation period should not be shorter than 12 - 18 months, and ALT determinations should be performed every 2 - 3 months.[4, 6]

Although liver damage is usually mild, [1, 2]the presence of more severe chronic hepatitis (CH) or cirrhosis has been reported despite consistently normal liver biochemistry.[8]Although some studies showed that HCV carriers with normal ALT have mild and rather stable disease, others reported a significant progression of fibrosis in approximately 20-30% of the patients with ALT normality.[9]The development of hepatocellular carcinoma (HCC) has been also described.[10]Sudden worsening of disease with ALT increase and histological deterioration has been reported after many years of follow-up.[11]

Finally, HCV carriers with PNALT may suffer from extra-hepatic manifestations, sometimes more severe than the underlying liver disease: lymphoproliferative disorders, mixed cryoglobulinaemia, thyroid disorders, sicca syndrome, porphyria cutanea tarda, lichen planus, diabetes, chronic polyarthritis, etc.[1, 2, 12]

Therefore, the possibility of progression to more severe liver damage despite persistently normal biochemistry, the risk of HCC, the possibility of extra-hepatic diseases, and economic considerations, suggest that HCV-infected persons with PNALT should not be excluded *a priori* from antiviral treatment.[1, 2]

The earliest guidelines discouraged interferon (IFN) treatment in patients with PNALT because of the cost and side effects of therapy,[1, 2] and of the low response rates to IFN monotherapy (<10-15%) with a risk of ALT flares in up to 50% of patients during treatment.[9]

The introduction of the combination of weekly subcutaneous pegylated-IFN (PEG-IFN) plus daily oral ribavirin (RBV) has led to response rates ≥50%, with a favourable risk-benefit ratio even in patients with slowly progressing disease.[1, 2, 9]The first trial of PEG-IFN plus RBV found a sustained virological response (SVR) in 40% of HCV-1 carriers with PNALT treated for 48 weeks, and in 72% of HCV-2 and HCV-3 treated for 24 weeks.[13]The efficacy of antiviral treatment with PEG-IFN plus RBVwas subsequently confirmed in clinical practice.[14, 15]

However, in everyday practice, management of carriers with PNALT may be paradoxically more difficult than that of patients with abnormal ALT levels. Indeed, it is not always so easy to ascertain in the single case whether it should be considered as healthy subject or true patient. Several topics to date remain unresolved: Should these 'seemingly healthy' people undergo routine liver biopsy? Is antiviral treatment justified in 'asymptomatic' subjects with persistently normal liver biochemistry? Is long-term follow-up needed in this setting, and how long it should last?[2]

Liver biopsy provides helpful information on liver damage, as it may reveal the presence of advanced fibrosis or cirrhosis. Without a biopsy, it is impossible to clinically distinguish true 'healthy' carriers from those with CH.[4] On the other hand, it is difficult to recommend routine biopsy for all HCV-PNALT .[4] The decision to perform a biopsy should be based on whether treatment is being considered, taking into account the estimated duration of infection, probability of disease progression, willingness to undergo a biopsy, motivation to be treated, and availability of non-invasive tools to assess liver fibrosis.[12] The recently developed transient elastography has improved our

ability to non-invasively define the extent of fibrosis in HCV persons.[5]

Careful evaluation of parameters associated with disease progression is mandatory to assess the actual need for antiviral treatment.[4] Indeed, it is really impossible to suggest antiviral therapy in *all* HCV carriers, as the costs would be exceedingly high, due to the high number of HCV patients with PNALT. Data from the literature indicate that the main factors of progression are male gender, advanced age, severe fibrosis, ALT flares, and steatosis.[1-2]

Cost/benefit might be particularly favourable in:

- Young patients, having high rate of SVR (e.g. females, low viral load, HCV genotype non-1, etc).
- Middle age patients with 'significant' liver disease and/or co-factors of progression of liver damage, thus at risk of developing more severe liver disease.[12]

The age issue has a critical role for decision making. Younger patients have a higher chance of achieving SVR and tolerating therapy better; they a have longer life expectancy, are often well motivated, usually have minimal disease and fewer contraindications. Thus, in this group decision to treat should be based more on expected response and motivation than on the severity of liver disease.

On the contrary, older patients respond less well to therapy, are more likely to have significant liver disease and/or co-factors, could experience more side effects and may be less motivated. Thus, in this group decision to treat should be based on the severity of liver disease and on the possibility of SVR.

A recent Italian Expert Opinion Meeting suggested the following recommendations:[12]

1. *HCV carriers with PNALT may receive antiviral treatment with PEG-IFN plus RBV using the same algorithms recommended for HCV patients with abnormal ALT.*
2. *Decision making should rely on individual characteristics such as HCV genotype, histology, age, potential disease progression, probability of eradication, patient motivation, desire for pregnancy, co-morbidities, co-factors, etc.*
3. *Treatment might be offered without liver biopsy in patients with a high likelihood of SVR (e.g. age <50 years + non-1 HCV genotype + low viral load), in the absence of co-factors of poor responsiveness.*
4. *Inpatients aged 50–65 years, and in those with a reduced likelihood of achieving a response, biopsy may be used to evaluate the need for therapy, with treatment being recommended only for patients with more severe fibrosis and higher possibility of SVR. Biopsy and therapy are not recommended in the elderly (>65-70 years).*

In patients who are not candidates for antiviral treatment, follow-up may be continued, and ALT should be monitored every 4-6 months. Avoidance of alcohol and obesity may be strongly recommended.[12] It is not clear whether these subjects should be routinely offered anti-HBV vaccine, given the risk of disease progression in the case of HBV infection.[12] Antiviral treatment should be re-considered in the case of ALT flares, US abnormalities or platelet count decrease. Repeated measurements of serum HCV RNA to evaluate disease progression is not recommended.[1, 9, 11, 12].

Competing Interests
None declared
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Research Article

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Efficacy of Fixed High Dose Radioiodine Therapy for Hyperthyroidism – a 14 year Experience: A focus on Influence of Pre-treatment Factors on Outcomes

Y Khalid, D M Barton, V Baskar, H Kumar P. Jones, T E T West and H N Buch

ABSTRACT

Background: Radioiodine therapy (RAI) is commonly used as a definitive treatment for hyperthyroidism. However there is no agreement on the regime or the dose of RAI used and success rate is quite variable. In addition, the literature on the factors governing the success of the initial dose is conflicting.

Objective: We have adopted a standard 550 MBq dose for all patients with hyperthyroidism. The aims of our study were (1) to assess the success rate of this regime in terms of cure of hyperthyroidism and (2) to evaluate the role of pre-treatment factors including age, gender, use of antithyroid medication prior to RAI, aetiology of hyperthyroidism and free thyroxine levels at diagnosis, as predictors of response to RAI.

Patients and methods: The study is a retrospective analysis of 584 patients treated at this centre over a 14 year period. All patients received a fixed 550MBq dose following withdrawal of antithyroid medication for 7 days. Repeat dose was administered if patients remained hyperthyroid at the end of one year after the initial dose. Success rate in terms of cure of hyperthyroidism was calculated. The association of pre-treatment factors and failure to respond to the first dose of RAI was studied using univariate and multivariate analyses.

Results: Mean age was 56 years (range 20-90 years) with female preponderance (82%). Of the 478 patients in whom the aetiology could be ascertained by the criteria used, 344(72%) patients had Graves' disease and 134(28%) patientshad toxic nodular disease. At the end of one year 545(93%) patients were either hypothyroid (411(70%)) or euthyroid (134(23%)) and were considered to be cured, while 39(7%) patients remained hyperthyroid and required further doses of RAI. Free thyroxine level at the time of diagnosis was the only pre-treatment factor, which independently influenced post-RAI outcome and a higher free thyroxine level predicted a lower cure rate.

Conclusion: A standard 550MBq dose of RAI has a low failure rate when used for the treatment of hyperthyroidism. In our experience, only high free thyroxine levels at diagnosis was associated with a lower cure rate.

Introduction

Hyperthyroidism is one of the most frequently encountered conditions in clinical endocrinology.[1] The modes of treatment available are antithyroid drugs, surgery and radioiodine (RAI) and although each of these is highly successful in controlling or curing hyperthyroidism none leads to permanent euthyroidism on a consistent basis. [2] Although over the last three decades RAI therapy has replaced surgery as the leading form of definitive treatment [3, 4, 5] there is no universally accepted dose or regime for its use. Previous attempts to individualise the dose of RAI to reduce the rate of post-RAI hyper- or hypothyroidism have been unsuccessful [6, 7]. Fixed dose RAI administration has therefore become the most commonly used regime although the actual dose of RAI used varies considerably and ranges between 185MBq to 600MBq [8, 9]. For the last two decades we have used a fixed RAI dose of 550MBq for all patients. Others have used this regime with a high success rate [10] and a prospective head to head comparison with the calculated dose method found the fixed dose regimen to be superior for curing Graves' hyperthyroidism [11].

Conflicting results have been produced in several studies that have attempted to predict outcome following RAI therapy by correlating cure rate with various pre-treatment factors including age, gender, aetiology of hyperthyroidism, goitre size, use of antithyroid drugs, free thyroxine levels at diagnosis and thyroid antibody status. Various forms of calculated or low fixed dose RAI therapy have been used in these studies but no study used a high fixed dose of 550MBq. In this study we have evaluated the overall success rate of high fixed dose RAI therapy and attempted to identify simple clinical predictors of failure to respond the initial RAI dose.

Patients and Methods

The study is a retrospective analysis of 584 consecutive patients referred to the Shropshire endocrinology service (Princess Royal Hospital and Royal Shrewsbury Hospital) over a 14 year period for the treatment of hyperthyroidism. These patients received RAI therapy at Royal Shrewsbury Hospital, which is the only centre providing facilities for RAI administration in the county of Shropshire and also draws referral from adjoining trusts in Powys, North Wales. Information for this study was obtained from the thyroid database which is maintained on all patients who have received RAI since 1985 at the above hospitals.

RAI was administered both as a primary (53%) and as secondary (47%) treatment. A majority of patients with moderate to severe hyperthyroidism were rendered euthyroid by antithyroid drugs (ATD). Ninety percent (518/584) patients were pre-treated to euthyroidism by antithyroid drugs (carbimazole in 95% and propylthiouracil in 5%) before RAI therapy. Carbimazole was withdrawn one week and

propylthiouracil 4 weeks prior to RAI therapy. A standard RAI dose of 550MBq was administered to all patients without a prior uptake study. Thyroid function was measured at 6 weeks and at 3, 6 and 12 months following RAI therapy. ATD drugs were not recommenced routinely following RAI therapy and were reserved for patients who were persistently and significantly hyperthyroid following RAI administration. Patients who developed clinical and biochemical hypothyroidism after the initial 6-8 weeks were commenced on thyroxine. Patients with high free thyroxine level (FT4) and a suppressed thyroid stimulating hormone (TSH) level and those on antithyroid medication were defined as being hyperthyroid, those with low FT4 or on thyroxine as hypothyroid and those with normal FT4 and a normal or low TSH as euthyroid. At the end of one year if a patient remained hyperthyroid, another RAI dose of 550MBq was administered. The patient was considered to have been "cured" if euthyroidism or hypothyroidism was achieved during the first year following RAI therapy and "not cured" if patient remained persistent hyperthyroidism at the end of this period.

Information recorded on the database included age, gender, aetiology, indication (primary or secondary), dose of RAI, number of RAI doses, name and duration of antithyroid drugs used, if any, and FT4 and TSH levels at diagnosis, at the time of RAI therapy and at 6 weeks, 3, 6 and 12 months after RAI therapy. Diagnosis of Graves' disease was based on the presence of Graves' ophthalmopathy or a combination of a diffuse goitre and a significant titre of thyroid peroxidase antibodies or if radionuclide scan showed diffuse uptake. Toxic nodular disease was diagnosed on the grounds of a nodular goitre and a focal increase in radionuclide uptake. Patients who could not be classified to either of the groups on clinical grounds and where a radionuclide scan could not be performed for a variety of reasons, were categorised as "unclassified" on aetiological grounds.

Statistical analysis

Continuous random variables were compared using t-tests and association of categorical variables by using chi-squared tests. The effect on outcome (cure of hyperthyroidism) of all variables was assessed by using logistic regression analysis and a step-wise routine was applied to choose the best set of predictors. All analyses were carried out by using NCSS2000.

Results

Data on 584 patients was included with a mean age of 56 years (range 20-90) and a female preponderance (82%). Assessment of the aetiology of hyperthyroidism was made by the above-mentioned criteria. In 110(15%) patients precise aetiological diagnosis could not be made. 344/474 (72%) patients had hyperthyroidism secondary to Graves' disease and 134/474(28%) had toxic nodular disease. 518 patients received pre-RAI antithyroid medications. Mean free thyroxine level at time of diagnosis was 45.4pmol/L in 259 patients in whom this information was available. Data for thyroid status at 3, 6, and 12 months post-radioiodine were available in 97, 94 and 100% patients respectively (see Table 1).

Table 1: Thyroid status at 3, 6 and 12 months

	Euthyroid (%)	Hypothyroid (%)	Hyperthyroid (%)
3 months	308 (54%)	176 (31%)	87 (15%)
6 months	210 (38%)	280 (51%)	59 (11%)
12 months	134 (23%)	411 (70%)	39 (7%)

FT4 values were entered onto the database more recently and this result was available in 259 patients. The group of patients where FT4 data was available was comparable to the group where this information was not available in all respects apart from age (mean age (SD) 54 (±15) vs 58 (±14) years respectively, $p<0.02$). Similarly, the group of patients in whom the aetiology could not be ascertained was not different from the group where the aetiology could be identified in any respect apart from the age (mean age (SD) 60 (±13) vs 55 (±15) respectively).

Table 2 – Forward Stepwise (Wald) logistic regression analysis to identify factors independently associated with failure to respond to first dose of RAI

Variables	P value	Adjusted r2; OR (95% CI)
Free T4 at diagnosis	0.005	0.084; 1.04 (1.01-1.07)
Free T4 > 45 pmol/l at diagnosis*	0.02	0.056; 3.43 (1.17-10.04)
Age	0.81	N/A
Gender	0.18	N/A
Aetiology	0.23	N/A
Pre RAI use of anti-thyroid drugs	0.42	N/A

* Regression analysis carried out with free T4 as a continuous variable and separately as a categorical variable at a cut off of 45pmol/l

One year following RAI treatment, 543(93%) patients were either euthyroid (162;28%) or hypothyroid (383;65%) and considered "cured"; 39(7%) patients remained hyperthyroid and required further doses of RAI, with 34(6%) patients requiring two doses and 5(1%) patients three doses. At 3 months, 484 out of 571 (85%) patients, and at 6 months, 490 out of 549 (89%) patients were "cured" (table 2). On univariate analysis no correlation could be established between the failure to respond to the first dose RAI and age, gender, aetiology or use of antithyroid medication (p = ns for all) although the rate of hypothyroidism was significantly higher at the end of one year in patients with Graves' disease as compared to those with toxic nodular disease (77.1% vs. 50.3%, $p<0.01$). These results were not affected by limiting the analyses to any of the following groups: only those patients in whom the aetiological diagnosis could be made (n=478), only those patients in whom FT4 value was available (n=259) or only those patients where

both FT4 was available and aetiology could be ascertained (n=209). On univariate analysis FT4 at diagnosis was associated with the outcome when it was used as a continuous variable ($p<0.05$) or as a categorical variable with the cut off set at mean FT4 value of 45pmol/L ($p=0.01$) and high values were associated with failure to respond to the first dose of RAI (mean ± SD, 57.28±20.1 v 44.58±16.1 pmol/L, $p<0.05$). On multivariate analysis with all variables, FT4 was found to be independently associated with outcome and again this association was seen when FT4 was used as a continuous variable ($p=0.01$) as well as a categorical variable ($p=0.02$). On using step-wise selection routine only FT4 could be chosen as a predictor when criterion for selection was set at $p=0.05$ and a value of over 45pmol/L predicted failure to respond to the first dose of RAI.

Discussion

The use of a standard fixed-dose RAI therapy is gaining increasing popularity and several studies have now shown that formal estimation of the required dose based on the thyroid size and iodine kinetics does not lead to a higher cure rate[6,7,10,11] or a lowerhypothyroidism rate [7]. For several years we have used 550MBq dose for all patients of hyperthyroidism. The overall success rate with this regime was 93% and only 7% of patients required a repeat RAI dose. These figures are comparable to those from most other centres, which have used a similar dose of RAI [10]. In addition to achieving a high cure rate, hyperthyroidism was controlled rapidly with 85% of the patients becoming either euthyroid or hypothyroid within 3 months of treatment. Early onset of hypothyroidism (>70% at 12 months) facilitated institution of thyroxine replacement therapy during the first year during which the patients were being closely followed.

The use of a relatively higher dose of RAI leads to more stringent restrictions to the normal life of patients and these have to be followed for a longer period of time than is the case with the use of a lower dose. Majority of patients accept these restrictions at the prospect of a cure of hyperthyroidism. However, even at this dose, 7% of patients required repeat dosing which in turn led to another restrictive period for these patients. In view of this it is useful to be able to predict failure of the first dose in an individual patient. This would enable us to warn these patients about the higher possibility of requiring repeat dosing, further period of post-RAI restrictions and target them for a closer follow up. To allow us to make this prediction we correlated simple clinical pre-treatment variables to the need for repeat dosing. We found that there was no statistically significant correlation between age, gender, aetiology and the use of anti-thyroid medication prior to RAI and the outcome following RAI therapy although a high free thyroxine level at diagnosis predicted a failure of the first dose to achieve a cure of hyperthyroidism. There are several conflicting reports in the literature on the correlation between these factors and the response to RAI therapy. Most of the studies have failed to show a significant association between the age of the patient and the outcome irrespective of whether the age was used as a continuous or a categorised variable [12-15] although in a study where a standard 150 gray RAI was used age >50 was found to be associated with a higher failure rate [16]. In one study, male gender was associated with a lower cure rate following a single dose of RAI in patients with Graves' disease [12] although others have failed to confirm this association [13,14]. Use of antithyroid drugs prior to RAI has been shown to independently reduce the success rate of RAI [17, 18] while other studies have shown such an association with the use of propylthiouracil but not with carbimazole[19, 20]. Literature on the association between the aetiology of hyperthyroidism and the outcome is even more confusing. Patients with toxic nodular disease have been considered to be more radio-resistant as compared to patients with Graves' disease [21] although opposite results have also been noted [22]. In other studies no correlation could be established on multivariate analysis between the aetiology and outcome following RAI [14, 18]. Our study is the only one which analyses the influence of these factors on the outcome following the use of a standard 550MBq RAI dose and the above studies which have attempted to identify clinical predictors of outcome have either used various forms of the calculated dose regime or a lower fixed-dose RAI regime. We feel that this is the reason for the inconsistencies in the results and when a 550MBq dose RAI is used only FT4 value at diagnosis could predict the failure of RAI therapy to achieve cure. This dose of RAI appears to override the variations in the response induced by the remaining pre-treatment variables studied.

Studies using smaller doses or calculated doses of RAI have shown the outcome to be inversely associated with the thyroid size [14, 16] although this could not be ascertained in our study due to the lack of consistent documentation of the size ofgoitre in the clinical notes. In addition there are several possible confounding factors. Firstly the overall cure rate could have been influenced by the long period of time over which patients have been included (15 years) and the resulting changes in the criteria and threshold for the use of RAI. However if we divide the figures into 3 time periods of 5 years each, the findings remain consistent during each of these periods. Secondly, in over 50% of our patients, RAI was administered as a primary measure and it could be argued that a larger number of patients with milder hyperthyroidism may have been included in our cohort as compared to the patients at other centres where RAI is mainly reserved for patients who fail to respond to ATD. However there was no significant difference in the cure rate between those patients who received RAI as a primary measure and those in whom RAI was administered as a secondary treatment (94% v 93%). Thirdly in 15% of patients the aetiology could not be ascertained by using our well-defined criteria, mainly because of the practical difficulty of performing radionuclide scans in some of the patients where the diagnosis could not be made clinically. We do not feel that our results on the association between the aetiology and the cure rate were affected, as the patients with undefined aetiology were

comparable to the remaining patients in all respects apart from age and had similar outcomes. Lastly the information on the FT4 value at diagnosis was available in only 259 patients. To exclude a selection bias this group was compared to the group of patients where this information was not available. Again the only difference between the two groups was the age distribution. In both instances this difference was not large (though statistically significant) and we do not feel it affected the outcome, especially as age does not appear to influence the outcome following RAI therapy. We could not assess the impact of post-RAI use of antithyroid drugs as these were not routinely restarted following RAI therapy at our centre.

In conclusion, high fixed dose RAI therapy is a very effective treatment for patients with hyperthyroidism and has a high success rate. Failure to respond to this dose cannot be predicted by most of the pre-treatment variables apart from the severity of the hyperthyroidism as judged by the FT4 value at diagnosis. Patients who present with severe hyperthyroidism should be warned regarding the higher possibility of requiring further doses of radioiodine even when treated with a dose of 550MBq.

Competing Interests
None declared
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Research Article

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Prevalence and Pattern of Self Medication use in coastal regions of South India

Balamurugan E and Ganesh K

ABSTRACT

Aim: Self medication (SM) is proportionately increasing in both urban and rural communities. The prevalence and pattern of SM use is not well established, hence a cross sectional survey was undertaken which recruited a sample size of 200 participants randomly from the coastal regions of south India.

Method: Each participant underwent a face to face interview with the help of a structured questionnaire; data collected was analyzed using descriptive and inferential statics in SPSS.

Result: SM use was reported by 71% of the subjects, which ranged from a frequency of at least one time to a maximum of 5 times and above. Lack of time (41.5%), minor illness (10.5%) and quick relief (10%) was cited as the most common reason for SM use. The majority of the participants (93.5%) were not aware about the side effects of SM. Findings revealed females and people living in urban areas are more likely to use SM than males and people in rural areas (P<0.001).

Conclusion: There may be a larger role for a training programme to empower people about safety and side effects of SM use, to achieve a greater sense of self control

Keywords: Self-medication, Rural, Urban, over the counter drug, Medicines

Introduction

William Osler has said that "A desire to take medicine is perhaps the great feature which distinguishes man from animals" This desire, however may play havoc when a person starts taking medicines on their own (i.e. self-medicating), forgetting that all drugs are toxic and their justifiable use in therapy is based on a calculable risk [1].

Self-medication (SM) can be defined as obtaining and consuming drugs without the advice of a physician[2]. There is a lot of public and professional concern about the irrational use of drugs in SM. In developing countries like India, easy availability of a wide range of drugs coupled with inadequate health services result in increased proportions of drugs used as SM compared to prescribed drugs[2]. Although, over-the-counter (OTC) drugs are meant for SM and are of proved efficacy and safety, their improper use due to lack of knowledge of their side effects and interactions could have serious implications, especially in extremes of ages (children and old age) and special physiological conditions like pregnancy and lactation [3], [4]. There is always a risk of interaction between active ingredients of hidden preparations of OTC drugs and prescription medicines, as well as increased risk of worsening of existing disease pathology [5] . As very few studies have been published in our community regarding usage of self medication we conducted this cross-sectional study in the coastal region of Pudhucherry, South India, t assess the prevalence and pattern of SM use.

Materials and methods:

The present study was a cross-sectional survey conducted in coastal region of pudhucherry, south India. For this study we recruited 200 patients randomly from both urban and rural communities (100 each) for a period of six months during 2009. Patients who were = 18 years of age and who were able to read and write the local language (Tamil) or English were included in the study after informed consent explaining the purpose of the study. Participants with intellectual, psychiatric and emotional disturbances that could affect the reliability of their responses were excluded from the study. To collect data regarding SM usage a structured questionnaire was prepared, after an extensive literature review.. The structured questionnaire contained 25 items in the form of closed and open ended questions. Initially the tool was validated by a panel of experts in the field of public health for the appropriateness of each item and assessment of content validity (0.91) and re-test reliability coefficient (0.89). Approval to conduct the study was granted by the Institute ethics committee prior to data collection. Each participant underwent a face to face interview to collect data followed by an informal educational counseling about potential adverse effects of consuming common SM. Data collected was analyzed using SPSS for windows statistical software version 14 (SPSS Inc., Chicago, Il, USA). Data was presented using descriptive statistics (i.e. numbers, percentage) and inferential statistics (i.e. Chi-square). A probability value of < 0.05 was considered to be significant.

Results

Basic demographic details:

The majority of the participants were female (56%). Most of the participants (60%) were between 26-45 years of age. There were an equal number of participants from the rural and urban

community. Among the total 200 participants 70% were literate.

Findings related to usage of SM:

Overall, out of 200 participants, 71 % of them reported that they have used SM in the past. The frequency of SM use varied among the subjects with a minimum of at least one time to maximum of 5 times and above See Figure 1. When the participants were asked about the reasons for SM use, the majority of them - 41.5% - stated lack of time to visit a doctor as the main reason followed by minor illness and quick relief. See Table 1. The major source through which the participants learned to use SM were as follows, directly from pharmacist (57.3%), prescription of previous illness (21.5%), friends (12.5%), television (5.5%) and books (3%).See Table 2. The main indications for SM use were fever (36%), headache (35%), then cough/cold/sore throat (20%). See Table 3 for detailed data.

While calculating chi-square to find out the association between usage of SM and selected demographic variables we found an association between residence (i.e. rural or urban) and gender; urban people were more likely to use SM than rural people (urban, 60/100 vs. rural 82/100, p value = .006). In relation to gender females were more likely to use SM in comparison to males (female, 78/112 vs. 43/88, p value= .002). Other variables were not significantly associated with SM use. Finally, when the subjects were asked about the side effects of their used self medications 93.5% of them said that they are not aware of the side effects and only the remaining 6.5% of them said they are aware of the side effects.

Figure 1: Frequency of self medication Use

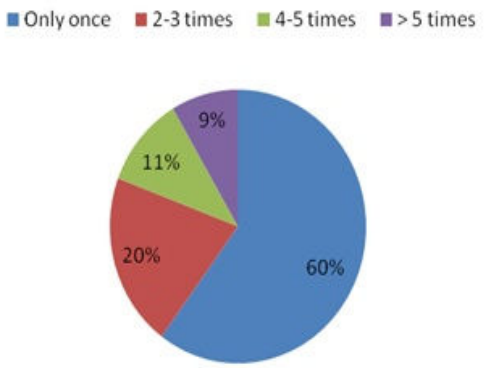

Table 1: Reasons for Self Medication Use

Reasons	Number (%)
Lack of time	41.5
Minor illness	10.5
Economical	14
Quick relief	10
Learning opportunity	2
Ease and convenience	10.5
Avoiding crowd in visiting doctor	6
Unavailability of doctor	5.5

Table 2: Sources of Self Medication Use

Sources for self medication use	Number (%)
Directly from pharmacy without prescription	57.3
Prescription of previous illness	21.5
Friends prescription	12.5
Television media	5.5
Book	3

Table 3: Indications for Self Medication Use

Indications for self medication use	Number (%)
Headache	35
Stomach ache	3
Vomiting	1
Eye symptoms	0.73
Diarrhoea	2
Cough, cold, sore throat	20
Fever	36
Skin symptoms	0.27
Ear symptoms	2

Discussion

The current study examined the prevalence and pattern of SM use in a coastal region of South India. The study findings revealed 71% of the people reporting SM use in the past, this prevalence rate in our study is consistent with previous finding[3],[6],[7],[8],[9],[10],[11] The figure of participants who use SM is very high, which requires immediate attention. The frequency of self medication use in our study ranged from a minimum of one time to a maximum of 5 times and above, this finding was in line with the findings of a study by Nalini (2010)[12].

Participants cited multiple reasons for use of SM like lack of time , quick relief from illness and ease and convenience, a similar reasons were cited in an another Indian study[13]. In the current study participants reported SM use in a variety of conditions like headache, stomach ache, cough and fever, this these finding are comparable with those of Sontakke et al (2011) [14]. The reason for SM use may be mufti-factorial, in our study an association was found between gender and residence, i.e. female and rural people reporting more SM use, this finding was similar to two previous studies[15],[16] To establish the reasons why requires further research. One potential limitation of this study is the limited sample size, which we tried to

overcome by adopting a random sampling method so as to generalize findings.

Conclusion

Factors influencing SM include patient satisfaction with the healthcare provider, cost of the drugs, educational level, socioeconomic factors, age and gender [17]. Interactions between prescribed drugs and the drugs taken for SM is an important risk factor of which healthcare providers must be aware of.[17,2]

Easy availability of wide range of drugs without a prescription is the major factor responsible for irrational use of drugs in SM as, thus resulting in impending health problems (antimicrobial resistance, increased load of mortality and morbidity) and economic loss. The need for promoting appropriate use of drugs in the health care system is not only for financial reasons, with which policy makers and manager are usually most concerned, but also for health and medical care of patients and the community. There is need for authorities to strengthen existing laws regarding OTC drugs to ensure their rational sale and use. Also, specific pharmacovigilance is needed and the patient, pharmacist and physician must be encouraged to report any adverse events. Periodic studies on the knowledge, attitude about and practice of SM may give insight into the changing pattern of drug use in societies.

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Competing Interests
None declared
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Review Article

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Recent Advances In Management Of Pre-Eclampsia

Pallab Rudra, Sonela Basak, Dilip Patil and M Y Latoo

Pre-eclampsia is a multisystem disorder of pregnancy that forms an integral part of the spectrum known as hypertensive diseases of pregnancy. The National High Blood Pressure Education Program (NHBPEP) Working Group[1]classifies hypertensive diseases in pregnancy into 4 groups:

1) Gestational hypertension
   - New onset hypertension in pregnancy presenting after 20 weeks
   - No proteinuria
   - BP returns to normal less than 12 weeks postpartum
   - Final diagnosis made only postpartum
2) Chronic hypertension
   - BP >140/90 mm Hg before pregnancy or diagnosed before 20 weeks gestation not attributable to gestational trophoblastic disease
     or
   - Hypertension first diagnosed after 20 weeks gestation but persistent after 12 weeks postpartum.
3) Pre-eclampsia/eclampsia
   - BP > 140/90 mm Hg after 20 weeks gestation in a women with previously normal blood pressure
   - Proteinuria (>0.3 gm urine protein in 24 hr).
   - Eclampsia is defined as seizures that cannot be attributed to other causes in a woman with pre-eclampsia
4) Superimposed pre-eclampsia (on chronic hypertension)
   - New onset proteinuria (>300 mg/24 hr) in a woman with hypertension but no proteinuria before 20 weeks gestation
   - A sudden increase in proteinuria or blood pressure, or platelet count less than 100,000 in women with hypertension and proteinuria before 20 weeks gestation

Epidemiology

Pregnancy induced hypertension complicates about 10% of pregnancies, but there is a widespread geographic variation in its incidence.The incidence is higher in developing countries. The highest reported rate of pre-eclampsia is 7.1% (deliveries) from Zimbabwe[2], while the incidence is as low as 0.81% (deliveries) in Colombia[3]. In UK, the incidence of severe pre-eclampsia is 5/1000 maternities[4], while the incidence of eclampsia is 4.9/10,000 maternities[5]. The incidence of severe pre-eclampsia in European countries ranges from 2/1000 (deliveries) in Norway to 6.4/1000 (deliveries) in Belgium and Hungary[6].

The 8th Confidential Enquiry into maternal and child heath[7] revealed pre-eclampsia and eclampsia as the second leading cause of direct maternal death, thereby contributing to a maternal death rate of 0.83 / 100,000 maternities.

Worldwide studies show that mortality from pre-eclampsia can be as high as 0.4%, while that in eclampsia varies from 6.1% in developing countries to 1.8% in UK [5, 8-9].

Estimates of maternal mortality from the developing countries (in Asia, Africa, Latin America and the Caribbean) suggest that 10-15% of maternal deaths are associated with hypertension in pregnancy, while eclampsia is associated with 10% maternal mortality[10].

Severe pre-eclampsia is also associated with significant maternal morbidity, including eclamptic seizures, intracerebral haemorrhage, pulmonary oedema due to capillary leak or heart failure, acute renal failure, liver dysfunction, and coagulation abnormalities.

Fetal complications include abruptio placentae, intrauterine growth restriction, premature delivery, and intrauterine fetal death. The incidence of stillbirths and neonatal deaths in mothers who suffered eclampsia was 22.2/1000 and 34.1/1000, respectively, in the UK with a higher incidence in developing countries[5].

More than half a million women die each year from pregnancy related causes across the globe. The Millennium Development Goals have placed maternal health as a basic human right, one that is integral to the core of the fight against poverty and inequality. The high incidence of pre-eclampsia and its complications makes its prevention and effective management important. The following article attempts to outline the pathophysiology and management of pre-eclampsia.

Aetiology & Risk factors

Pre-eclampsia is commonly referred as the "disease of theories" making its prevention and management an ongoing challenge worldwide. Although the aetiology is still largely unknown, there are a few hypotheses regarding the pathophysiology and prediction of pre-eclampsia.

It has been postulated that pre-eclampsia may be autoimmune in nature. Seminal-vesicle-derived transforming growth factor 1 (TGF-1) initiates a post mating inflammatory reaction, which is a type 2 immune response towards paternal antigens resulting in maternal-fetal (paternal) immune maladaptation[11]. This idea originates from epidemiological studies demonstrating the protective effect of long-term sperm exposure and is supported by the fact that frequency of pre-eclampsia is higher in nulliparous women or multiparous women with a new partner, teenagers, women who conceive after donor insemination or oocyte donation, and women with autoimmune conditions.

Another potential mechanism responsible for pathogenesis of pre-eclampsia is placental hypoperfusion which in turn releases various factors that trigger endothelial activation / dysfunction. Nitric oxide, disordered endothelin metabolism, thromboxane/prostaglandin imbalance, cellular fibronectin, inflammatory cytokines (TNF-α, IL-6, IL-1α, and IL-1β) and otherfactors such as lipid peroxides and reactive oxygen intermediateshave all been implicated in mediating the endothelial cell injury[12]. This is well-supported by the fact that pre-eclampsia commonly occurs in pre-existing metabolic (diabetes, hypercholesterolemia), renal, vascular disorders (hypertension) and connective tissue disorders that result in poor placental circulation. In cases of multiple gestation or increased placental mass, it is not surprising for the placenta to become underperfused.

However, majority of the pre-eclamptic women do not suffer from any underlying medical conditions. In these women, lack of placental cytotrophoblastic invasion of uterine spiral arterioles and arrest of arteriolar remodelling results from failure of pseudo-vascularisation of the invasive cytotrophoblasts[13]. Deregulation of angiogenesis-related gene products such as vascular endothelial growth factor (VEGF), angiopoietin and ephrin family proteins, placental growth factor (PlGF) and their receptors have been implicated in this process[14].Shallow placentation leads to reduced placental perfusion and subsequent ischaemia.

Obese (BMI ≥30 Kg/m2) women are at higher risk for pre-eclampsia compared to lean women (odds ratio = 3.3). The exact mechanism is not completely understood but possible explanations are: increased stress due to the hyperdynamic circulation associated with obesity; dyslipidaemia or increased cytokine-mediated oxidative stress; and direct haemodynamic effects of hyperinsulinaemia[15] (increased sympathetic activity and increased tubular sodium resorption).

On the other hand, smoking actually decreases a woman's risk of pre-eclampsia. Inhibition of thromboxane A_2production by nicotine might explain the decreased risk. However, the adverse effects of smoking on pregnancy significantly outweigh any beneficial effects[16].

Epidemiological and clinical risk factors for pre-eclampsia are classified as maternal, paternal, and/or pregnancy-specific[2, 17] (Table 1, below).

Table 1: Pre-eclampsia Risk Factors

Maternal Considerations
Inherent
➢ Age < 20 or 35–40 years
➢ Nulliparity
➢ Afro-Caribbean origin
➢ Prior or family history of PE or cardiovascular disease
➢ Woman born small for gestational age
Medical conditions
➢ Obesity
➢ Chronic hypertension
➢ Chronic renal disease
➢ Diabetes mellitus (insulin resistance, type 1, and gestational)
➢ Antiphospholipid antibody syndrome
➢ Connective tissue diseases
➢ Thrombophilia
➢ Stress
Pregnancy specific
➢ Multiple gestation
➢ Oocyte donation
➢ New partner
➢ Urinary tract infection
➢ Congenital conditions affecting the fetus
➢ Hydatidiform mole
➢ Hydrops fetalis
➢ Structural anomalies
Paternal Considerations
➢ Limited sperm exposure
➢ Barrier contraception
➢ First-time father
➢ Donor insemination
➢ Partner who fathered a pre-eclamptic pregnancy in another woman

What exactly happens in Pre-eclampsia?

The triad of physiological derangements in pre-eclampsia include

1. Vasospasm
2. Plasma volume contraction
3. Local or disseminated intravascular coagulation.

Although the cause of pre-eclampsia is unknown, we have already discussed that the placenta is largely implicated. The sequence of events starts with vasospasm caused by increased production or sensitivity to vasoconstrictors (angiotensin II, serotonin and endothelin) and/or decreased production or sensitivity to vasodilators (prostacyclin and nitric oxide). This is followed by plasma volume contraction, increased capillary permeability and, in severe cases, low plasma oncotic pressures. Redistribution of fluid occurs from the intravascular to interstitial fluid spaces causing peripheral tissue oedema. Along with this, intravascular coagulation may occur due to platelet activation, thrombocytopenia and, often, reduced production of anti-thrombin III.

The net effect is organ hypoperfusion. Commonly affected systems are kidney (manifested by reduced GFR, proteinuria, hyperuricaemia and occasionally oliguria), liver (manifested by elevated transaminases with or without epigastric and right upper quadrant pain), and the brain (manifested by headaches, transient visual disturbances due to occipital lobe ischaemia and rarely convulsions, i.e. eclampsia). This leads to increased maternal morbidity.

Placental insufficiency resulting from uterine hypoperfusion is characterised by intrauterine fetal growth retardation and less commonly placental abruption or fetal death. Preterm delivery, low birth weight, respiratory distress syndrome, and admission to the neonatal intensive care lead to increased perinatal morbidity.

In spite of major advances in understanding the pathophysiology of the disease in recent years, interventions to prevent hypertensive disorders in pregnancy have had disappointing results, hence early detection, continued surveillance and timely intervention still remains the key towards decreasing the inherent maternal and fetal morbidity and mortality associated with severe pre-eclampsia and eclampsia.

Prevention of pre-eclampsia

Till date there is no well-established measure for prevention of pre-eclampsia in the general population. Calcium is clearly of benefit amongst high risk women in communities where low dietary calcium intake is prevalent. A Cochrane systematic review in 2010 concludes that calcium supplementation approximately halves the risk of pre-eclampsia, reduces the risk of preterm birth and the rare occurrence of the composite outcome 'death or serious morbidity[18].

Low dose aspirin (antiplatelet agent) therapyefficiently reduces the development of pre-eclampsia in women with abnormal uterine artery Doppler studies. If started in early gestation (< 16 weeks), it also causes a significant reduction in the incidence of severe pre-eclampsia, gestational hypertension and IUGR[19].

Some studies have suggested that prophylactic use of antioxidants (vitamin C, E) may be beneficial as well but this is not routinely recommended[20] in practice.

Evidence is also lacking to support lifestyle preventative interventions for pre-eclampsia, such as rest, exercise and reduced dietary salt intake.

The pre-eclampsia community guideline (PRECOG)

This has been developed for screening and detection of onset of pre-eclampsia in the community[21]. It includes:

- Initial risk assessment at community booking using pre-determined criteria, to identify factors that predispose women to pre-eclampsia in a given pregnancy. Following this, women are offered referral before 20 weeks gestation for specialist input to their antenatal care plan if they have been identified as high risk: this may be for clarification of risk, necessary investigations, advice on early intervention or pharmacological treatment.

- Systematic community assessment for onset of pre-eclampsia from 20 weeks gestation. The frequency of assessment is determined by the likelihood of developing pre-eclampsia. Women with no risk factors for pre-eclampsia are offered assessments at weeks 16, 28, 34, 36, 38, 40, and 41 weeks.Women with one risk factor for developing pre-eclampsia (excluding previous pre-eclampsia, multiple pregnancy and underlying medical conditions like hypertension, renal disease, diabetes, antiphospholipid syndrome) are reviewed in the community at least once every three weeks before 32 weeks, and then at least once every two weeks, until delivery. At every visit, recommendation is to look for presence of any signs or symptoms like new hypertension, new proteinuria, headache/visual disturbance, or both, epigastric pain/vomiting, or both, reduced fetal movements, small for gestational age infant. In the presence of two such, they are referred for early specialist input, individual assessment, and discussion of obstetric risk.

- Recommendations have been made within the scope of this guideline for improving accuracy inblood pressure measurement, increasing reliability of proteinuria test with dipstick and community assessment of fetal growth and well being which provide the parameters for referral. Referral is made forstep-up assessment in hospital day unit within 24/48 hoursor admission in accordance with set criteria. All pregnant women are also made aware that pre-eclampsia may develop between antenatal assessments, and they could self-refer at any time.

- It is recognised that all women benefit from a continuity of care in the community and need midwifery or GP care as part of their individual antenatal care plan, whatever be their obstetric risk.

Management of Pre-eclampsia

Antenatal Care

These patients should be under consultant led care with multidisciplinary input from the anaesthetic and neonatal teams as necessary.

Women with risk factors for developing pre-eclampsia may be considered for uterine artery doppler velocimetry at 20-24 weeks to look for increased impedance to flow (resistance index >95th centile or early diastolic notch), which is predictive of developing pre-eclampsia or IUGR in late gestation, however the specificity and sensitivity varies widely between different studies[22-25].

At diagnosis of pre-eclampsia, the best practice is to offer initial hospital admission for assessment and formulation of follow-up care. Assessment of proteinuria should be done by automated reagent strip reading device. Visual assessment of the dipstick is not recommended nowadays because of high error rates[26-28]. If the automated reagent strip reading of urine yields a result of 1+ or more, this should be followed up with a spot urinary protein:creatinine ratio or a 24 hour urine collection to quantify the proteinuria. Significant proteinuria is diagnosed if the urinary protein:creatinine ratio is more than 30mg/mmol or the validated 24 hr urine sample has more than 300 mg of protein. Baseline blood investigations should include full blood count, liver function (bilirubin and transaminases), electrolytes and kidney function tests. Antihypertensive medications may need to be commenced with the aim of maintaining the systolic blood pressure below 150 mm Hg, and the diastolic pressure between 80 - 100 mm Hg. Labetalol is the first line treatment. However, in patients in whom labetalol cannot be used (e.g. in patients with bronchial asthma), alternatives include nifedipine (contraindicated before 20 weeks of gestation), methyldopa, atenolol and metoprolol. 4-6 hourly blood pressure, daily assessment of proteinuria, along with haematological and biochemical monitoring are also carried out. Inpatient management is required till the blood pressure stabilises.

Following discharge blood pressure can be checked in the community or in antenatal day assessment 2-3 times a week depending on clinical circumstances. Quantification of urinary protein is not necessary after the initial assessment, however, blood tests for full blood count, liver and kidney functions need to be repeated at least twice weekly (thrice weekly if the hypertension is moderate or severe). There is often a rise in serum uric acid level, which has been associated with poor maternal and fetal outcome[29, 30]. However, there is no evidence to use serum uric acid levels for clinical management.

Fetal monitoring:

Ultrasound assessment of fetal growth and amniotic fluid volume along with umbilical artery doppler velocimetry needs to be done at initial diagnosis of pre-eclampsia to exclude IUGR and then every 2 weeks if the pregnancy is managed conservatively and the results remain normal CTG monitoring is commonly done at diagnosis, along with the ultrasound assessment. If normal, further CTG should be performed weekly unless otherwise clinically indicated.

Delivery

In pre-eclampsia with mild or moderate hypertension, women may be delivered between 34 and 37 weeks of gestation, depending on maternal and fetal condition, presence of risk factors and availability of neonatal intensive care facilities. If severe pre-eclampsia develops, refractory to treatment or fetal wellbeing delivery may need to be done earlier.

Pre-eclampsia is considered to be severe in case of

1) Severe hypertension with proteinuria **or**
2) Mild / moderate hypertension and proteinuria with one or more of the following signs / symptoms:
   - Severe headache , not responding to medications
   - Visual disturbance (blurring or flashing of light)
   - Severe pain in upper abdomen or vomiting
   - Papillo-oedema
   - Signs of clonus (³ 3 beats)
   - Liver tenderness
   - HELLP syndrome
   - Decrease in platelet count to less than 100 x 109 per litre
   - Abnormal liver enzymes (ALT or ASTrising to above 70 iu/litre).

HELLP syndrome

HELLP Syndrome (haemolysis, elevated liver enzyme, low platelets) is a form of severe pre-eclampsia that is associated with high maternal and perinatal morbidity and mortality and may be present without hypertension or, in some occasions, without proteinuria.

A diagnosis of HELLP syndrome is made after confirmation of haemolysis, either by blood film microscopy showing fragmented red cells or increased serum LDH level. An AST or ALT level of above 70 iu/l is significant while a level more than 150 iu/l is associated with increased morbidity to the mother, though neither of them are independent risk factors for increased maternal morbidity [31]. A low platelet count (less than 100 x 10 ^{6}/ml) supports the diagnosis.

There is some evidence to suggest that the severity of pre-eclampsia differs according to the time of onset. More severe form occurs with the onset of pre-eclampsia prior to 34 weeks of gestation. This form is associated with abnormal uterine artery blood flow, IUGR and adverse maternal and fetal outcomes[32-33].

There may be some difference in the pathophysiology of these two disease types. The early onset disease may be associated with placental abnormalities, while the late onset one is more linked to maternal constitutional factors such as increased BMI[34].

In severe pre-eclampsia, delivery is appropriate anytime beyond 34 weeks of gestation following corticosteroid administration to achieve fetal lung maturity. Delivery before 34 weeks is only indicated in maternal/fetal compromise or hypertension refractory to treatment[35-37]. Prolonging pregnancy at early gestation may improve the perinatal outcome but has to be carefully balanced against maternal wellbeing. If conservative management is planned, ultrasound assessment of fetal growth, amniotic fluid volume and umbilical artery doppler flow should be done at admission, and thereafter, every two weeks. In case of normal ultrasound findings, weekly CTG monitoring should suffice, unless clinically indicated otherwise (for e.g. reduced fetal movement, vaginal loss, abdominal pain or deterioration of maternal condition).

Eclampsia

Generalised tonic-clonic seizures, with or without raised blood pressure and proteinuria, occurring during or after pregnancy with no other identifiable cause is classified as eclampsia. The cause is usually multi-factorial including cerebral vasoconstriction, ischaemia, vasogenic oedema, or other pathology. Although it is more likely to occur in women with severe rather than mild pre-eclampsia, there is no convincing test for predicting the onset of eclampsia. Convulsions may occur antepartum (38-53%), intrapartum (18-36%), or postpartum (11-44%)[38]. Women with a history of previous eclampsia are at increased risk of eclampsia (1-2%) and pre-eclampsia (22-35%) in subsequent pregnancies[39].

Intrapartum Care

During labour, hourly blood pressure monitoring in women with mild or moderate hypertension, and continuously in severe hypertension is ideal. Antenatal hypertensive treatment should be continued, with the aim of maintaining the systolic blood pressure below 150 mm Hg, and the diastolic pressure between 80-100 mmHg. If oral medications fail to control the blood pressure, then intravenous anti-hypertensives are indicated to prevent the known risk of vascular damage due to uncontrolled hypertension.

Hydralazine, a peripheral arteriolar vasodilator, has been widely used as the first-line treatment for acute hypertension in pregnancy, in the past.It is administered as bolus doses (5-10 mg) intravenously, every 20 minutes to a maximum dose of 30 mg, with careful monitoring of blood pressure. The side effects include headache, nausea, and vomiting. Importantly, hydralazine may result in maternal hypotension, which may subsequently cause fetal distress. Preloading with 500 ml of crystalloid fluid before or with the first dose of intravenous hydralazine may avoid this[40]. Labetalol is another antihypertensive that can be given intravenously, either as bolus doses or as an infusion to manage severe hypertension. It is commonly used as the first line drug in many centers in UK. However, it is not suitable for patients with bronchial asthma. Nifedipine may also be used orally to control blood pressure (sublingual administration is not recommended).However, it can interact with magnesium sulphate to produce profound muscle weakness, maternal hypotension and fetal distress[41-43]. Recent evidence suggests labetalol and nifedipine as better alternatives than hydralazine[40]. In all cases, the blood pressure should be monitored closely, along with fetal monitoring, as sudden decrease in maternal blood pressure will reduce the utero-placental blood flow, resulting in fetal distress.

Magnesium sulphate isthe agent of choice for treatment of eclampsia. It is also used in women with severe pre-eclampsia for prophylaxis of eclampsia andis usually commenced once delivery decision is made or in immediate postpartum period. In women with less severe disease the decision will depend on individual case assessment. Evidence shows that magnesium sulphate more than halves the risk of eclamptic seizures[44].It has also been shown to reduce maternal morbidity related to pneumonia, mechanical ventilation and intensive care[45].However, there is little evidence to suggest that it decreases the risk of stillbirth or neonatal death.Magnesium sulphate is usually continued for 24 hours following delivery or 24 hours after the last seizure, whichever is the later, unless there is a clinical reason to do otherwise. This is based on the findings of the Collaborative Eclampsia Trial, 1995. However, recent evidence suggests that magnesium infusion may be stopped earlier (12 hours postpartum), especially when used in conjunction with other clinical parameters[46, 47]. Regular assessment of the urine output, deep tendon reflexes, respiratory rate, oxygen saturation and serum concentration is done as long as magnesium sulphate is continued to avoid toxicity. Features of magnesium toxicity include suppression/loss of patellar reflexes, drowsiness and respiratory depression. Intravenous calcium gluconate is used for reversal of magnesium toxicity.

Fluid restriction is the usual practice, unless there is associated maternal haemorrhage, to reduce the chance of fluid overload and pulmonary oedema. As per NICE guidelines, total fluids should be limited to 80 ml/hour in women with severe pre-eclampsia. Strict intake-output chart should be maintained. The regime of fluid restriction should continue until postpartum diuresis commences.

The mode of delivery should be individualised taking into account the gestation, presentation, cervical favourability for induction of labour and well-being of the fetus. Vaginal delivery is generally preferable but in case of extreme prematurity or fetal compromise, caesarean section is more likely.

Haematological and biochemical monitoring needs to be continued in labour and is dictated by the patient condition and need for analgesia/anaesthesia. For those on magnesium sulphate, bloods must be repeated every 6 hours.

Anaesthetic management

The anaesthetic management in pre-eclamptic patients is important, and should start with a detailed pre-anaesthetic assessment. Appropriate history and physical examination are important. Pre-eclamptic patients are at increased risk of oedema of the pharyngolarynx and assessment of airway is vital[48-49]. Clinical assessment of the cardiopulmonary and fluid status is required, along with laboratory investigations including renal biochemistry and coagulation status.An appropriate understanding of the obstetric interventions such as antihypertensive medications, and magnesium sulphate infusion is required.

Anaesthetic management should include appropriate monitoring, and should include NIBP, pulse oximetry and urine output. Invasive blood pressure monitoring (arterial line) is indicated in patients with poorly controlled blood pressure, or when NIBP is difficult to obtain (e.g. in the obese patients).

Pulmonary oedema is a rare but serious complication of severe pre-eclampsia, which can lead to increased maternal mortality (10%) and perinatal mortality as high as 50%[50]. Central venous pressure monitoring is indicated in patients with pulmonary oedema, poor urine output or when difficulty in fluid management is anticipated in the peripartum period. Pulmonary arterial catheters are rarely needed. Non-invasive monitoring of cardiac output may be required in patients with difficult fluid management or coexisting cardiac problems.

The safety of regional anaesthesia in pre-eclamptic patients is now well established[51]. Lumbar epidural may be used for labour analgesia in women with pre-eclampsia if the mothers opt for it. Early epidural should be considered as it helps to diminish the hypertensive responses to pain. Platelet count >75x10^9/L in the absence of other coagulation abnormalities is not associated with increased likelihood of regional anaesthetic complications in the setting of pre-eclampsia[52]. The presence of a functioning epidural catheter allows the epidural block to be titrated for LSCS if indicated. If central neuraxial block is contraindicated, then intravenous opioids may be used for labour analgesia[53-54]. Few studies have mentioned the successful use of remifentanil PCA in these patients[55].Regional blockade is currently the preferred mode of anaesthesia for caesarean section. It has long been argued that while titrated epidural blocks are safe, single shot spinal or CSE techniques may produce profound hypotension. However, multiple studies have demonstrated the safety of spinal and CSE in pre-eclamptic patients for LSCS with no adverse effects on mother or fetus[56-58]. In fact the incidence of hypotension in pre-eclamptic patients following regional anaesthesia is less than that in healthy patients, and is successfully managed by intravenous boluses of ephedrine or phenylephrine[59-60].Doses of local anaesthetics in regional anaesthesia remain the same in pre-eclamptic patients as in normal healthy parturients.

Though regional anaesthesia is preferred for LSCS, a general anaesthesia may still be needed if regional anaesthesia is contraindicated (e.g. coagulopathy as in HELLP syndrome), and in emergency situations where the baby has to be delivered as early as possible. General anaesthesia increases the risk of hypertension during induction and emergence, loss of airway due to pharyngolaryngeal oedema, aspiration and transient neonatal depression. Extreme care is to be undertaken to obtund the hypertensive response during induction-intubation, as this has been a significant past cause of maternal mortality[61]. Several agents (alfentanil, fentanyl, remifentanil, magnesium sulphate, intravenous lignocaine and esmolol) have been suggested for induction, and clinicians should use familiar ones. All opioids rapidly cross the placenta and increase the risk of neonatal depression, and appropriate facilities for neonatal resuscitation must be available. Remifentanil has the advantage as it is rapidly metabolised by the neonate, and any respiratory depression is usually brief[62- 63].Maintenance of anaesthesia is done by inhalational anaesthetic agents. Isoflurane is considered to be a good choice, because of its vasodilating properties. Vigilance is also required during emergence from anaesthesia, to prevent hypertension, as well as aspiration.

Anaesthetists must also be aware of the potential drug interactions of agents commonly used in pre-eclampsia. Magnesium sulphate and calcium channel blockers may potentiate the action of muscle relaxants and appropriate monitoring is vital.

Post delivery analgesia

This is maintained by simple analgesics like paracetamol. Non-steroidal anti-inflammatory agents have been used; however, caution must be exercised due to their effect on cyclo-oxygenase pathway, especially those with renal insufficiency and coagulopathy. A few case reports of significant increase in blood pressure in postpartum women have been reported following their use[64]. Patient controlled analgesia with opioids has been used widely, and is considered to be a safe option.

Use of oxytocic agents

Syntocinon is the drug of choice. Ergometrine should be avoided because of its propensity to cause hypertension. Synthetic prostaglandins such as Carboprost (15 methyl PGF_2 alpha) may be given with caution after considering the risk-benefit ratio, especially because it can aggravate hypertension.

Use of thromboprophylaxis

This should be considered in all patients with pre-eclampsia.

Table 2: Management strategies for chronic hypertension and gestational hypertension

	Preconception	Antenatal	Delivery	Postpartum	Further follow-up
Chronic Hypertension	Optimise antihypertensives, change ACE inhibitors, diet and lifestyle modification	Continue treatment to maintain BP <150/100. Offer uterine artery dopplers to detect risk of developing pre-eclampsia/IUGR	At 37 weeks, if BP is controlled.	Aim to maintain BP <140/90 with antihypertensives	Medical review at 6-8 weeks
Gestational Hypertension	Assessment of risk factors	Hospital admission if severe hypertension. Antihypertensive if BP > 150/100. Test for proteinuria at each visit, blood tests as indicated	At 37 weeks, if BP <160/110, with/without antihypertensives	Titrate antihypertensives to keep BP <140/90	Medical review at 6-8 weeks, or earlier if need to continue antihypertensives
Pre-eclampsia	Assessment of risk factors.	Hospital admission at diagnosis. Antihypertensives to be started if BP>150/100. Regular blood investigations (2-3/week)	Delivery between 34-37 weeks, depending on maternal/ foetal condition	Initial monitoring as inpatient, to be discharged to the community when BP <149/99 with/without treatment and blood results are stable	Medical review at 2 weeks, if continuing antihypertensives. Otherwise at 6-8 weeks

Postpartum Care

increasing the blood pressure. This fluid shift also increases the risk of pulmonary oedema, cerebral oedema and eclampsia.

Most of the existing guidance focuses on management of blood pressure and its associated problems in the antenatal and intrapartum period but the postpartum phase can often be poorly looked after [65]. Regular blood pressure monitoring at an interval of 4-6 hours should be done as an inpatient initially and blood platelet count, transaminases and creatinine should be measured to note any changing trends. The aim is to maintain blood pressure <160/110mmHg, thereby preventing cerebral injury from occurring. In order to achieve this, beta-blockers, calcium-channel blockers and ACE inhibitors can be used in a stepwise manner. Use of methyldopa is usually avoided as it has the potential to cause depression and psychosis in postpartum period. Women are discharged to the community care if they are asymptomatic, blood pressure, with or without treatment, is 149/99 mmHg or lower and blood test results are stable or improving. Blood pressure isthen checked daily/alternate days in the community till 2 weeks postpartum. Antihypertensives should continue till blood pressure falls below 130/80 mm of Hg and the dose adjustments need to be made by the GP. If blood pressure becomes uncontrolled, then women would require urgent referral to the hospital.

In most cases, the hypertension and/or proteinuria resolve within six weeks postpartum. Any women whohad pre-eclampsia complicating their pregnancy, needs to have blood pressure and urine protein checked at 6-8 week postnatal visit at the GP surgery. If still requiring antihypertensive treatment at that stage or persistent proteinuria further assessment is warranted to find out cause for raised blood pressure if any and also identify and advise on risk factors for cardiovascular disease and lifestyle changes.

Following childbirth, mobilisation of the extravascular fluid occurs increasing the intravascular volume, and consequently

For all these women preconception counselling should be offered for subsequent pregnancies especially if risk factors are identified so that potentially preventative strategies can be initiated.

Table 2 outlines briefly the management strategies for mothers with chronic hypertension and gestational hypertension. However, a detailed discussion is outside the scope of this article.

Competing Interests
None Declared
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Review Article

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Diagnosis and Management of Stable COPD

Katerina M Achilleos and Duncan J Powrie

Chronic obstructive pulmonary disease (COPD) is a debilitating condition resulting in significant morbidity and mortality. It is the fifth leading cause of death in the UK [1], estimated to be the third by 2020 [2].

Definition:

COPD is a preventable and treatable disease with some extra-pulmonary effects that may contribute to the severity in individual patients Its pulmonary component is characterised by airflow limitation that is progressive and not fully reversible. There is an abnormal inflammatory response of the lung to noxious gases and particles, most commonly cigarette smoke [3].

Airflow obstruction is defined as post-bronchodilator FEV_1/FVC ratio (where FEV_1 is the forced expiratory volume in one second and FVC is the forced vital capacity) of less than 0.7 If FEV_1 is ≥ 80% predicted, a diagnosis of COPD should only be made in the presence of respiratory symptoms [4].

Incidence/ Prevalence:

Within the UK it is estimated that 3 million people are affected with COPD [4]. However, only 900,000 are diagnosed [4]An estimated two million people who have COPD remain undiagnosed [4].

Causes:

90% of cases are smoking related [4], particularly those with >20 pack year smoking histories [5]. Environmental and occupational factors can also play a role, including exposure to biomass fuels such as: coal, straw, animal dung, wood and crop residue which are used to cook in some countries and heat poorly ventilated homes COPD occurs in 10-20% of smokers, suggesting there is an element of genetic susceptibility [2-3, 5].

Diagnosis:

To make a diagnosis of COPD an obstructive deficit must be demonstrated on spirometry in patients over the age of 35 years with risk factors (mainly smoking) and signs and symptoms of the disease [4].

Signs and Symptoms:

1. Progressive dyspnoea on exertion
2. Chronic cough
3. Chronic sputum production
4. Wheeze
5. Frequency of exacerbations – particularly during winter months [4]
6. Functional status – bearing in mind gradual progression of disability, effort intolerance and fatigue.
7. Features suggestive of Cor pulmonale [5]:
   a) Peripheral oedema
   b) Elevated jugular venous pressure
   c) Hepatomegaly
   d) Right ventricular heave
   e) Tricuspid regurgitation

Investigations/ Tests to consider:

1. Post-bronchodilator Spirometry – essential in confirming the diagnosis of COPD.
   a) Demonstrating an obstructive picture.
   b) FEV1 is used to assess the progression and severity of COPD, but correlates poorly with the degree of dyspnoea [3-6]. (Table 1)

2. Pulmonary functions tests – Markers suggesting the presence of emphysema include:
   a) Reduced TLCO and KCO due to a reduced surface area for gaseous exchange [5].
   b) Raised Total lung capacity, residual volume and functional residual capacity due to air trapping [5].

3. Chest radiograph – Is not required for the diagnosis, but is recommended to exclude other conditions such as interstitial lung disease, pleural effusions or pneumothorax. It may demonstrate features of the condition, such as [3, 5]:
   a) Hyperinflated lung fields
   b) Flattened diaphragms
   c) Bullous changes, particularly at the apices

4. BODE index prognostic indicator – This is grading system shown to be better than FEV1 at predicting the risk of hospitalisation and death in patients with COPD. Patients are scored between 0 and 10, with higher scores having an increased risk of death. It encompasses [3, 5-7]: (Table 2)
   a) BMI
   b) Airflow Obstruction – taking into account the FEV1
   c) Dyspnoea – in accordance with the Medical Research Council (MRC) scale 5.
   d) Exercise capacity – measured by the distance walked in 6 minutes. (Table 3)

Table 1. Severity of airflow obstruction [4]

Stage	Severity post-bronchodilator	FEV1 (%) Predicted	Comments
1	Mild	≥ 80%	Only diagnosed in the presence of symptoms
2	Moderate	50- 79%	Managed within the community
3	Severe	30-49%	TLCO usually Low Hospitalization may be needed only with exacerbations
4	Very Severe	<30%	Or FEV1 <50% with respiratory failure

Table 2. BODE Index [3, 5-8]

	1	2	3	
FEV1 Predicted (%)	≥ 65	50- 64	36- 49	≤ 35
Distance walked in 6 minutes (meters)	≥ 350	250- 349	150- 249	≤ 149
MRC dyspnoea scale	0-1	2	3	4
BMI	≥ 21	≤ 21		

Table 3. Medical research council (MRC) Dyspnoea scale [5, 8]

1	Dyspnoeic only on strenuous activity
2	Dyspnoeic on walking up a slight incline or when hurrying
3	Walks slower than contemporaries on the flat, or has to stop for breath, or has to stop for breath when walking at own pace
4	Stops for breath on walking 100m or after a few minutes on walking on the flat
5	Breathless on minimal exertion e.g. dressing/ undressing. To breathless to leave the house

Differential Diagnosis:

1. Asthma – the most important differential diagnosis to consider.
   a) This is steroid and bronchodilator responsive
   b) Indicative of reversible airway obstruction.
   c) It is not associated with smoking.
   d) Patients with asthma may exhibit [3, 9]: chronic non-productive cough, variability in breathlessness, diurnal /day-to-day variation, nocturnal wheeze and dyspnoea
   e) However both conditions may coexist creating diagnostic uncertainty.
2. Alpha1 antitrypsin deficiency is an autosomal dominant condition associated with an increased risk of developing emphysema at an early age [3, 5, 9.]
   a) It can occur in non-smokers
   b) Can be asymptomatic and thus under-diagnosed with an estimated 1 in 2000-5000 individuals being affected [5].
   c) The disease is worse in smokers
   d) COPD can develop in patients < 35years of age
   e) It is associated with liver cirrhosis.
   f) All patients with COPD should be screened.
   g) Emphasis should be made to avoid smoking, including passive smoking.
3. Other conditions to consider include:
   a) Bronchiectasis
   b) Interstitial lung disease
   c) Cardiac failure.

Treatment:

Goals of management include:

1. Early and accurate diagnosis
2. Improve symptoms and quality of life
3. Reduce the number of exacerbations
4. Improve mortality

Non-pharmacological management:

1. **Smoking cessation** – an accurate smoking history should be obtained, including the number of pack years smoked. All current smokers with COPD should be encouraged to stop at every opportunity, and offered smoking cessation advice. Advising the patient alone will help a certain proportion to stop, whilst referral to smoking cessation services has been shown to further increase in quit rates. There are a range of nicotine and other pharmacological therapies available such as Bupropion (Zyban®) and Varenicline (Champix®) [3-4, 7, 8.]
2. **Vaccinations** – A once off Pneumococcal and annual Influenza vaccine should be offered.
3. **Pulmonary rehabilitation** – Should be offered to patients who have had a recent exacerbation requiring hospitalisation and those that have an MRC score of ≥ 3, but are still able to mobilise and thus have the potential for further rehabilitation. It is not suitable for those patients that are immobile or limited in their mobility due to symptoms of unstable angina or a recent cardiac event. Benefits are seen in terms of reduced hospital admission, improved quality of life and exercise tolerance Commitment to the programme should be relayed to the patient, and each programme should be tailored to their individual needs. This usually includes [3-5]:

a) Disease education – which can improve the ability to manage their illness.
b) Exercise – tailored programmes to prevent de-conditioning and improve functional exercise capacity, dyspnoea and quality of life [4]. This includes strength and endurance training of upper limbs and respiratory muscles Benefits may be seen even after 6 months.
c) Physiotherapy – to teach active cycle breathing techniques or to use positive expiratory pressure masks in patients with excessive sputum production.
d) Nutritional support – in the form of supplementation or dietician advice in patients with a suboptimal BMI. A low BMI is associated with increased mortality as it is associated with poor exercise capacity, reduced diaphragmatic mass and impaired pulmonary status. Alternatively, weight loss is recommended in patients who are in the obese range.
e) Psychological – Assessment for support at home, introduction of patients to day centres, assessing for features of depression and anxiety, and aiding in the obtainment of a car disability badges may require referral to occupational therapy and social services.

4. **Travel advice** – Patients who are planning air travel and have FEV1 <50%, Sa02 < 93%, or are on long term oxygen therapy (LTOT) should undergo formal assessment - 4Patients with bullous disease should be informed that they are at increased risk of pneumothorax during high altitude flights [4].

Pharmacological management:

1. **Bronchodilators** – Provide long term benefit in reducing dyspnoea. This is not reflected in improvements in FEV_1as it may not show reversibility [4].

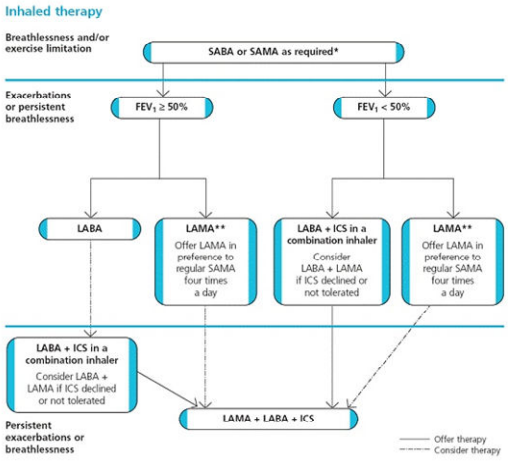
a) Start with an inhaled SABA (short-acting beta2-agonist) or a SAMA (short-acting muscarinic antagonist) on an as required basis for symptomatic relief. If symptoms remain despite regular SABA therapy (i.e. four times a day), then treatment will need to be stepped up.
b) If symptoms persist or if the patient is having recurrent exacerbations add in a LABA (long-acting beta2 agonist) or a LAMA (long acting muscarinic antagonist).
c) If symptoms continue, add in a LAMA if already on a LABA (or vice versa).
d) If FEV1 <50% add in an inhaled corticosteroid (ICS). This can be offered as a combination inhaler.

Inhaled therapy should offer sufficient bronchodilator response. A spacer can be used for those with poor technique. Nebulisers are reserved for patients who demonstrate respiratory distress despite maximal inhaled therapy, and for those that show an improvement in symptoms or exertional capacity [4].

2. **Corticosteroids** – A short course of oral steroids may be used during exacerbations. A maintenance course however is not recommended Any patients on long term steroids should be weaned off.

3. **Mucolytic agents** – May be considered in patients with a chronic cough who have difficulty expectorating. They should only be continued if symptomatic benefit is evident, otherwise they can be stopped. There is no evidence to show that they reduce the exacerbation frequency.

Diagram 1: Summary of step-by-step management [4]



4. **Theophylline** – Should only be offered in people that are unable to use inhaled therapy or after trials of SA and LA bronchodilators [4]. The same generic brand should be prescribed as individual brands will have different efficacy. It is usually used as an adjunct to $beta_2$-agonists and muscarinic antagonists. Interactions with macrolides and fluroquinolones and other drugs are also common, and as such the theophylline dose should be reduced if interactions are known. Caution should be taken in prescribing theophylline in the polypharmacy patient [3, 5]. Little evidence has been shown to support theophylline usage in COPD (compared to asthma), however it is used for its anti-inflammatory effects As such levels are only performed if toxicity is suspected and should not be adjusted if in the sub-therapeutic range.

5. **Oxygen therapy** – Patients should be assessed for long-term oxygen therapy (LTOT) if they exhibit [4]:

a) Severe airflow obstruction
b) Features of Cor pulmonale
c) Hypoxaemia (Sa02 ≤ 90%)
d) Cyanosis
e) Polycythaemia

Patients with stable COPD who are receiving maximum medical therapy are assessed by measuring arterial blood gases

taken on two separate occasions at least 3 weeks apart. To meet the criteria patients must have [4]:

1. A Pa02 < 7.3 kPa when stable, or
2. A Pa02 >7.3 but < 8.0 kPa when stable and:
   a) Pulmonary hypertension or
   b) Peripheral oedema or
   c) Secondary polycythaemia or
   d) Nocturnal hypoxaemia

LTOT should be used for a minimum of 15L per day, including during sleep [3-4].

Patients who continue to smoke should be made aware of the serious risk of facial injuries due to the highly flammable nature of oxygen.

When to refer:

Referrals for specialist advice or specialist investigations may be appropriate at any stage of the disease.

Other possible reasons for referral 4

* Diagnostic uncertainty	* Suspected severe COPD
* Onset of Cor pulmonale	* Rapid decline in FEV1
* Assessment for LTOT, home nebulisers or oral corticosteroid therapy	* Symptoms that do not correlate to lung function deficit
* Pulmonary rehabilitation assessment	* Frequent infective exacerbations
* Family history of alpha-1-antitrypsin deficiency	* Haemoptysis
* Onset of symptoms < 40 years	* Bullous lung disease
* Assessment for lung volume reduction surgery/ lung transplantation	* Dysfunctional breathing

Follow-up:

Patients with stable mild-moderate COPD should be reviewed by their general practitioner at least once a year and those with severe COPD twice yearly.

At each visit [4]:

1. An opportunity should be taken to ask about their current smoking status and the desire to stop.
2. Assessment of adequate control of symptom: dyspnoea, exercise tolerance and the estimated number of exacerbations per year.
3. Assessment of inhaler technique.
4. To assess the effects/side effects of each drug treatment.
5. The need for pulmonary rehabilitation.

For those patients with very severe airflow obstruction (FEV_1 < 30%), the above still remains, in addition to the assessment of [4]:

1. Features of Cor pulmonale
2. Nutritional status
3. The need for LTOT
4. Signs of depression
5. The need for occupational therapy and social services input
6. Referral to specialist and their services
7. Measurements of:
   a. FEV1 and FVC
   b. BMI
   c. MRC dyspnoea scale
   d. Sa02 via pulse oximetry

Those patients requiring long term non-invasive ventilation will be reviewed by a specialist on a regular basis.

Patient Information:

* www.patient.co.uk/health/Chronic-Obstructive-Pulmonary-Disease.htm
* www.lunguk.org/you-and-your-lungs/conditions-and-diseases/copd
* http://smokefree.nhs.uk/ways-to-quit

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Case Report

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Use of TAP block in a patient with poor CPEX testing during major abdominal surgery

AM Sherratt, H Wallace, A Banerjee, S Singh and J Hunter

Abstract

The transversus abdominis plane (TAP) block provides anaesthesia to the anterior abdominal wall. It can be performed using landmark techniques via the Triangle of Petit or using ultrasound guidance. It is an effective tool in postoperative pain management for patients undergoing anterior abdominal wall surgery. It produces a significant reduction in postoperative pain scores, thereby reducing opioid consumption and the incidence of associated side-effects.

Cardiopulmonary exercise (CPEX) testing provides a non-invasive method of assessing combined pulmonary, cardiac and circulatory function. It quantifies patient's functional ability to respond to the increased metabolic demands of major surgery and is commonly used to assess mortality risk preoperatively. The use of CPEX testing to predict postoperative complications is not fully defined. We report the case of a patient with poor functional capacity and a CPEX test indicating high risk, who underwent uneventful intra-abdominal surgery with the use of bilateral TAP blocks.

Case report

A 78 year old man was admitted for re-fashioning of a prolapsing colostomy. Nine months previously he had undergone a juxtarenal aortic aneurysm repair complicated by ischaemic colitis, for which he had a sigmoid colectomy and a further laparotomy for refashioning of the stoma.

His past medical history consisted of anaemia, stable angina, superficial bladder cancer, Stage 4 chronic kidney disease, type 2 diabetes mellitus and osteoarthritis. He weighed 77 kg and his exercise tolerance was 100 yards, with the aid of a stick. His medications included doxazosin, quinine sulphate, perindopril, simvastatin, ferrous sulphate, isosorbide mononitrate and aspirin.

On examination, he was apyrexial with a blood pressure of 170/70 mm Hg, a heart rate of 65 bpm, a respiratory rate of 14 bpm and $Sa0_2$ of 98% on room air. Serum laboratory tests showed a prothrombin time of 13.4 sec (normal range 9.0 – 13.0 sec), haemoglobin 10.2 g/dL (13.0 – 16.7 g/dl), platelets 131 $x10^9$/L (150 – 400 $x10^9$/L), sodium 139 mmol/L, potassium 4.2 mmol/L, urea 15.7 mmol/L (2.5 – 7.0 mmol/L), creatinine 196 umol/L (50 – 130 umol/L) and eGFR 29 ml/min/1.73m^2 (>60ml/min/1.73m^2).

His preoperative pulmonary function tests showed an FVC of 2.78L (93.8% predicted), a reduced FEV1 of 1.66L (75.2% predicted) and FEV/FVC of 59.87%. His ECG showed normal sinus rhythm. A CPEX test taken 12 months previously showed moderately reduced peak aerobic capacity, with a peak $V0_2$ of 11 ml/kg/min and an anaerobic threshold (AT) of 7 ml/kg/min.

In the anaesthetic room, the patient was connected to standard monitoring in accordance with AAGBI Guidelines and venous access secured with an 18 g biovalve cannula. Following pre-oxygenation, anaesthesia was induced using fentanyl 200 mcg, midazolam 2 mg, propofol 120 mg and atracurium 50 mg. Tracheal-intubation was achieved (grade 1 view) using an 8.0 mm cuffed endotracheal tube (lo-contour). A TAP block was administered following induction using ultrasound guidance (Sonosite 'micromax'). A 50 mm insulated Stimi-Plex needle was used to inject a total of 40 ml levobupivacaine 0.375% bilaterally. Anaesthesia was maintained using a mixture of air, oxygen and sevoflurane (1.3 – 2.3 ETAA range). Intravenous (IV) paracetamol 1 g was given intraoperatively. The prolapsing colon was dissected through a circumstomal incision. A 10 cm length of colon was resected after ligation and division of the mesenteric vessels. The new end colostomy was fashioned with interrupted mucocutaneous sutures. Blood loss was minimal and there were no intraoperative complications. The duration of surgery was 1.5 hrs.

The patient spent 30 minutes in the postoperative recovery unit. He was awake, orientated and pain free throughout this period and clinical observations were stable. The patient remained pain-free on the ward and did not require any postoperative opioids. He was medically fit for discharge the following day.

Discussion

There are no previous case reports to our knowledge describing the use of TAP blocks in a patient with such poor CPEX testing preoperatively (AT = 7 ml/kg/min). CPEX testing has been shown to be an independent predictor of morbidity, mortality

and length of hospital stay after major abdominal surgery.[1] The anaerobic threshold marks the onset of anaerobic metabolism as a result of inadequate oxygen delivery. It is not affected by patient effort and therefore provides a reliable patient specific measurement of functional capacity.[2] An AT of at least 11 ml/kg/min is recommended to safely undertake major surgery.[2] A combination of an AT of <11 ml/kg/min with ECG evidence of myocardial ischaemia is associated with high mortality and poor outcome. [3]One study showed a mortality of 42% in those with ischaemic heart disease (IHD) and an AT <11 ml/kg/min, compared with just 4% in those with no IHD.[4]

Postoperative morbidity and mortality most often occurs in patients with pre-existing cardiorespiratory disease and a reduced functional capacity, due to their inability to withstand the additional physiological demands placed upon them by major surgery. Many of these patients develop features of organ hypoperfusion due to poor cardiorespiratory reserve.[5]

Our patient had an AT of 7 ml/kg/min and poor respiratory reserve (exercise tolerance of 100 yards, FEV/FVC 59.87% of predicted) but underwent uneventful intra-abdominal surgery with a good recovery and short length of hospital stay. Contributing factors may have been the anaesthetic technique used, as well as the surgical approach via a parastomal incision. Good intraoperative and postoperative control of cardiovascular parameters, temperature and pain are well known to reduce the surgical stress response and postoperative morbidity, and to improve postoperative outcome.[6]Our patient was cardiovascularly stable throughout the perioperative period. His pain was well controlled with no opioid requirements due to the use of bilateral TAP blocks, and this probably contributed to his uneventful recovery, with no critical care requirement.

CPEX testing is not universally accepted as a useful preoperative assessment tool. In studies assessing it as a reliable predictor of outcome, there is heterogeneity in the degree of clinician blinding used. Blinding was used in some studies,[1] whilst in other instances, clinicians were aware of the CPEX results and changed their management accordingly. This obscures the true relationship between patient outcome and CPEX-derived measures of risk.[7]

TAP blocks were first described in 2001[8] and have been shown to significantly reduce postoperative morphine consumption following abdominal surgery by up to 70%. They reduce pain scores at rest and during mobilisation in the early postoperative period (0-6 hours), and in the first 24 hours.[9] The reduced requirement for morphine also leads to a reduction in postoperative nausea, vomiting and sedation.[9] It may be possible that the ultrasound guided TAP block confers advantages in procedures with moderate surgical trauma to minimize pain and reduce opioid usage, thereby promoting faster recovery and discharge.[8] TAP blocks were the chosen method of analgesia in our patient as they would elicit the least physiological disturbance, but would provide good postoperative analgesia, without opioid-related side effects. This was particularly beneficial, as his pre-existing renal impairment put him at increased risk of opiate toxicity. TAP blocks eliminate somatic pain relating to the surgical incision but do not treat visceral pain. However, our patient tolerated a 10 cm bowel resection with bilateral TAP blocks and intravenous paracetamol. A similar effect has been observed in other studies but the mechanisms behind it are unclear. One theory is that there is an analgesic effect due to high systemic levels of local anaesthetic.[10]

The use of CPEX testing to determine fitness for surgery should be interpreted with caution as newer anaesthetic and surgical techniques develop. Our patient had IHD and an AT which showed a significantly increased level of risk. However, a combination of regional anaesthesia and a cardio stable general anaesthetic with minimally invasive surgery, allowed a rapid and uneventful recovery with no opioid requirements and a short length of hospital stay.

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Case Report

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Painful legs and moving toes – Case report and Review of literature

Roy Liu, Mohammed Moizuddin and Serena Hung

ABSTRACT

Objective: Painful legs and moving toes (PLMT) is a syndrome consisting of pain in the lower legs with involuntary movements of the toes or feet. Its incidence and prevalence remain largely unknown since it is still a relatively rare disorder. We are reporting a case of PLMT along with the first review of literature on all previously reported cases and a discussion on its clinical management.

Methods: A review of published literature on PLMT was done using MEDLINE and PubMed databases. Searches were conducted to find articles from 1971 – 2010. Medical subject headings used to search the databases included PLMT with subheadings of painful legs/moving toes, electromyography, polysomnography, as well as keyword search using "PLMT". Single author reviewed titles and abstracts of potentially relevant articles.

Results: We reviewed approximately 19 PLMT articles that have been published to date, with a total of 72 patients: 30.5% males and 69.5% females (median age 55 & 64 yrs, respectively). The most common predisposing conditions were neuropathy and radiculopathy. Numerous treatments including antiepileptics, benzodiazepines, antispasmodic agents, and antidepressants have been tried with little success. GABAergic agents such as gabapentin and pregabalin were the most effective in attenuating the pain and the movements, possibly via both central and peripheral mechanisms.

Conclusion: Physicians should be aware of this rare debilitating condition. Though much progress has been made in elucidating its etiology, the exact mechanism still remains a mystery. It is important to consider PLMT in a patient with painful legs and/or restless leg syndrome without any significant history of neurological disease or trauma. Diagnosis is essentially clinical and treatment is complex, which includes different combinations of medications and invasive techniques that generally produce a poor outcome.

KEYWORDS

Painful legs, Moving toes, GABA agonists, Peripheral Neuropathy

Introduction

First described in 1971 by Spillane et al.[1], painful legs and moving toes (PLMT) is a syndrome consisting of pain in lower legs with involuntary movements of the toes or feet. Pain varies from moderate discomfort to diffuse and deep and usually precedes movements by days to years. The movements themselves are often irregular and range from flexion/extension, abduction/adduction to clawing/straightening and fanning/ circular movements of the toes.[1,2] This syndrome may affect one leg or spread to involve both legs.[3]

PMLT incidence and prevalence remain largely unknown since it is still a relatively rare disorder worldwide. Age of onset is between the second and seventh decades of life. It has been postulated that lesions of the peripheral or central nervous system after nerve or tissue damage might lead to impulse generation that subsequently causes the symptoms seen in PLMT.[4] We report a case of PMLT that presented to our Neurology Movement Disorder Clinic along with a discussion on the pathophysiology, differential diagnosis and clinical management of this rare debilitating condition.

Case report

63 year old, morbidly obese (BMI 41.7) Caucasian male patient with past medical history of stroke 10 years ago, on long term anticoagulation, hypertension, type II controlled diabetes mellitus, asbestos exposure, bilateral hip and knee osteoarthritis, left total knee replacement 2 years ago, and non-traumatic ruptured Achilles tendon; presented with complaints of involuntary movements in both legs over the last 8-10 years.

He had unprovoked flexion and extension of the toes along with feet movement at all times with no diurnal variation. He admitted to having a constant severe pain described as 'twisting a rubber band' with 10/10 intensity that radiated up to his calf accompanied by numbness and dorsal swelling of both feet for many months. He claimed to have partial relief whilst walking but had difficulty walking without a cane as he '"could not balance with constantly moving [his] feet"'. Tylenol 500mg as required and amitriptyline 20mg at night prescribed by his primary care physician provided no relief. He also has a history of snoring, daytime fatigue, and non-restorative sleep with frequent nocturnal awakenings due to bilateral feet pain. He recalled having a stroke with transient confusion and focal hand weakness along with visual problems about 10 years previously. All laboratory and radiological investigations were negative and he recovered fully. He had previously served with the US armed forces and had been exposed to 'Agent Orange' in Vietnam.

He had no medical allergies and his current medications include amitriptyline 25mg at night, hydrochlorothiazide 25mg once daily, lisinopril 10mg once daily, loradatine 10mg once daily, metoprolol tartrate 20mg twice daily, simvastatin 20mg once

daily, vitamin B complex one tablet once daily and warfarin once daily. He denied any history of alcohol, tobacco, or recreational drug abuse in the past. His mother had a history of hypertension and chronic low back pain; no members of his family had any neurological or movement disorders.

Physical examination revealed an alert, awake, and well oriented male with bilateral lower extremity varicose veins. He was observed to have semi-rhythmic flexion-extension and occasionally abduction movements of the phalanges, especially in the great toes. There was a profound decrease in vibration sense below both knees and it was almost absent on both feet, decreased reflexes in both feet, and absent proprioception in the phalangeal joints. He was also observed to have decreased pinprick and monofilament sensation in both legs below the knee. Bilateral ankle reflexes were diminished with negative Babinski sign. Both lower extremity dorsalis pedis and posterior tibial pulsations were palpable. He did not have any cerebellar signs. He did have pitting oedema up to his shins in both lower extremities, extending from his feet to upper one third of the legs. There were no abnormalities noted on the bilateral lower extremity EMG and there was no electrodiagnostic evidence of large-fiber neuropathy.

He was diagnosed with painful legs and moving toes syndrome and started on a trial of gabapentin 300mg at night. He was advised to increase it to 1200mg and to continue taking his amitriptyline 25mg at night. Scheduled MRI of the brain could not be done due to his morbid obesity. He was arranged follow up in three months in the clinic.

Methods

A review of published literature on PLMT was done using MEDLINE and PubMed databases. Searches were conducted to find articles from 1971 – 2010. Medical subject headings used to search the databases included PLMT with subheadings of Movement disorder, Electromyography, and Polysomnography as well as keyword search using 'PLMT'. Single author reviewed titles and abstracts of potentially relevant articles.

Review of current literature

We reviewed approximately 19 PLMT articles that have been published to date with a total of 72 patients: 30.5% males, 69.5% females (median age 55 & 64 years, respectively). Clinical presentations in the majority of the cases were burning pain in lower extremities and involuntary movements of the toes. The most common predisposing conditions were neuropathy and radiculopathy (see Table 1).

In 1981 Schott GD et al reported that in 3 PLMT patients the EMG revealed evidence of denervation in the affected muscles. Montagna et al of the University of Bologna, Italy reported 3 cases of PLMT that exhibited evidence of peripheral neuropathy on EMG. Polysomnography (PSG) studies on these patients showed reduced movements during sleep with increase in slow wave or rapid eye movement sleep.[5] This suggested the movements could have arisen centrally.

Guimaraes et al of the Universidade Nova Lisboa, Portugal reported one patient with a history of Hashimoto's disease whose lower extremity EMG showed spontaneous arrhythmic bursts of the affected muscles during wakefulness which disappeared during sleep[6]. Both suggested the movements could have arisen centrally.

Alvarez et al of the Mayo Clinic described 14 cases of PLMT in 2008 in which burning pain often preceded the movements. PSG studies confirmed these movements would also persist in light stages of sleep which pointed to a central origin.[7] Eisa et al of Yale University School of Medicine, Connecticut described 2 cases of PLMT in which one patient had a past history of lumbosacral root injury and the other systemic lupus erythematosus with peripheral neuropathy on EMG.[8] Interestingly, in the latter patient her pain occurred years after the onset of involuntary toe movements.[8]

Discussion

Spinal cord and cauda equina diseases, neuropathies, radiculopathies, drugs and other systemic diseases are the main cause of this syndrome although many cases are still idiopathic. The most common predisposing conditions were neuropathy (i.e. polyneuropathy from alcoholism, hypertrophic mononeuritis, or tarsal tunnel syndrome) and radiculopathy.[7] Other etiologies include nerve root lesions, peripheral nerve trauma, spinal ganglia lesions, cauda equina lesion, Wilson's disease, herpes zoster myelitis, HIV, neuroleptics, and chemotherapeutic agents.[9-19]

The involuntary movements appeared bilaterally in the toes in our patient, which suggests that central reorganization (especially in the spinal level) is the cause of PLMT. EMG and nerve conduction studies have proven helpful in demonstrating spontaneous arrhythmic bursts of affected muscles and underlying neuropathy in some patients. Although the exact mechanism remains elusive, it has been proposed that impulses generated in lesioned peripheral nerve, posterior nerve root/ganglion, or afferent fibers pass into the spinal cord - some to higher areas to cause pain, while others into the local interneuron and motor neurons to generate involuntary movements of the toes.[5]

In patients with clinical or electrophysiological evidence of peripheral nerve or root problem, these lesions can initiate or even alter afferent input to the spinal cord and cause subsequent central and efferent motor reorganization, which may explain the limited success these patients had with nerve blocks or lumbar sympathetic blockade.[2] Similarly, some have suggested that even though the radiation of pain following local trauma seemed to resemble causalgia,[20] there was a lack of hyperpathia and changes in the soft tissue, bones, and blood vessels as well

Table 1 - Painful Legs & Moving Toes Syndrome ~ Review of Literature (1971- 2010)

Author	Year	Sex/Subjects	Subject age	# of cases	Clinical presentation
Spillane et al	1971	M (4) F (2)	51, 52, 52, 53 66, 68	6	Burning/throbbing LE pain followed by writhing/clawing and flexion/extension movements of the toes
Dressler et al	1994	M (4) F (16)	28, 36, 54, 73 28-76	20	Pain in LE followed by involuntary flexion/extension and abducion/adduction of the toes
Shime et al	1998	F (1)	63	1	Involuntary flexion/extension of the toes bilaterally and aching/crampy pain in both feet
Schott et al	1981	M (1) F (4)	66 56, 57, 69, 77	5	Crushing pain in both feet followed by involuntary writhing and flexion/extension of the toes; burning pain in foot followed by writhing toe movements
Montagna et al	1983	M (1) F (2)	57 74, 76	3	Burning pain in one or both LE followed by involuntary flexion/extension, abduction/adduction, and fanning/clawing of the toes
Shime et al	1998	F (1)	63	1	Involuntary flexion/extension of the toes bilaterally and aching/crampy pain in both feet
Villarejo et al	2004	M (1)	66	1	Paresthesias/burning pain in both feet followed by involuntary flexion/extension and abduction/adduction of the toes
Aizawa et al	2007	F (1)	73	1	Tingling pain in both feet followed by involuntary abduction/adduction of the toes
Guimaraes et al	2007	M (1)	60	1	Wringing-like pain in in L foot and R leg followed by flexion/extension and abduction/adduction of the toes
Eisa et al	2008	M (1) F (1)	62 76	2	Burning pain in bilateral LE followed by semirhythmic flexsion/extension of the toes
Alvarez et al	2008	M (6) F (8)	25-84 (mean 69)	14	Burning pain of LE followed by involuntary flexion/extension, abduction/adduction, fanning, or clawing of the toes
Tan et al	1996	F (1)	57	1	Severe burning pain in both LE followed by involuntary flexion/extension and abduction of the toes
Dressler et al	1994	M (4) F (16)	28, 36, 54, 73 28-76	20	Pain in LE followed by involuntary flexion/extension and abducion/adduction of the toes
Yoon et al	2001	F (1)	56	1	Burning pain in R foot with flexion and lateral deviation of the toes
Miyakawa et al	2010	M (1) F (1)	36 26	2	Burning pain in R arm followed by involuntary flexion/extension of R thumb; pain in L leg accompanied by flexion/extension and abduction/adduction of L toes
Schoenen et al	1984	M (2) F (4)	49, 74 68, 69, 71, 80	6	Burning/aching pain in LE followed by involuntary flexion/extension and writhing of the toes
Sanders et al	1999	F (1)	76	1	Deep/throbbing pain in L leg followed by invloluntary flexion/extension and abduction/adduction of L toes
Ikeda et al	2004	F (1)	75	1	Involuntary flexion/extension of the toes bilaterally followed by pain in both legs
Kwon et al	2008	F (1)	75	1	Painless wriggling movements of the toes in both feet

Total Number of articles reviewed = 19
Total Number of Cases: Male = 22 (Median Age = 55 years); Female = 50 (Median Age = 64 years)
Author/Article References in chronological order (Top to below): 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 16, 17, 23, 24, 25, 29, 31, 32, 33

as a poor response to sympathetic blockade, thus making clinical features of PLMT inconsistent with known radicular disorders.[3]

Interestingly, some believed that the central nervous system played an essential role in PLMT via a central oscillator.[21] It has also been proposed that hyper-excitability of the damaged peripheral nerves could cause symptoms of PLMT by way of the sympathetic nervous system. More specifically, the sympathetic nervous system could potentially serve as a bridge between injured afferent fibers and sympathetic nerve fibers,[22] allowing abnormal afferent impulse to travel to efferent fibers and ultimately leading to continuous pain with involuntary movements. This was evident in the fact that lumbar sympathetic ganglion blockade provided moderate symptomatic relief for some patients even though it was short-lived.[4] Interestingly, one of the explanations put forth was the possibility of spinal/supraspinal reorganization,[23] which coincided with the hypothesis of central reorganization mentioned above.

Clinical Management

Numerous treatments including antiepileptics, benzodiazepines, antispasmodic agents, and antidepressants have been tried with little success.[1,2,24,25] However, temporary success was observed with local anesthetic nerve blocks, epidural blocks, sympathectomy/sympathetic blockade, neurectomies, botulinum toxin type A injection, transcutaneous electrical nerve stimulation, vibratory stimulation, and epidural spinal cord stimulation.[1,2,15,26,27] Analgesics, steroids, anti-inflammatory agents, vitamin B12 injections, propranolol,

quinine sulphate, and local anesthetics only offered temporary relief as well.[3] GABAergic agents such as gabapentin and pregabalin were the most effective in attenuating the pain and the movements, possibly via both central and peripheral mechanisms.[7,24,25] It has been reported that gabapentin as high as 600mg three times daily could control symptoms of PLMT long-term.[25]

Treatment of PLMT has also been attempted with botulinum toxin A at the level of lumbosacral roots and peripheral nerves with moderate relief of symptoms, although toe movements did return after a few months.[8] It was suggested that botulinum toxin A might have acted via reduction of muscle spindle discharge leading to decreased central sensitization, as well as antisympathetic, antiglutamergic, or anti-inflammatory effects.[28]

Differential Diagnosis

The syndrome of PLMT exhibits certain features similar to the restless leg syndrome (RLS). In RLS the sensation in the legs could be burning, creeping, or tingling coupled with an urge to move them, especially early in the night. Movements such as walking or stretching relieve the symptoms whereas rest makes them worse. However, in PLMT pain is severe, constant, unrelated to the sleep-wake cycle, and is not relieved by movements or walking.[23] In addition, its involuntary movements of the toes or feet also differ from the myoclonic jerks of RLS.

In conditions such as thalamic syndrome and limb pain with myoclonus, patients may experience pain and involuntary movements as well but they often occur simultaneously as opposed to in PLMT where pain often precedes the movements.[17] In disorders such as Parkinson's disease and dystonia, sustained involuntary movements in the feet can be present and pain can be an associated feature. But the movements are typically sustained muscle contractions, which are different from the typical movements associated with PLMT.

Prognosis

PLMT is a newly discovered syndrome and since there has not been a systematic study following these patients long-term, it is currently quite difficult to predict the outcome of this syndrome and its effect on lifespan, though there has yet been a report of a patient actually dying from this syndrome. However, it is known that PLMT is a debilitating condition that greatly reduces patients' quality of life.

Conclusion

Since Spillane et al first described it in 1971, there have been more reported cases of PLMT and its variants over the years. Though much progress has been made in elucidating its etiology, its exact mechanism still remains a mystery. Similarly, even though EMG and nerve conduction studies have proven helpful in demonstrating spontaneous arrhythmic bursts of affected muscles and underlying neuropathy in some patients, diagnosis of PLMT remains largely on history and clinical presentation.

Physicians should be aware of this rare debilitating condition. It is important to consider PLMT in a patient with painful legs and/or restless leg syndrome without any significant history of neurological disease or trauma. Treatments such as different combinations of medications and invasive techniques are complex and generally lead to a poor outcome.

Competing Interests
No sources of funding were used to assist in the preparation of this case report. Dr Serena Hung is a full time employee of Biogen Idec and owns stock in the company. The authors have no conflict of interests that are directly relevant to the content of this case report and review of literature.
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Case Report

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Thyrotoxic Periodic Paralysis

M Suresh Babu, H Basavanna Gowdappa, M R Aiyappa and Sasidharan Sameer

ABSTRACT
Thyrotoxic periodic paralysis (TPP) is an alarming and potentially lethal complication of hyperthyroidism characterised by muscle paralysis and hypokalaemia. It is often not recognised when first seen because of lack of familiarity with the disorder and partly due to the subtleness of thyrotoxicosis. Early diagnosis and treatment can prevent severe cardiopulmonary complications. We hereby report a male patient who was evaluated and diagnosed to have TPP.
KEYWORDS
Thyrotoxic Periodic Paralysis, hypokalaemia, thyrotoxicosis

Introduction

Thyrotoxic periodic paralysis (TPP) is an uncommon disorder characterised by simultaneous thyrotoxicosis, hypokalaemia, and paralysis that occurs primarily in males of South Asian descent.[1] Many affected patients do not have obvious symptoms and signs of hyperthyroidism and hence may be misdiagnosed or overlooked on presentation.[2] We hereby report a male patient who presented to us with weakness of all four limbs. The patient was evaluated and diagnosed to be having TPP.

Case History

A 30-year-old male patient, who was an agriculturist by profession, presented with weakness of all four limbs of one-day duration. The weakness first appeared in his lower limbs and then in the upper limbs. There were no sensory symptoms or bladder involvement. He was not a known hypertensive, diabetic or thyrotoxic patient. He was not on any medication for any significant illness.

On general physical examination, there was no pallor, icterus, cyanosis, clubbing, lymphadenopathy or pedal oedema. Multinodular goitre was noted on thyroid examination. There was no exopthalmos, lid lag, pretibial myxoedema or other signs of thyrotoxicosis. Thyroid bruit was absent. Pulse rate was 96/minute, blood pressure of 140/80mmHg, and respiratory rate 18/minute. On central nervous system examination, the higher mental functions and cranial nerve examination were within normal limits. Motor system examination showed the presence of flaccid quadriparesis with areflexia. Sensory system examination was within normal limits. Cardiovascular and respiratory system examination were normal.

Investigations revealed: haemoglobin (Hb) -13.1 gm%, total count (TC) - 11,400/cmm, platelet count - 49,000/cmm, random blood sugar (RBS) - 110mg/dl, blood urea - 29 mg/dl, serum creatinine - 0.8 mg/dl. Serum electrolyte profile showed sodium - 143 mEq/L, potassium - 2.2mEq/L, chloride - 112mEq/L. Serum calcium and magnesium levels were within normal limits. Electrocardiogram (ECG) was normal. Human Immunodeficiency Virus (HIV) ELISA was non reactive. Bone marrow biopsy and ultrasonography of abdomen were normal. Fine Needle Aspiration Cytology (FNAC) of thyroid showed features of hyperplastic colloid goitre. Ultrasonography of thyroid showed hyperechoic small nodules in both lobes as well as isthmus suggestive of multinodular goitre. Thyroid profile was: total T3 - 2.34 (normal: 0.60 - 1.81ng/ml), total T4 - 13.9 (normal: 4.5 - 10.9 mcg/dl), thyroid-stimulating hormone (TSH) - 0.01 (normal: 0.35 - 5.5IU/ml). Antithyroid antibodies and antiplatelet antibodies were negative. Nerve conduction study was normal. A final diagnosis of TPP with idiopathic thrombocytopenia was made.

The patient was administered 40mmol potassium chloride intravenously. He was treated with tablet carbimazole 10mg three times a day and tablet propanolol 10mg twice a day. The patient's weakness in all four limbs improved dramatically within an hour after potassium chloride administration. As he had persistent thrombocytopenia during his stay in hospital, he was commenced on tablet prednisolone (1mg/kg body weight). His platelet count normalized in one month after which the steroid dose was tapered and stopped.

Discussion

TPP is an uncommon disorder characterised by simultaneous thyrotoxicosis, hypokalaemia and paralysis that occurs primarily in males of South Asian descent. The overall incidence of TPP in Chinese and Japanese thyrotoxic patients is 1.8% and 1.9% respectively.[3, 4] Sporadic cases have been reported in non-Asian populations such as Caucasians, Afro-Americans, American Indians and Hispanics. With population mobility and admixture, TPP is becoming more common in Western countries. Many affected patients are in the age group of 20 - 40 years and do not have obvious symptoms and signs of

hyperthyroidism.[5] The attack is characterised by recurrent, transient episodes of muscle weakness that range from mild weakness to complete flaccid paralysis. The proximal muscles are affected more severely than distal muscles. Attacks usually first involve the lower limbs, and progress to the girdle muscles and subsequently the upper limbs. Sensory function is not affected. Although patients can present with quadriparesis that resembles Guillain-Barre Syndrome or transverse myelitis, the bladder and bowel functions are never affected. Patient may experience recurrent episodes of weakness that last from a few hours up to 72 hours with complete recovery between the attacks. In the majority of patients, deep tendon jerks are markedly diminished or absent although some patients may have normal jerks.

Patients with TPP usually experience the attacks a few hours after a heavy meal or in the early morning hours upon waking. More than two-thirds present to the emergency department between 2100 and 0900 hours; hence it was initially described as nocturnal palsy or night palsy.[6] It has been shown that plasma glucose and insulin responses to meals are markedly higher in the evening than in the morning in control subjects. Such a phenomenon suggests a possible mechanism for the nocturnal preponderance of TPP. Another explanation could be the circadian rhythmicity of many hormones reaching their peak levels during sleep. Hypokalaemia is considered to be the most consistent electrolyte abnormality in TPP and a hallmark of the syndrome along with hyperthyroidism. It has been demonstrated that hypokalaemia is a result of potassium shift into cells and that it is not caused by total body potassium depletion.[7]Patients with thyrotoxic periodic paralysis have an underlying predisposition for activation of Na+/K+-ATPase activity either directly by thyroid hormones or indirectly via adrenergic stimulation, insulin or exercise. Increased Na+-K+ ATPase activity is postulated to contribute to hypokalaemia.[8]

The majority of cases of hyperthyroidism associated with thyrotoxic periodic paralysis are due to Graves disease although other conditions including thyroiditis, toxic multinodular goitre, toxic adenoma, TSH secreting pituitary tumour, ingestion of T4 and inadvertent iodine excess have also been implicated.[9] Assaying of thyroid function in patients with hypokalaemic paralysis distinguishes thyrotoxic periodic paralysis from other forms of hypokalaemic periodic paralysis. Thyrotoxic periodic paralysis occurs only in the presence of hyperthyroidism and is abolished when thyroid hormones are normalised.

Immediate therapy with potassium supplementation and beta-adrenergic blockers can prevent serious cardiopulmonary complications and may hasten recovery of periodic paralysis.[10] Potassium chloride is given intravenously and/or orally. Regular potassium supplementation as prophylaxis against further paralysis when the patient has normal serum potassium level is ineffective. Effective control of hyperthyroidism is indicated to prevent recurrence of paralysis.

Conclusion

To conclude, although the association of thyrotoxicosis and periodic paralysis has been well known, TPP is often not recognised when first seen because of lack of familiarity with the disorder and partly because of the subtleness of thyrotoxicosis. When a young male of South Asian descent is initially seen with severe lower limb weakness or paralysis, TPP should be considered in the differential diagnosis and investigated for its presence since it is a curable disorder that resolves when euthyroid state is achieved.

Competing Interests
None declared
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Case Report

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'Well the doctors should check the side-effects shouldn't they?' A case of Nitrofurantoin-induced liver injury

Louise Macdougall, Kate Armitage, Richard Thomson and Robert Stirling

ABSTRACT
This case report discusses an interesting case of drug- induced autoimmune hepatitis following the long term use of nitrofurantoin for recurrent urinary tract infections (UTIs). Recurrent UTIs are common and the evidence for long term antibiotics are discussed along with the difficulty in deciding whether drugs are implicated as the cause of deranged liver function tests.

An 80-year old lady was referred to a gastroenterology clinic in August 2009 with deranged liver function tests; alkaline phosphatase 180 IU/L (35-120), alanine transferase 147 IU/L (<40), gamma glutamyl transferase 384 IU/L (<45) and globulins 45 g/L (20-35). She had initially presented to her general practitioner with symptoms of lethargy and malaise four months previously. She denied any symptoms of obstructive jaundice and there were no risk factors for hepatitis; she seldom consumed alcohol.

Past medical history included osteoarthritis, migraines and recurrent urinary tract infections; these had been investigated by urology and the patient had undergone cystoscopy and urethral dilatation in September 2003; despite this she continued to experience urinary tract infections and was therefore commenced on prophylactic nitrofurantion by her General Practitioner with approval by the Urologist. This was initially commenced at 50mg at night. This regime was continued for approximately three years however during this time she had a further three treatment courses of nitrofurantoin. In October 2005 her prophylactic dose was therefore increased to 100mg at night. Other medication included lansoprazole 30mg daily, pizotifen 500 micrograms at night, metoprolol 100mg twice daily, simvastatin 10mg at night, senna 15mg at night and furosemide 40mg daily.

On examination there was evidence of palmar erythema and Dupuytren's contractures but no other stigmata of chronic liver disease. The liver was tender and palpable 4 cm below the costal margin. A liver ultrasound was performed which was normal. Liver screen and autoimmune profile are shown in table 1; notably a positive nuclear antibody was found (1 in 1280 IgG) with Hep 2 cell staining showing a homogenous (ANA) pattern at 1:320 IgG, and a nuclear lamin pattern at 1:1280 IgG;. Due to the positive ANA and raised globulins a suspected diagnosis of nitrofurantoin-induced autoimmune hepatitis was made and a liver biopsy performed.

Test	Result
Hepatitis C antibody	Negative
Hepatitis B surface antigen	Negative
Ferritin	85 ug/L (15-300)
Caeruloplasmin	0.33g/L (0.19-0.71)
Double-stranded DNA antibody	4.44 IU/ml (<10)
Nuclear antibody	1 in 1280 IgG
Mitochondrial antibody	Negative
Smooth muscle antibody	Negative
Reticulin antibody	Negative
ENA- Ro/La/RNP/Sm/Jo-1/Scl-70	Negative
Liver kidney microsomal antibody	Negative
Soluble liver antigen antibody	Borderline
Liver cytosol antibody	Negative

Table 1: liver screen and autoimmune profile

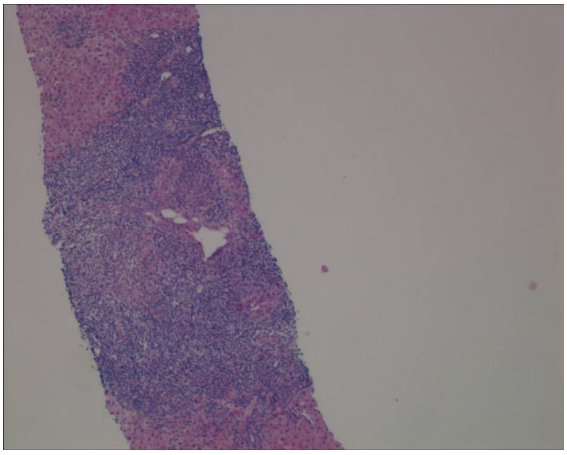

Figure 1a. Liver biopsy showing portal-based interface hepatitis

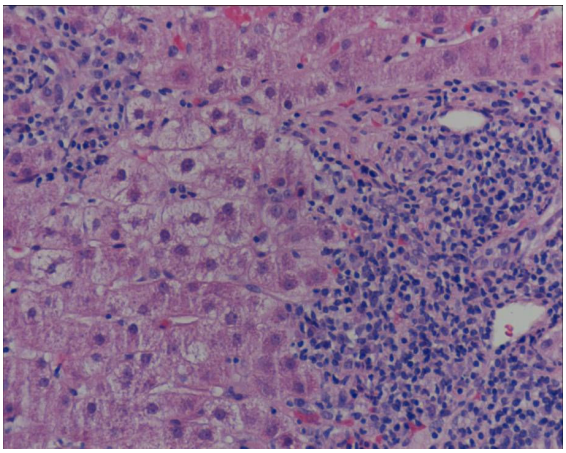

Figure 1b. Liver biopsy showing portal-based interface hepatitis

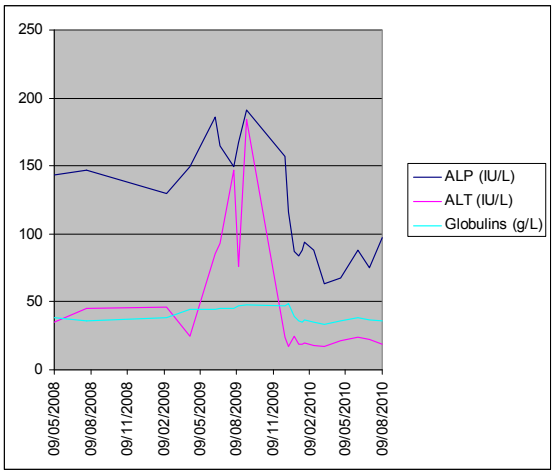

Figure 2. Serial LFTs over time

Liver biopsy (figure 1) indicated a moderate hepatitis which was mainly portal based with multifocal interface hepatitis; these morphological appearances were consistent with those of an autoimmune hepatitis. The patient was advised to immediately stop nitrofurantoin and was commenced on prednisolone 30mg which caused a rapid improvement in LFTs (figure 2). This improvement was maintained following a step-wise reduction in steroid dose and prednisolone was discontinued after eight months of treatment. LFTs are currently normal one month following cessation of steroids

Discussion

This case raises two points of discussion. The first is whether the long term use of nitrofurantoin as prophylaxis for urinary tract infections is appropriate and based on solid evidence. Nitrofurantoin has many side effects and is well documented to cause liver derangement[1,2,3]. The patient described in this case had been taking nitrofurantoin for seven years and had received a large cumulative dose, on the basis that this was effective prophylaxis. The continuous, long term use of antibiotics as prophylaxis for urinary tract infections is debatable. Madersbacher et al[4] recommend the use of prophylactic antibiotics but only after or alongside additional measures including behavioural change, the use of topical oestrogens and the use of alternative therapies; this view is supported by the European Association of Urology[5].A Cochrane Review[6] in 2004 found that antibiotic use did decrease the number of urinary tract infections compared to placebo but only for the duration of treatment; antibiotics do not alter the natural history of the underlying condition[7]. There is no clear evidence for duration of treatment and any trials have only been continued for six or twelve months[6]. It has been noted that all antibiotics had a worse adverse event profile compared to placebo. There was no consensus as to which antibiotic should be used although nitrofurantoin has been associated with a greater withdrawal rate[6]. One study[8] comparing nitrofurantoin and trimethoprim revealed no significant difference in recurrence rates or side effects between the two antibiotics, although this involved a lower dose of nitrofurantoin than was used in this case, and a treatment duration of just 6 months. We would argue that due to the side effect profile of nitrofurantoin and the evidence base available, it is not appropriate to continue it for a duration beyond 6 months.

The second discussion point is whether nitrofurantoin was actually the cause for liver derangement in this case. As documented in a recent review article on the diagnosis of drug-induced liver injury, establishing with any certainty whether liver injury is drug induced can be very difficult[3]. The key issues are whether there is a temporal relationship between the drug and the onset of liver injury, and whether other causes have been excluded. In this case the patient had negative viral serology and a normal ferritin and caeruloplasmin but her positive autoantibodies raise the possibility of autoimmune hepatitis. Guidelines from the American Association for Liver Diseases[9] suggests that the diagnosis of autoimmune hepatitis should be made on the following criteria

- laboratory abnormalities (serum AST or ALT, and increased serum total IgG or gamma-globulins)
- positive serological markers including ANA,SMA, anti-LKM1 or anti- LC1
- histological changes consistent with autoimmune hepatitis i.e. interface hepatitis

This case meets these above criteria for autoimmune hepatitis however the presence of nitrofurantoin does confound the issue. Other case reports[10] have reported nitrofurantoin to have caused autoimmune hepatitis based on the relationship between the timing of the drug and the onset of biochemical abnormalities. Bjornsson et al[11] performed a comparative study of patients with autoimmune hepatitis and found drugs, particularly nitrofurantoin and minocycline were causally implicated in 9% of cases. When they compared the two groups no significant differences were found in the diagnostic parameters of biochemical, serological and histological

abnormalities. In fact the only difference was that no drug-induced cases relapsed on withdrawal of steroids whereas nearly two third of those with non-drug-induced hepatitis relapsed. Bjornsson et al therefore argue in favour of autoimmune immune hepatitis being induced by drugs such as nitrofurantoin; rather than particular drugs simply unmasking sporadic cases based on these management differences.

The patient in this case so far has shown no signs of relapse following steroid withdrawal. We believe that this case does represent one of nitrofurantoin-induced autoimmune hepatitis. In view of the above we would urge readers to consider their use of nitrofurantoin for recurrent urinary-tract infection prophylaxis.

Competing Interests
None declared
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Clinical Practice

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A Comparison of Methods of Producing a Discharge Summary: handwritten vs. electronic documentation

Claire Pocklington and Loay Al-Dhahir

ABSTRACT

Background: It is a compulsory requirement that a hospital produces a discharge summary. This is often the only documentation a GP receives in relation to a recent admission. Traditionally the discharge summary is hand-written and commonly known as the TTA ('to take away'). Recently the EDS (electronic discharge summary) has been introduced. This audit provides a comparison of the TTA and EDS.

Methods: A random sample of 50 TTAs and 50 EDSs were selected from one ward over a two-month period. Completion rates for criteria of the discharge summary were analysed.

Results: The EDS is a superior form of discharge summary, significantly for documenting diagnosis, co-morbidities, investigations, drug history and instructions for the GP.

Conclusions: Junior doctors should be more aware of the importance of the discharge summary; therefore they should provide clear, complete and concise information. In order to ensure EDSs are completed correctly training on using the computer programme should be more thorough. Documenting co-morbidities has implications on clinical coding. Other healthcare professionals should contribute to the discharge summary.

KEYWORDS Discharge Summary, TTA, EDS, Handover, Information

Introduction:

On discharge from hospital, secondary care providers have a duty and obligation to communicate with primary care provides – particularly the general practitioner – to give information regarding the reasons for admission, results of investigations, procedures performed, treatment instigated and importantly follow-up management. Therefore the transition of information between secondary and primary care is vital for care management and hence patients' safety.

This information is shared in the form of a 'discharge summary'. It is the responsibility of the secondary care team to provide this. The level of detail given has been found to vary not just between different NHS trusts or hospital but also between different wards and individual doctors completing the discharge summary – this can create many problems as communication plays a pivotal role in patient care.

The information given in the discharge summary is all that a patients' GP knows in regards to their hospital admission and management. A discharge summary is effectively a form of 'handover'. A hospital physician may instruct the GP to do certain things in regards to follow-up; for example check blood results, review results of investigations arranged as outpatients or simply review the patient clinically. The more information that is transferred across from secondary to primary care the more awareness the GP has to what has happened and what needs to happen, which leads to better patient care.

A discharge summary can also be a valuable document for when a patient is admitted to hospital; if their notes are not available a past discharge summary will provide useful information (re. past medical history and drug history in particular) to the medical team who may have no prior knowledge of the patient, this is invaluable if it not possible to take a history from a patient and is also useful in directing investigations if a patient has been admitted with the same complaint(s). Of course this depends on the patient having a copy of the discharge summary with them on admission or the ability to access previous discharge summaries electronically.

Good documentation is vital in the healthcare setting. All documentation, no matter in what form, must be clear, accurate and legible. Any type of document is useless if it cannot be read. The GMC and Royal College of Physicians stress the importance of documentation[1, 2].

The importance of the discharge summary has been highlighted in the last few years. There has been a move from the traditional hand-written discharge summary – commonly referred to as the TTA (to take away) – to the use of computer software providing an electronic discharge summary (EDS). The latter not only provides more detail but also aims to deliver it to the

primary care setting in a timelier manner; for example, in the future, once all EDSs are completed at Barking, Havering and Redbridge University Hospitals NHS Trust there are plans for them to be automatically emailed to a patients GP surgery – currently this scheme is being trailed at certain GP surgeries. This complies with the requirement and recommendations made to secondary care trusts to provide the GP with a discharge summary within 24hrs of a patients' discharge from hospital – consequently reducing previous financial penalties when not achieved and thus being more cost efficient.

The advent of the EDS has impacted the daily working of the junior doctor, who is commonly, the individual on the secondary care team whose role it is produce the discharge summary. Previously with a TTA a patient could be discharged home without all the constituents on the form being completed and so a GP would be provided with an incomplete discharge summary. At BHR University Hospital NHS Trust in order to produce a finished EDS - and essentially discharge the patient - all constituent sections have to be completed before it can be electronically sent to pharmacy so that the patient sent home with their medications (the discharge summary acts as a prescription). Therefore producing an EDS is more time consuming in comparison to a TTA. However an EDS does have advantages (see Table 1).

Table 1: Comparison of EDS and TTA

Advantage of EDS	Advantage of TTA
Provides more information Improve clinical coding Always legible Permanent electronic record Sent to GP immediately	Less time to complete No computer access required
Disadvantage of EDS	**Disadvantage of TTA**
More time consuming Computer access required	Provides less information Not always legible Carbon copies No permanent record (can be lost) Time delay before GP receives

Any form of discharge summary is user dependent; what is written is determined by the individual doctor producing the document therefore there is no guarantee that they have documented everything that occurred during admission. In the case of the TTA user dependence also refers to the legibility of the writing, the durability of the carbon copies produced, as well as the level of detail of the discharge summary produced.

In 2008 Newham University Hospital Trust introduced the EDS, the trust audited this process and found it to be successful[3]. 2010 saw the introduction of the EDS at BHR University Hospital NHS Trust. The EDS was piloted on Sunrise B ward of Queen's Hospital, Romford. The purpose of this audit is to establish if the introduction of the EDS at BHR University Hospital NHS Trust has been successful. The audit aims to determine if the EDS method is superior to that of the traditional TTA – this will be achieved by comparing the completion rates for specific criteria of the discharge summary. This audit also aims to identify areas of improvement and recommendation for the EDS.

Design and Method:

An opportunistic sample of 50 TTAs and 50 EDSs were selected from the patients admitted to Sunrise B ('Care of the elderly') ward, Queen's Hospital, Romford in a two-month period (January to February 2011). Thus this is a retrospective audit. No exclusion criteria for selection of discharge summaries was set. For each discharge summary completion rates for the different fields of the discharge summary were recorded. *Table 2* shows the criteria fields included in each type of discharge summary.

Table 2: Comparison of EDS and TTA criteria

	EDS	TTA
Criteria fields included	Patient details Responsible consultant Admission date Diagnosis Co-morbidities Investigations/procedures Drug history Review of case Discharge date Discharge destination Follow-up arrangements Instructions for GP Functional state	Patient details Responsible consultant Admission date Diagnosis Past medical history Investigations Drug history Discharge date Follow-up arrangements

The Royal College of Physicians have published their recommendations for the structure and content of the discharge summary. Section headings include

- GP details - name, address, practice code
- Patient details – surname, forename, date of birth, gender, NHS number, address, telephone number
- Admission details – method of admission, source of admission, hospital site, trust, date of, time of
- Discharge details – date of, time of, discharge destination, discharging consultant, specialty
- Clinical information – diagnosis at discharge, operations/procedures, reason for admission/presenting complaint, allergies, investigations and results, treatments, discharge medications, medication changes
- Advice, recommendations and future plan – hospital/GP/community
- Person completing summary – doctors name, grade, specialty, signature, date of completion[4]

This audit establishes which method of discharge summary is more compliant with these recommendations.

Data analysis was mainly descriptive. Data collected was tabulated and represented as percentages. Graphical representation of the data was performed using Microsoft Excel. Due to the nature of the study and data collected more

sophisticated statistical analysis, such as that requiring the use of SPSS software, was not warranted.

Results:

Results demonstrate significant differences between the TTA and EDS completion rates for criteria of the discharge summary. *Table 2* presents the data as percentages in a tabulated form. Compared to the TTA, the EDS had a higher rate of the following six criteria of the discharge summary documented; diagnosis, co-morbidities, investigations, drug history, discharge destination and instructions for GP.

Table 3: Summary table of data

	% of discharge summaries completed					
	TTA			EDS		
Discharge summary criteria	**Completed**	**Partially**	**Not**	**Completed**	**Partially**	**Not**
Patient details	86	14	0	100	0	0
Responsible consultant	92	-	8	96	-	4
Admission date	80	-	20	100	0	0
Diagnosis	38	48	14	88	8	4
Co-morbidities	16	0	84	38	8	54
Investigations	14	24	62	62	30	8
Drug history	64	18	18	100	0	0
Review of case	0	14	86	88	4	8
Discharge date	66	-	34	100	-	0
Discharge destination	0	-	100	98	-	2
Instructions for GP	8	-	92	92	-	8
Functional state	0	-	100	64	-	36

Patient details and admission date.

The TTA had lower completion rates for these fields than the EDS. The EDS software automatically enters these fields therefore it is not possible for this criterion to be incomplete. The correct patient details ensure continuity of care and patient safety. If patient details – i.e. full name, date of birth, hospital number and address - are not present those with similar names could be mixed up.

Diagnosis.

The TTA performed poorly on documenting diagnosis. The EDS had a completion rate significantly higher than that of the TTA (EDS completion rate = 88%, TTA completion rate = 48%). *Figure 1* represents these findings. The main objective of a discharge summary is to inform primary care of the diagnosis to enable healthcare management, therefore it is crucial and pivotal information, for it not to be included in the discharge summary is illogical.

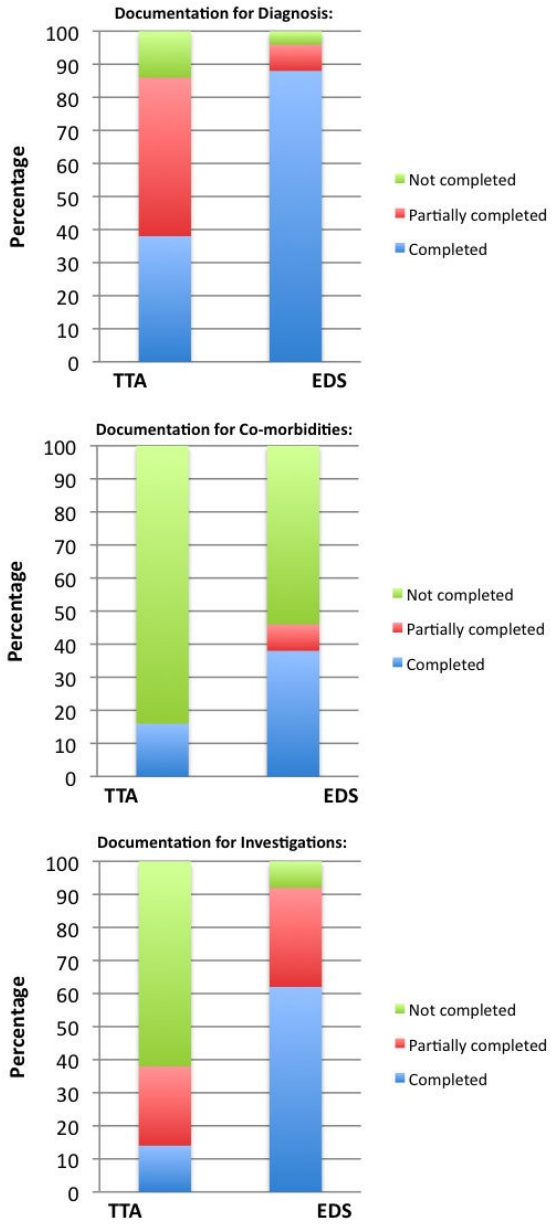
Co-morbidities.

Neither TTAs nor EDSs documented co-morbidities well. However the EDS, yet again, outperformed the TTA. See*Figure 1*. Documenting co-morbidities has important repercussions for clinical coding and financial incentives (see below).

Investigations.

Coincidently, 62% of TTAs did not document investigations that the patient had had in contrast to 62% of EDSs that did. See *Figure 1*. There is no guarantee for either discharge method that all investigations are listed; it is dependent upon the doctor who is producing the discharge summary.

Figure 1: Graphical representation of data



Drug history.

As previously mentioned, EDS has to have a completed drug history before the patient can be discharged and hence they have to have a 100% completion rate for this criterion. TTAs only achieved a 64% completion rate as *Table 3*demonstrates.

Review of case.

This is not a criteria field on the TTA document. Therefore 86% of TTAs provided no review. 88% of EDSs did provide a case review. Just fewer than 10% of EDSs were incomplete for this item.

Discharge date.

Like the admission date, a discharge date is automatically completed on an EDS thus the completion rate is 100%. However, this date is the date in which the EDS is completed and may not be the actual day the patient leaves hospital because sometimes the EDS is completed (and so the medications dispensed) the day prior to discharge or patient discharge may be delayed. The TTA achieved a 66% completion rate.

Discharge destination.

This is not a criterion present on the TTA and thus 100% of TTAs did not fulfil this requirement. EDSs had a 98% completion rate.

Follow-up arrangements.

The majority of EDSs documented the follow-up plans for a patient (88% in total, 70% specifically for GP follow-up). 46% of TTAs documented patient follow-up required, specifically 44% for hospital follow-up. 54% of TTAs documented no follow-up. In summary, 88% of EDSs documented follow-up in comparison to 46% of TTAs. These findings may be a limitation of the study i.e. patient selection rather than failings in documentation.

Instructions for GP and functional status.

Coincidently, 92% of TTAs did not document 'instructions for GP' in contrast to 92% of EDSs that did. 'Instructions for GP' is not a criterion on the TTA document.

Functional status.

'Functional status' is also not a criterion on the TTA document and so all TTAs were not complete for this. 64% of EDS had a completion rate for documenting 'functional status'. Functional status indicates a patient's mobility status, self-care abilities, hearing and sight impairment.

Discussion:

This audit has established that the EDS has a higher completion rate for criteria on the discharge summary, significantly so for documenting diagnosis, co-morbidities, investigations, drug history and instructions for the GP.

One major concern that has been highlighted in performing this audit is the documentation of co-morbidities. Due to variations in training many doctors are unaware of how and where to enter this information on the EDS – there is a specific window that opens on the software program to input this information. Junior doctors were documenting patients' past medical history under the field of 'diagnosis'. Co-morbidities should not be listed under 'diagnosis' - this infers a new diagnosis - as they are not the acute problem.

The coding of the diagnosis [the acute problem], in context of a patients co-morbidities, results in a condition specific 'fee' being paid to secondary care. For example the 'fee' received for a patient diagnosed with a respiratory tract infection is different for that when the patient is diagnosed with a respiratory tract infection on the background of dementia. Inaccuracies in diagnosis lead to incorrect coding and measures of incidence. Co-morbidity is 'any condition which co-exists in conjunction with another disease'. It is a requirement of the discharge summary to document certain co-morbidities – as determined by the Clinical Coding Co-morbidity Working Group (CCCWG)[5]. Although the discharge summary is not the recommended source documents for use in clinical coding – patients medical notes are used instead – it can help direct and inform those responsible for clinical coding. In should be borne in mind that it is the treating clinicians' responsibility to document co-morbidities relevant to the current admission. Accurate and correct clinical coding will result in financial gains. Clinical coding has more important purposes other than just financial; it allows the monitoring of health services, epidemiological research, NHS planning of provisions, as well as clinical audit and governance[6].

The amount of information documented is user dependent; the level and amount of detail written is subjective. For example there is no guarantee that all the investigations that a patient had are documented. One doctor may provide a whole paragraph to summaries ['review of case'] whereas another may just write one sentence. Educating those whose task it is to complete the discharge summary about how vital and important it is, along with the role it serves in healthcare management, may influence the effort and time dedicated to producing an EDS. The principles of clear, complete and concise documentation should be applied to both the patients' discharge summary and their medical notes.

Other healthcare professionals should also contribute to producing the discharge summary, in particular occupational therapists and physiotherapists who are more aware of a patients 'functional status' than the doctors. More accurate completion of this item could be achieved with their input.

At the moment with the EDS software system used at BHR University Hospital Trust once an EDS has been printed there is no means of changing any of the information. It cannot be re-accessed to document new or change existing details. Often an EDS will be finalized and so printed for a patient to be discharged home on that day for the discharge then to be delayed. The discharge date document on the EDS should be the actual date the patient is discharged from hospital. Therefore it should be possible to be able to re-access and change details on the EDS.

The results of this audit show that the EDS system used at BHR University Hospital Trust is better then the EDS system audited at Newham in 2008. The Newham audit did not focus

on all the criteria fields of the discharge summary or compare with a hand-written discharge summary method, however there is place for comparison with the results of this audit.

Table 4: Comparison of results with findings of Newham audit

	% of EDSs documenting	
Criteria of EDS	**Newham audit**	**Findings of this audit**
Admission date	100	100
Discharge date	79.8	100
Discharging consultant	60.6	96
Diagnosis	69.1	88

This audit has established that the EDS method provides a discharge summary more compliant with the Royal College of Physician's recommendations on the structure and content of discharge summary in comparison to the TTA.

The EDS will inevitably replace the TTA in time. However it should be remembered that there is still a place for the TTA in clinical practice e.g. locums do not have passwords to access the software programme, if computers are not working, fail or are unavailable. At the end of the day, a discharge summary is better than no discharge summary.

Conclusion:

The findings of this audit show that the EDS is a far superior method of producing a discharge summary than the TTA. The EDS provides a more informative and detailed discharge summary, which is always legible. The discharge summary is often the only source of information a GP is given in regards to a hospital admission and therefore secondary care providers have an obligation to provide clear, complete and concise information.

This audit does highlight that there are areas for improvement and recommendation:

The importance of a discharge summary should be highlighted to all individuals whose responsibility it is to complete them. This could promote better compliance at completing all items and completing them more thoroughly.

EDS training should make users aware of the 'co-morbidity' section. Past medical history should not be listed under new diagnosis. This should be a compulsory part that has to be completed before an EDS can be finished.

Occupational therapists and physiotherapists should be able to complete the 'functional status' criterion. This should be expanded to give more information and details to primary care providers.

The documentation of certain co-morbidities (those determined by the CCCWG) should be done by 'tick list' selection therefore it will not rely upon the individual doctor to remember to document such co-morbidities. All the co-morbidities that should be documented could be listed and the user selects those that the patient has. This will improve the trusts performance in regards to the financial rewards linked to discharge summaries.

The audit should be performed again in 12 months to access if EDS are maintaining high completion rates, to identify further improvement in completion rates and identify any further areas for improvement or recommendation.

Discussion of both TTA and EDS could be a part of the regular weekly supervision of junior medical staff by their prospective consultants.

A discharge summary should also be checked by nursing or clerical staff prior to letting the patient leave the ward to see if all components are completed.

Competing Interests
None Declared
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Viewpoint

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Ethical Debate: Ethics of xeno-transplantation

Murali Krishna and Peter Lepping

Interest in cross-species transplantation has recently been rekindled[1]. This is due to many developments including the shortage of donor organs, advances in transplant medicine, investment in biotechnology research, and the non-availability of more ethically suitable alternatives to human organs. Increasing success rates in allotransplantations (organs from different member of the same species) has increased the demand on donor organs[1, 2]. Other types of transplantation include autotransplants (a person's own organs or tissues are used for transplantation) and isotransplants (organs from one person are transplanted into another genetically identical person, like an identical twin). These options are limited in terms of body parts used and numbers.

Good facts inform good ethics. It is therefore obligatory to look into the current research knowledge about xenotransplants (organs from one species to another, for example animal to human) in more detail. The advocates of xenotransplantation argue that it could provide organs "relatively quickly" and hence save more lives. If animal organs were easily available for transplantation most eligible recipients would receive the transplantation much earlier on in their illness. It is argued that this may decrease distress and suffering. Whilst xenotransplantation may theoretically increase the survival time, it is unclear, however, whether the negative impact on recipients' quality of life due to long-term immunosuppressant therapy and the risk of zoonotic infections would in fact worsen the overall long-term outcome[3]. Recent research suggests that xenotransplantation may be associated with the transmission of pig microorganisms including viruses, bacteria, fungi, and parasites. Because of the recipient's likely immunosuppressed state, infection and pathologic consequences may be more pronounced. Transmission of most microorganisms with the exception of the porcine endogenous retroviruses may be prevented by screening the donor pig and qualified pathogen-free breeding. However, porcine endogenous retroviruses represent a special risk as they are present in the genome of all pigs and infect human cells in vitro. Until now, no porcine endogenous retrovirus transmission was observed in experimental and clinical xenotransplantations as well as in numerous infection experiments[4]. Nevertheless, strategies need to be developed to prevent their transmission to humans. It is equally possible that many eligible recipients may be denied having a trial of xenotransplantation by doctors who believe that there is an unfavourable risk-benefit ratio. The limited long-term data on outcomes of xenotransplants thus renders ethical analysis difficult.

There is some evidence to suggest that the recipients of animal organ donation may develop a different self image with possible consequences for their identity[5,6]. This happens with human organs at times, but may be a more significant problem with animal organs, as the recipient knows that they have been given a non-human organ. Loss of identity jeopardises the core principle of autonomy, which underpins all medical treatment.

The risk of zoonosis to the recipient and to the wider society cannot be accurately estimated[7]. Hence there is a requirement for vigilant post-operative monitoring[5] with a possibility of engaging article5 and 8 of the European Convention of Human Rights (for England and Wales: Human Rights Act 1998)[†]. Article 12 may also be engaged as the recipients may be restricted from having physical relationships, carrying out their routine day to day activities and socialisation. This is because the prevention of possible risk to the wider public from zoonosis may require the recipient to be put under restrictions with regard to their engagement with others. This may include restrictions to go out, which can result into de facto temporary detentions at home. Hence consenting to xeno-transplantation would be "binding and contractual" over a long period of time. The subject may not have the right to withdraw. This is entering into a de facto contract with potential restrictions or even deprivation of human rights. This would restrict the ability to give informed consent even for a well informed patient, as it is difficult to be fully appreciative of future restrictions of one's liberty.

Autonomous decision making and thus informed consent may also be put at risk by other factors surrounding xenotransplantation. The decision to embark on xenotransplantation may be primarily driven by an instinctual wish to survive due to a lack of other viable alternatives. Patients in these circumstances may have little or no consideration to medium and long-term effects on themselves

and society. However, it is the consideration of such long-term consequences that make a truly autonomous decision, and differentiate it from a decision that is purely based on immediate instinct. Whilst the wish to survive is legitimate it is difficult to make decisions free of the pressure to survive when there is a lack of alternatives.

It also brings up an even more important question: Can any person ***ever*** consent to a future restriction or deprivation of their liberty or other human rights? Even if there were an option to define acceptable future restrictions it would be likely that patients could still challenge the legality of any such agreements. They could quite reasonably argue that they have agreed to the restrictions under duress because of a lack of viable alternatives to their xeno-transplants.

Xenotransplantation touches questions of utilitarianism (greatest good for the greatest numbers) and public protection[2]. Utilitarianism takes into account the reasonable interests of society in good outcomes, fairness in the distribution of resources, and the prevention of harm to others. The Nuffield council on bio-ethics embraces a utilitarian approach. However, there are limits to the utilitarian argument for xenotransplants. Even if they were widely available, the treatment would be immensely expensive. Production of a pathogen free donor organ would involve rearing animals in strictly controlled environments, subjecting them to rigorous standards of examination and surveillance. The additional costs of developing a sustainable work force to provide transplantation and post-transplant surveillance of the patient and the community would be high. The insurance providers may not cover expenses of a xenotransplant. Public health care providers may decline to provide this treatment as it may not be recommended by expert groups as cost effective. Xenotransplantation may commence in the developing world where the regulations are lax and the poor can be more easily exploited[8]. Patients who would potentially benefit from xenotransplantation may not be able to afford it due to its cost with serious implications for fairness.

Xenotransplantation also raises other ethical questions in relation to the wider community. We have seen that consent of an individual to a xenotransplant has significant bearing on the protection of society[7]. Should the members of a community therefore be consulted if there were any xeno-transplantation experiments in their region? The risk is primarily due to the risk of zoonotic infections, the need for surveillance, and possible quarantine of contacts[7,9]. In addition, if health authorities were to fund expensive experimental interventions like xenotransplantation, other routine treatments of greater potential benefits to society may be jeopardised. Society may also have views about particular animals being used as donor animals[10]. For example religions like Islam and Judaism may feel that pigs are 'ritually unclean'. They may therefore not approve of certain animals to be used for donation, and more worryingly may fail to socially accept recipients with such 'unclean' transplants[11].

From a deontological perspective (this judges the morality of an action based on the action's adherence to a ruleor principle) some authors assert that animals have rights similar to those considered appropriate for humans[12,13]. The protection of animals has legal status in many countries. Consequentialists may view the suffering and death of an animal as acceptable for the betterment of a human patient, as they would judge the morality of an action primarily by its end result. They would argue that potential benefits and improvement in human welfare arising from xenotransplantation may justify the loss of animal life. However, this will never satisfy the animal rights lobby; especially as whilst minimising the risk of acquired infections, the animals have to forgo greater suffering in the form of isolation, monitoring and investigations. Furthermore, genetic modification can have both immediate and long-term negative effects on animals.

In summary, xenotransplantation has significant ethical consequences. On an individual level, there are the questions of pressure to consent that may negate autonomy and the validity of that consent as well as the difficulties that arise when patients are asked to consent to future restrictions of their human rights. On a societal level there are questions of cost and benefit analysis as well as risks from zoonotic infections. In addition, questions of animal rights need to be addressed before any programs are likely to go ahead.

†Appendix of articles of the Human Rights Act.

- Article 8 of the Human Rights Act 1998 (The right to respect for private and family life, home and correspondence)
- Article 5 (The right to liberty).
- Article 12 (The right to marry and found a family)

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E-Interview

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Interview with Doris-Eva Bamiou

Doris-Eva Bamiou is a Department of Health HEFCE funded Senior Lecturer at the UCL Ear Institute, and Consultant in Audiovestibular Medicine at the National Hospital for Neurology and Neurosurgery. She is also Honorary Consultant at the RNTNE Hospital and Great Ormond Street Hospital. She sees both adults, with vertigo, hearing problems or auditory processing disorders, and children with auditory processing disorders and complex communication needs in her clinics. She works in an academic, multidisciplinary environment.

After completing specialty training in ENT in Greece, Ms Bamiou trained in Audiological Medicine in the UK. During her training, she spent a three-month fellowship in Professor Musiek's department in the States (on a stipendium from Professor Musiek and a grant from the TWJ foundation), where she trained in the diagnosis and management of patients with auditory processing disorders. Her PhD degree is onauditory processing in patients with structural brain lesions.

She is Director of the MSc in Audiovestibular Medicine at UCL. In addition, she has been Director and Organiser of the Current Trends in Auditory Processing Disorders instructional courses for the past several years. She is immediate past Secretaryof the British Society of Audiology (BSA), and Chair of the Auditory Processing Disorders Special Interest Group of the same Society. She is adviser in Audiology to the JLO, and in the Editorial Board of the Audiological Medicine journal.

She has a keen interest in research. Interests include the aetiology of hearing loss, auditory processing disorders in the presence of other neurological conditions as well as in the normal population, auditory neuropathy, vestibular rehabilitation and overlap between psychiatric and vestibular disorders.

How long have you been working in your speciality?

I first became interested as an ENT trainee in Greece, in 1993. At the time I was at a paediatric hospital, and we did a lot of paediatric testing (distraction and ABR). In 1994 I moved to an adult hospital, where I came across and learned to test and manage adult patients with vertigo and hearing loss.

Which aspect of your work do you find most satisfying?

Solving clinical problems, teaching postgraduate students, designing research projects and interpreting research results give me equal satisfaction – I enjoy equally the patient/doctor or student/teacher interaction and the intellectual challenges.

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

I set up the first adult clinic for patients with auditory processing disorders at the National Hospital for Neurology, and the first multidisciplinary clinic in this field, again at the same hospital.

Which part of your job do you enjoy the least?

Administration and form filling exercises.

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

I wonder whether trainees get enough proper training in their very early days on and whether the length of the training is sufficient for them to be able to function independently by the end of their training.

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

We do Audiovestibular Medicine Taster days, and we encourage them to come and "shadow" us to see what it is really like.

What qualities do you think a good trainee should possess?

He/she should be kind, hard working, highly motivated to learn and able to develop independent thinking.

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

It may be hard work training as a Doctor, but it's all worth it!

What qualities do you think a good trainer should possess?

Amongst many other things, empathy, and the ability to teach each trainee at their own level.

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

Not more than is required.

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

I think it is difficult to reconcile managerial activities with a doctor's role.

Which scientific paper/publication has influenced you the most?

Several. I tend to read a lot of papers for lectures etc so this changes every few weeks!

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

I could not separate one more than others.

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

Rehabilitation (auditory and vestibular) of the patient with complex needs.

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

More funding and more rationalized use of free NHS services, depending on the patient's income.

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

Yes, by working closely and by educating managers.

How has the political environment affected your work?

Not at all.

What are your interests outside of work?

I read a lot of books of every kind, I go to the theatre and to art exhibitions.

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

This will sound very boring. I would still like to be a doctor!