Volume 40, Issue 5, May 2010, Pages 321–394

The Royal Australasian College of Physicians

INTERNAL MEDICINE JOURNAL

Volume 40
Issue 5
May 2010
ISSN 1444-0903

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ISSN 1444-0903 (Print)
ISSN 1445-5994 (Online)

IMJ.JEBNov09

The Royal Australasian College of Physicians

INTERNAL MEDICINE JOURNAL

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Internal Medicine Journal **40** (2010) 321–322

EDITORIAL

Ethical issues associated with gifts provided to physicians by the pharmaceutical industry

It is not known exactly how much money the pharmaceutical industry spends on promotional activities. It is, however, clear that it is a very large amount – some estimates put it at more than $US50 billion per year in the USA alone – and that it exceeds industry expenditure on research and development.[1] Promotional activities take many forms, including provision of samples, face-to-face 'detailing' meetings between industry representatives and prescribers, advertising in print and the electronic media, and support for meetings and travel. One of the activities that has come under closest scrutiny in recent years is the provision of gifts to physicians, which themselves may vary from practice-related items of trivial value to expensive goods intended for the exclusive personal use of the recipients.

There is nothing untoward about the concept of promotion of commercial goods as such. It is, after all, a familiar feature of all modern economies and can provide a useful means for disseminating information about available products and, by contributing to a healthy competitive market, help stimulate innovation and enterprise. However, promotion of pharmaceutical goods – and in particular, the use of gifts to do so – has been seen as a special case that raises serious ethical issues. The concern is not merely that the evidence shows that all promotional activities influence prescribing behaviour (contrary to the protestations of many physicians):[2] the sheer volume of resources devoted to them shows that this must be the case. What is of concern is the possible impact of this influence on both the form and content of healthcare delivery.

There are three major areas of ethical concern in relation to gift-giving.[3] First, there is the kind of impact gifts may have on clinical deliberations. Prescribing decisions should be based on careful analyses of the circumstances of individual patients in light of available evidence and the doctors' professional knowledge and experience. Gifts, however, are not directed at rational prescribing principles, but instead seek to persuade doctors by appealing to them in a personal or emotional way. It is possible that through such a mechanism receipt of gifts may lead to outcomes that are not in the patient's best interests. Second, there is a possible negative impact on the public standing of doctors and medicine as a whole. Acceptance of gifts by doctors may create a public perception that the latter are not independent advocates for the welfare of their patients, but rather representatives or functionaries of business or other organizations, thereby undermining the basic, constitutive trust that is at the heart of all clinical relationships. Finally, there is the potential impact on the health system as a whole. While adding nothing to the value of a product, gifts – like other promotional activities – invariably add to the price, which ultimately has to be borne either by individual patients or by the community as a whole. In this manner, gift-giving may redirect scarce health resources away from areas of high need, thereby acting against the broader pubic interest.

From an ethical point of view, these concerns raise two questions: should industry representatives offer gifts to physicians, and if they do, should the latter accept them? The question about industry poses the problem of the power of pharmaceutical companies to set the agenda for clinical practice and to limit the authority of government to make decisions about health resource allocation; that about physicians raises issues regarding the behaviour of individual doctors and the kinds of ethical decisions they make on a personal level and in the context of the clinical encounter. As with all other ethical questions, the answers depend on both an understanding and analysis of the problems, dialogues around value-related issues, and factual knowledge about current circumstances, common behaviours and implications for both individual patients and society. If the attitudes and behaviours of doctors fail to show a sensitive appreciation of the ethical issues, or if they are shown to be seriously at odds with the interests of the community, action on the part of either government or the professional associations may become necessary.

The article by Macneill *et al*. in this issue makes a useful contribution to this debate.[4] The authors conducted a survey of medical specialists and the general public in the Hunter River region of New South Wales. This survey inquired into attitudes about the 'appropriateness' of particular kinds of gifts that may be offered to doctors by industry representatives. The authors concede that response rates were suboptimal, raising the possibility of response bias, and they provide no breakdown of responses from practitioners in different specialities, despite different cultures and different approaches adopted by the various specialist colleges. In addition, the criteria for 'appropriateness' are left open, making the basis for the respondents' judgements uncertain. In spite of these limitations, the results are of considerable interest and raise useful questions. They suggest four main conclusions: (i) that there is considerable variability in opinion about the 'appropriateness' of certain gifts, among both specialists and the general public; (ii) that

although both groups accept gift-giving in some circumstances, both also feel that there are limits to what is acceptable; (iii) that most specialists are aware of published guidelines with respect to relationships with industry and, in general, specialists' views about what is acceptable are consistent with current guidelines; and (iv) that the views of the public are somewhat more permissive than those of the practitioners. The last conclusion is contrary to what appears from the limited evidence to be the case overseas[5–7] and in addition, the specialists appear to be more critical of pharmaceutical gifts than their overseas colleagues.[8,9]

These conclusions might give some encouragement to those working to develop guidelines that seek to promote critical attitudes among doctors to their relationships with industry. They also pose the question of what, if any, implications they have for the substantive content of such guidelines or for public policy. After all, while it may be true that there is a strong ethical case against receiving gifts from pharmaceutical companies, this does not in itself justify mandatory measures to prevent doctors from accepting gifts.

Surveys of attitudes do not solve ethical problems. However, they may give some clues about the nature of the social context within which ethical decision-making is taking place and practices that may need to be subjected to critical questioning. As in many other areas in medical ethics, with respect to relations with industry there are frequent calls for mandatory systems to control doctors' behaviours.[10,11] It is true that such systems may be the only way to curtail industry practices that are potentially contrary to the public interest – a judgement that is perhaps implicit in the recent decision of the peak industry association in Australia to introduce strict limitations on the use of gifts in pharmaceutical promotion.[12] However, in relation to the behaviour of clinicians, mandatory regulation may actually be counter-productive. The primary responsibility of clinicians is to make decisions in the interests of their patients, taking into account the manifold complexity of the latter's personal and social circumstances. This requires a high level of ethical competence, including an ability to engage in open critical dialogue about one's own personal values and professional role. If one is simply following a rule or obeying a law, one is not making an ethical judgement: the risk of increasingly elaborated and directive codes of conduct is that they may erode such competence and undermine the fecundity of the dialogical process on which the clinical encounter is based.[13]

The article by Macneill *et al*. contributes to the ongoing ferment about dealings between physicians and industry and it may add to the broader debate about the nature of the relationship between clinical practice and the for-profit sector. Even if the arguments and the evidence suggest that doctors should refuse gifts from industry – as they evidently do – we need to convince doctors, not force them, to do so.

Received 28 February 2010; accepted 1 March 2010.

doi:10.1111/j.1445-5994.2010.02215.x

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Internal Medicine Journal **40** (2010) 323–334

REVIEW

Corticosteroid insensitivity in severe asthma: significance, mechanisms and aetiology

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Key words
asthma, steroid, drug effect, drug therapy, aetiology.

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Received 12 May 2009; accepted 20 July 2009.

doi:10.1111/j.1445-5994.2010.02192.x

Abstract

Chronic severe asthma remains a challenging clinical problem despite the availability of modern treatments. Relative corticosteroid insensitivity is present in severe asthma and may contribute to continuing disease severity. Advances in the understanding of molecular mechanisms underlying corticosteroid insensitivity may yield new therapeutic targets. Furthermore, aetiological factors for corticosteroid insensitivity have been identified and these may be amenable to modification.

Introduction

Up to 10% of asthmatics suffer from severe asthma, despite optimal medical therapy.[1] These patients experience chronic symptoms as well as intermittent attacks which increase their risk of asthma death. Their medical care can be challenging.[2]

Strikingly, these patients often do not respond fully to corticosteroid treatment. In this review, we examine the phenomenon of corticosteroid insensitivity in severe asthma and argue that one way of improving asthma control in these patients is by attempting to restore corticosteroid sensitivity.

Severe asthma overview

Evaluation

Most patients with asthma are managed successfully in primary care. Specialist referral is triggered only when disease control cannot be achieved despite maximal doses of inhaled therapy, a situation often termed *difficult asthma*.[3] Severe asthma is only one of a number of factors leading to difficult asthma, and other contributory factors must be considered (Fig. 1).[4,5] The diagnosis must be reviewed, concomitant conditions identified and patient factors explored (Table 1).

Consensus guidelines suggest that the evaluation of difficult asthma patients be performed by a dedicated asthma service.[6] Prolonged investigation and observation may be needed. Only when a difficult asthma patient continues to have poor asthma control following comprehensive assessment should a diagnosis of severe asthma be given.[7]

Definition

Different expert groups define severe asthma differently and there is poor agreement between these definitions.[1,7–9] Descriptors of asthma severity are based on pragmatic clinical criteria, as the biology of severity remains unclear.

An adequate definition of severe asthma must consider both *asthma control* and *treatment intensity*.[9] Asthma control is measured by symptoms, airflow obstruction and healthcare utilization. Treatment intensity is

Funding: None.
Conflict of interest: None.

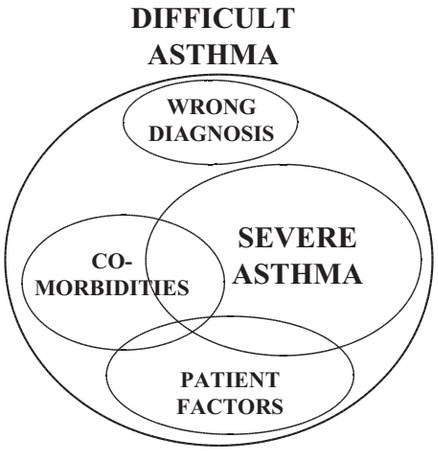

Figure 1 The relationship between difficult asthma and severe asthma. Disease severity is only one of a number of factors contributing to difficult asthma.

indicated by the number and doses of medications required. The truly severe asthmatic is one who achieves good asthma control only when administered high-intensity treatment, or who continues to have poor asthma control despite high-intensity treatment.[10]

Such definitions of asthma severity are context-specific, as treatments vary depending on the level of available medical care. In Australasia, the intensity of treatment required to place a patient in the severe asthma category includes high-dose inhaled corticosteroids (ICS). This establishes a pivotal relationship between asthma severity and corticosteroid treatment response.

Characterization

Efforts have been made to identify clinical features, which characterize severe asthma patients. Hopefully, if a typical clinical profile can be determined, greater understanding of disease mechanisms will follow.

Table 1 Difficult asthma evaluation: the three 'C's

Correct diagnosis?
Alternative or additional diagnoses – central airway tumours, obstructive sleep apnoea, hyperventilation, vocal cord dysfunction, chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, extrinsic allergic alveolitis, heart failure.
Comorbidities
Associated diagnoses – allergic bronchopulmonary aspergillosis, Churg–Strauss syndrome.
Accompanying diagnoses – rhinosinusitis, gastro-oesophageal reflux and psychological illness.
Compliance and other patient factors
Psychological issues, treatment adherence, misperception of asthma symptoms, unreported smoking and understanding of self-management plans and devices.

According to two recently described cohorts, severe asthma patients are more likely to be female, overweight, and to have aspirin sensitivity and rhinosinusitis.[2,11] A greater degree of air-trapping for the same severity of airflow obstruction is present, possibly reflecting heightened inflammation in distal airways.[12] Some patients have predominantly eosinophilic inflammation, but many have neutrophilic inflammation measured in induced sputum or bronchial biopsies.[13] Airway remodelling may be prominent, with increased basement membrane thickness and airway smooth muscle mass.[14,15] Levels of the anti-inflammatory mediator lipoxin A4 (an arachidonic acid product involved in the resolution of inflammation) are reduced in bronchoalveolar lavage fluid (BAL), while levels of proinflammatory cysteinyl leukotrienes are elevated compared with levels found in non-severe asthma patients.[16]

These characteristics of severe asthma focus attention on mechanisms, which may be particularly relevant to severe asthma pathogenesis. However, when asthma patients are considered individually, there is substantial overlap in these parameters between severe and non-severe asthma.

Phenotypes of severe asthma

Severe asthma is a heterogeneous disorder. It may be stratified into distinct phenotypes, although it is unclear whether these phenotypes represent different aspects of the same disease, or instead reflect distinct disorders, which overlap only in symptomatology.[17]

Some patients experience frequent exacerbations; others develop persistent airflow obstruction. Within the group with frequent exacerbations, a subgroup suffers sudden catastrophic attacks punctuating periods of clinical stability, a condition termed 'brittle asthma'.[18] Severe asthma patients may also be stratified according to extrinsic triggers of their asthma, or according to the inflammatory profile of their induced sputum.

An exploration of severe asthma phenotypes can lead to targeted therapies for specific subgroups. A recent example of phenotype-focused treatment is seen in a subgroup of severe asthmatics who exhibit sputum eosinophilia and suffer frequent severe exacerbations. Treatment with monoclonal antibodies against interleukin-5 (IL-5) reduces eosinophils in the airways and peripheral circulation, and significantly reduces the exacerbation rate.[19] This contrasts with the lack of efficacy reported for this approach in a more 'general' cohort of moderately severe asthmatics.[20] It would be intriguing to examine whether specific therapies targeting the neutrophil, such

as the macrolide clarithromycin, are similarly efficacious in severe asthmatics exhibiting a neutrophil-predominant pattern of inflammation, because this cellular phenotype is also associated with increased disease severity.[21]

Future approaches to phenotyping severe asthma may involve the use of *novel parameters* to classify patients, such as the profile of cytokines in BAL.[22] *Novel methodologies* may also be used to stratify patients, by using statistical tools, such as cluster analysis which minimize a priori bias.[23]

Corticosteroid insensitivity in severe asthma

Implicit in the definition of severe asthma is the absence of a beneficial therapeutic response to high doses of corticosteroids. This implies that there may be an impaired biological response to corticosteroids, and it is plausible that such a blunted response results in continuing disease severity.

Steroid-resistant asthma

One approach to the investigation of corticosteroid insensitivity is seen in steroid-resistant asthma, defined as the persistence of airflow obstruction associated with an increase of less than 15% in the forced expiratory volume in 1 s (FEV_1) following 2 weeks of high-dose prednisolone.[24] Importantly, not all severe asthmatics are steroid-resistant. In one study, only 21 of 87 adolescents with severe asthma (24%) were steroid-resistant.[25]

There are limitations to this dichotomous view of steroid-resistant asthma and steroid-sensitive asthma. First, the degree of steroid responsiveness among asthmatics to ICS therapy follows a bell-shaped, rather than biphasic, curve.[26] The cut-off point of 15% for the FEV_1 response is arbitrarily defined and simply divides this curve in two without a true biological basis. Second, steroid responsiveness may vary over time in the same individual, and factors that control this variation are unclear.[27] Third, it may be difficult to differentiate truly steroid-resistant asthma because of unsuppressed airway inflammation from the separate issue of fixed airflow obstruction caused by airway remodelling. In this instance, a preserved acute bronchodilator response to beta-agonist would suggest the former rather than the latter.[28]

Nevertheless, the concept of steroid-resistant asthma has helped advance our understanding of severe asthma. Using peripheral blood mononuclear cells from steroid-resistant asthmatics, it is possible to show *in vitro* cellular correlates of steroid resistance. The proliferation of, or release of cytokines from, peripheral blood mono-nuclear cells (PBMC) from this group of patients exhibits resistance to suppression by methylprednisolone in cell culture.[29,30] From these and subsequent studies, various mechanisms of steroid resistance have been proposed, of which some are described below.

Relative corticosteroid insensitivity

In severe asthma cohorts, one-third of patients are on a daily oral dose of prednisolone for their asthma.[5] These patients are often termed 'corticosteroid-dependent' because any reduction of the maintenance steroid dose worsens asthma control. Conversely, escalating the steroid dose improves asthma control further.[31] These observations strongly argue that the problem of corticosteroid insensitivity in severe asthma is one of relative insensitivity rather than absolute resistance. This concept is illustrated in Figure 2.

The relative corticosteroid insensitivity in severe asthma is also accompanied by abnormalities in cellular responses to corticosteroids *in vitro*. Using PBMC and alveolar macrophages, we showed that these cells were less inhibited by dexamethasone in terms of stimulated cytokine release, when obtained from severe asthma patients compared with non-severe asthma patients or to non-asthmatic subjects.[32,33] In future, the detection and measurement of steroid insensitivity in severe asthmatics using such cellular correlates may provide helpful guidance in the selection of optimal treatment.

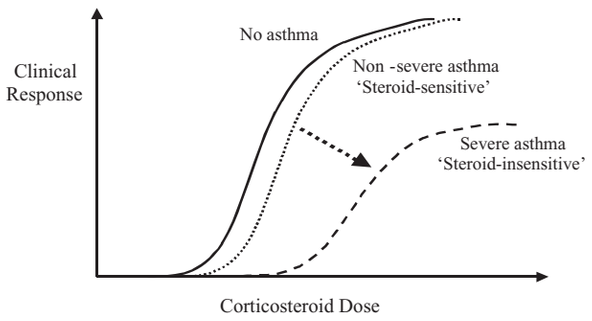

Figure 2 Relative corticosteroid insensitivity in severe asthma. The concept of corticosteroid insensitivity is illustrated by the suppressive dose–response curve of corticosteroids. Corticosteroid insensitivity is expressed as a shift of the curve to the right *and* a reduced maximal response. For a similar therapeutic response, higher doses of corticosteroids are needed in patients with severe asthma compared with a non-severe asthmatic. Furthermore, even at high doses, the beneficial effects of corticosteroids may be blunted.

Therapeutic approaches to corticosteroid insensitivity

The association of relative corticosteroid insensitivity with asthma severity also suggests that addressing the former may improve the latter.

Bypassing corticosteroid insensitivity

Many treatments for severe asthma have been developed to modulate inflammatory pathways without directly addressing corticosteroid insensitivity, in other words, bypassing the problem of corticosteroid insensitivity. These agents have only modest clinical utility, and include immunosuppressants, such as methotrexate[34] and cyclosporine A, and biological molecules, such as omalizumab[35] (targeted against immunoglobulin E, IgE), mepolizumab[36] (targeted against IL-5) and etanercept[37] (targeted against tumour necrosis factor-α). Although their effects on corticosteroid responsiveness are generally unknown, some of these treatments do have clinical steroid-sparing effects. In a minority of patients, the use of methotrexate (see below), omalizumab (in allergic patients) or mepolizumab (in eosinophilic patients) may enable a reduction in the dose of chronic corticosteroid use.[34–36]

Overcoming corticosteroid insensitivity

The most direct approach to relative corticosteroid insensitivity is to overcome it using higher doses of corticosteroids. However, the clinical cost of such a practice is prohibitive because of serious side-effects, such as osteoporosis and Cushing's syndrome. This therapeutic dilemma is the context for pharmaceutical efforts to develop 'dissociated corticosteroids', that is, glucocorticoids with enhanced anti-inflammatory efficacy but a decreased side-effect profile. The successful development of corticosteroids with such an improved therapeutic index would allow higher effective corticosteroid doses to be administered.[38]

Restoring corticosteroid insensitivity

The most rational way to deal with corticosteroid insensitivity in severe asthma is to restore corticosteroid sensitivity in relevant immune effector cells. This might be achieved in one of two ways. First, the molecular mechanisms which underlie corticosteroid insensitivity could be reversed. Second, the aetiological factors responsible for corticosteroid insensitivity could be removed. The remainder of this review will therefore discuss the current understanding of molecular mechanisms underlying corticosteroid insensitivity, and the aetiological factors that have been identified.

Molecular mechanisms of corticosteroid insensitivity

Corticosteroid anti-inflammatory action

Within the cytoplasm of a target cell, a corticosteroid ligand binds to the glucocorticoid receptor (GR).[39] This binding triggers the dissociation of chaperone proteins from GR and permits nuclear translocation of the freed corticosteroid–GR complex.

Within the nucleus, corticosteroids first exert their anti-inflammatory effects through the *induction of anti-inflammatory genes* (Fig. 3). This occurs by the binding of GR dimers to glucocorticoid-responsive elements (GRE) located within the promoter regions of corticosteroid responsive genes.

Second, corticosteroids *repress pro-inflammatory genes* (Fig. 3), usually through the direct binding of GR to transcription factors, inhibiting their pro-inflammatory function. Alternatively, pro-inflammatory gene repression may occur through *chromatin modification* (Figs 3,4). DNA is packaged within nuclei as chromatin, which consists of DNA wound around core proteins known as histones. When histones are *acetylated* by histone acetyl transferase (HAT), chromatin undergoes a conformational change which leads to unwinding of DNA and permits recruitment of transcription factors to gene promoters, resulting in gene induction. Conversely, when histones are *deacetylated* by histone deacetylase (HDAC), chromatin becomes tightly knit, inhibiting access of transcription factors to gene promoters, resulting in gene repression. Importantly, chromatin structure is modified by corticosteroids. GR both inhibits HAT activity and enhances HDAC activity, resulting in repression of pro-inflammatory genes.[39]

Impaired glucocorticoid receptor function

Diminished quantities of GR, reduced binding affinity of GR to corticosteroids, impaired nuclear translocation of GR and reduced binding of GR to GRE have all been described in cells from steroid-resistant asthmatics.[40–42]

In addition, GR occurs in two isoforms known as GR-α and GR-β. Anti-inflammatory effects are exerted through GR-α. GR-β does not induce transcriptional activity and is usually expressed at only a fraction of the level of GR-α. Increased levels of GR-β have been found in cells from steroid-resistant patients and this appears to impair steroid sensitivity by inhibiting GR-α nuclear translocation.[43]

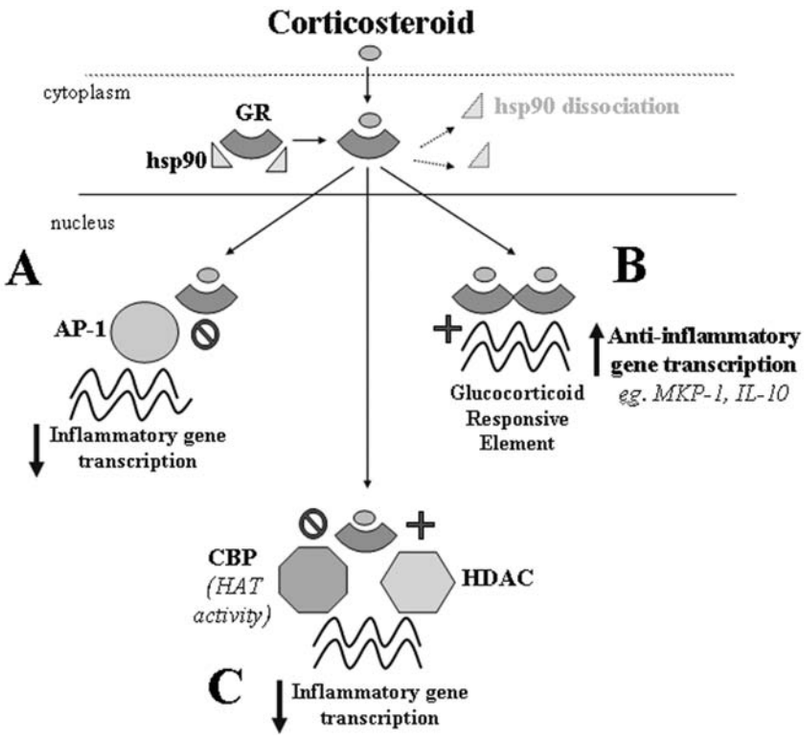

Figure 3 Intracellular anti-inflammatory effects of corticosteroids. Glucocorticoid ligand binds to the glucocorticoid receptor in the cytoplasm and the resulting complex translocates into the nucleus. (A) A direct inhibitory action by GR on transcription factor AP-1 leading to *pro-inflammatory gene repression*. (B) GR binding to the glucocorticoid responsive element of the promoter region of an anti-inflammatory gene, such as MKP-1 or IL-10, causing *anti-inflammatory gene induction*. (C) An inhibitory interaction of GR with CBP and recruitment of HDAC to promoter regions of inflammatory genes, resulting in reduced histone acetylation and subsequent *inflammatory gene repression*. AP-1, activator protein-1; CBP, CREB-binding protein; GR, glucocorticoid receptor; HDAC, histone deacetylase; hsp90, heat shock protein 90; IL-10, interleukin-10; MKP-1, MAP kinase phosphatase-1.

Drugs to improve GR function have not been developed. However, there is some evidence that low-dose methotrexate, which acts as a steroid-sparing agent in steroid-dependent asthmatic patients, may improve GR function. In PBMC, methotrexate increases the expression of GR-α, and prior methotrexate treatment of steroid-resistant asthmatics improves *in vitro* sensitivity of their PBMC to dexamethasone, perhaps providing an explanation for its clinical steroid-sparing effects.[44,45] The mechanisms behind these effects require further elucidation.

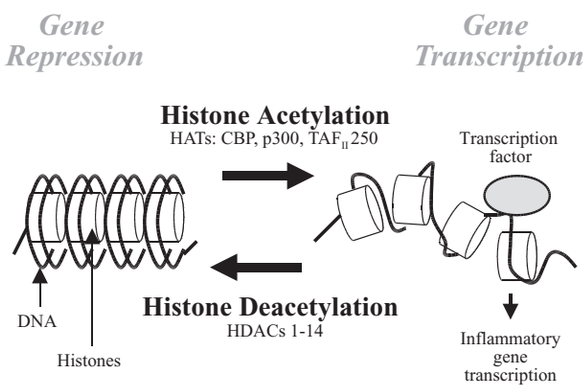

Figure 4 Role of chromatin modification in inflammatory gene transcription. Histone acetylation enhances gene transcription, but histone deacetylation leads to gene repression. CBP, CREB binding protein; HAT, histone acetyltransferase; HDAC, histone deacetylase; TAF II250, TBP-associated factor II250.

Impaired induction of pro-inflammatory genes

Interleukin-10

One anti-inflammatory gene induced by GR is interleukin-10 (IL-10). In alveolar macrophages taken from asthmatic airways, the expression of IL-10 is increased by the prior administration of ICS.[46] Furthermore, the induction of IL-10 expression from regulatory T cells (Tregs) causes inhibition of T-cell pro-inflammatory responses, such as antigen presentation. It now appears that in some steroid-resistant asthmatics, there is a defect of steroid-induced IL-10 expression by Tregs.[47]

This impairment of IL-10 expression is reversible. In Tregs from steroid-resistant asthmatics, vitamin D_3 reverses the impaired steroid-induced IL-10 production.[48] Prior ingestion of vitamin D_3 in steroid-resistant asthmatics also enhances steroid-induced IL-10 expression in Tregs. It remains to be seen whether administration of vitamin D_3 to severe asthmatics restores clinical corticosteroid sensitivity or improves asthma severity.

Impaired induction of MAP kinase phosphatase-1

Another anti-inflammatory gene induced by GR is mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1). MKP-1 is responsible for the dephosphorylation and inactivation of MAP kinases such as p38 MAPK, which have important pro-inflammatory actions (Fig. 5).[49] In alveolar macrophages from severe asthmatics, there is an impaired induction of MKP-1 by dexamethasone, and this results in unrestrained activation of p38 MAP kinase.[33]

Promisingly, the downstream effects of impaired MKP-1 induction are reversible. In alveolar macrophages taken from severe asthmatics, inhibitors of p38 MAP kinase restore the ability of dexamethasone to suppress pro-inflammatory cytokine release.[50] Several p38 inhibitors are undergoing clinical trials in the treatment of rheumatoid arthritis.[51] However, liver toxicity has been a concern, and it remains unclear whether this issue is compound specific or mechanism based.[52]

Impaired repression of pro-inflammatory genes

GR binds directly to pro-inflammatory transcription factors, such as activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), inhibiting their effects on pro-inflammatory gene expression. However, in cells from steroid-resistant asthmatics, AP-1 is over-expressed, overwhelming available GR and allowing unrestrained pro-inflammatory action of the remaining AP-1

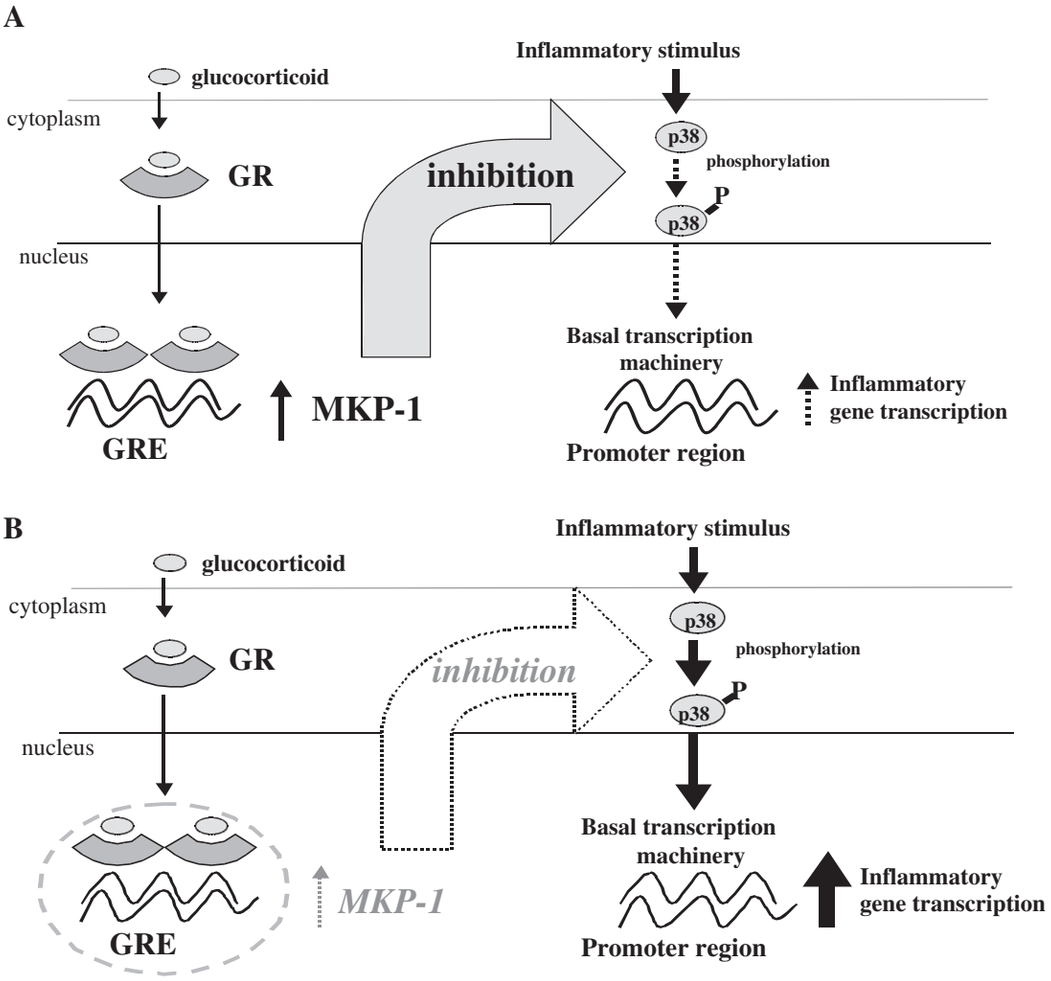

Figure 5 Role of MAP kinae phosphatase-1 (MKP-1) in modulating inflammatory gene transcription. (A) A steroid-sensitive cell with intact GR-induction of MKP-1 able to inhibit p38 MAP kinase activation with consequent attenuation of pro-inflammatory gene transcription. (B) A steroid-insensitive cell with impaired GR-induction of MKP-1 (broken circle) allowing unrestrained p38 MAP kinase activation with a consequent increase in pro-inflammatory gene transcription. GR, glucocorticoid receptor; MKP-1, MAP kinase phosphatase-1.

molecules.[53,54] Agents with activity against AP-1 are being studied in experimental animals.[55]

Chromatin modification

In PBMC from severe asthmatics, HDAC activity is diminished.[32] This reduction in HDAC activity correlates in those cells with an impaired ability of dexamethasone to suppress pro-inflammatory cytokine release, suggesting that abnormalities in HDAC function influence cellular responses to corticosteroids.

HDAC activity can be restored pharmacologically. The prior administration of theophylline to patients with COPD can restore HDAC activity in airway cells.[56] However, the clinical effects of theophylline in asthma are modest. New compounds with effects on histone acetylation and HDAC activity are under development.

Therapeutic implications

For a fuller treatment of the molecular mechanisms regulating corticosteroid sensitivity, the reader is referred to more comprehensive reviews.[57,58] However, even a selective discussion such as this illustrates how gaining an understanding of the molecular mechanisms behind corticosteroid insensitivity provides a rational basis for developing new therapies.

Aetiological factors in corticosteroid insensitivity

Corticosteroid insensitivity may partly be an inherent genetic trait of the individual, but interactions with the environment are also contributory.

Genetic factors

When PBMC from healthy individuals are examined, they exhibit resistance to the effects of dexamethasone in a quarter of cases.[59] This could be interpreted to suggest that a proportion of the healthy population has a reduced sensitivity to corticosteroids even in the absence of disease.

In the rare condition of familial glucocorticoid resistance, a mis-sense mutation of the GR causes global insensitivity to steroid action and leads to an Addisonian syndrome.[60] However, this condition is unrelated to corticosteroid insensitivity in asthma.

Studies of gene expression have linked alterations in the expression of specific genes, such as p50 (a component of NF-κB), FKBP51 (a GR chaperone protein) and corticotrophin releasing hormone receptor-1, with the degree of responsiveness of asthmatics to corticosteroids.[61–63] These gene associations are biologically plausible, but causal relationships remain to be proven.

Disease factors

Incubation of T cells with pro-inflammatory cytokines such as IL-2 and IL-4 results in cellular resistance to the effects of dexamethasone.[64] This suggests that in the presence of heightened airway inflammation in severe asthma, the cellular milieu is itself able to induce a lack of response to treatment, thereby establishing a vicious circle of increasing disease severity and corticosteroid insensitivity.

Environmental factors

A number of environmental triggers may adversely affect corticosteroid sensitivity. Incubation of PBMC from atopic asthmatics with allergens induces cellular steroid resistance by reducing the binding affinity of GR for its corticosteroid ligand.[65] Rhinovirus infection of airway epithelial cells impairs GR nuclear translocation.[66] Stimulation of T cells with staphylococcal superantigens also induces steroid resistance by impairing nuclear translocation of GR.[67]

Cigarette smoking

Smoking increases asthma incidence among adolescents, increases asthma severity and induces airway neutrophilia.[68–70] Importantly, cigarette smoking also impairs the clinical response to inhaled and oral corticosteroids in terms of symptoms and lung function.[71] Post-hoc analysis of a large study shows impaired clinical efficacy of ICS in both current and (to a lesser degree) former smokers.[72] Mechanistically, alveolar macrophages from smokers have a reduced cellular steroid responsiveness, which is associated with reduced HDAC activity.[73] PBMC from smoking asthmatics also have an elevated GR-β to GR-α ratio.[74]

Can this corticosteroid insensitivity be reversed? Probably. *In vitro*, transfection of HDAC into steroid-resistant alveolar macrophages from smokers restores cellular steroid sensitivity.[75] Clinically, the cessation of smoking in asthmatics leads to an impressive increase in FEV_1 of 400 ml.[76]

If these patients continue to smoke, can this corticosteroid insensitivity be improved pharmacologically? Possibly. Among smoking non-severe asthmatics, the addition of long-acting beta-agonists or theophylline to ICS reduced exacerbations and improved lung function respectively.[72,77] In another study, smoking non-severe

asthmatics had an impaired response to ICS, but a preserved response to leukotriene antagonists.[78] These findings have not been replicated in severe asthmatics. Overall, the data suggest that if smoking asthmatics (regardless of severity) are poorly responsive to ICS, the single most effective intervention is smoking cessation.

Obesity

Obesity increases both asthma risk and asthma severity.[79,80] Importantly, a post-hoc analysis of 3000 patients enrolled in pharmacological trials also showed that clinical responsiveness to ICS was diminished in overweight patients.[81] A molecular explanation for these clinical observations has recently been furnished by the demonstration that in PBMC and alveolar macrophages from obese asthmatics, MKP-1 induction by corticosteroids is impaired.[82]

The effect of weight loss on corticosteroid sensitivity in obese asthmatics is unknown. However, weight loss in overweight patients reduces asthma severity and improves symptom control.[83] From a pharmacologic viewpoint, obese asthmatics with relative corticosteroid insensitivity retain the ability to respond to leukotriene antagonists.[79] These retrospective data require prospective confirmation.

Vitamin D

Vitamin D deficiency may contribute to the development of asthma.[84] Dietary and serum vitamin D_3 levels are inversely associated with lung function, while maternal dietary and serum vitamin D_3 are inversely associated with wheeze and asthma respectively. In childhood asthmatics, reduced vitamin D levels increase the risk of severe asthma exacerbations.[85]

As discussed, vitamin D_3 when administered to steroid-resistant asthmatics reverses defective steroid induced IL-10 expression from Treg cells, potentially reversing corticosteroid insensitivity. Although these data are intriguing, the relationship between asthma incidence, severity and steroid responsiveness in severe disease on the one hand and vitamin D on the other remains speculative. Prospective studies to examine vitamin D metabolism and the effects of vitamin D supplementation in severe asthma are important areas for future investigation.

Clinical implications

The identification of aetiological factors for corticosteroid insensitivity in severe asthmatics opens new avenues for management (Table 2). Smoking cessation and weight loss in smoking or overweight severe asthmatics is obviously beneficial in many respects, quite apart from any effects on steroid sensitivity. More work is needed to determine if limiting exposures to triggers, such as aeroallergens or bacterial superantigen, have any clinical effects on steroid sensitivity. The true role of vitamin D in steroid insensitivity also needs exploration.

It is striking that results from studies of molecular mechanisms of corticosteroid insensitivity on the one hand, and epidemiological aspects of clinical steroid insensitivity on the other, have begun to dovetail. Most of the aetiological risk factors for steroid insensitivity discussed above have now been linked to molecular pathways associated with steroid insensitivity (Fig. 6).

Conclusion

In summary, severe asthma remains a clinical challenge partly because the therapeutic effects of corticosteroids are blunted in this population. A variety of molecular mechanisms has been proposed to explain clinical corticosteroid insensitivity. While steroid insensitivity may well have a genetic basis, it has now also been linked to an increasing number of environmental and behavioural factors.

Table 2 Behavioural factors in corticosteroid insensitivity

	Smoking	Obesity	Reduced vitamin D
Asthma risk	Increased	Increased	? Increased
Asthma severity	Increased	Increased	Increased (exacerbations)
Airway inflammation	Neutrophilia	Decreased eosinophils	?
Response to ICS	Impaired	Impaired	?
Molecular mechanisms	Reduced HDAC, increased GR-β	Decreased MKP-1	Reduced IL-10
Reversible	Smoking cessation	? Weight loss	? Vitamin D_3
Add-on treatment	LABA, LTRA, theophylline	LTRA	?

?, No data available; GR-β, glucocorticoid receptor-β; HDAC, histone deacetylase; ICS, inhaled corticosteroid; IL-10, interleukin-10; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; MKP-1, MAP kinase-1.

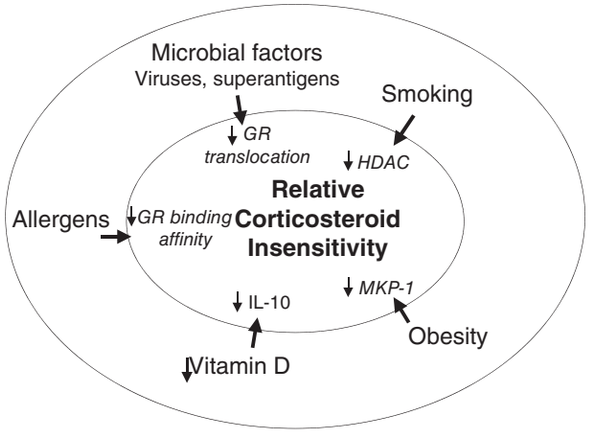

Figure 6 Corticosteroid Insensitivity. Relationship between aetiological factors and molecular mechanisms. All the aetiological factors depicted have been linked to specific molecular abnormalities in corticosteroid action. GR, glucocorticoid receptor; HDAC, histone deacetylase; IL-10, interleukin-10; MKP-1, MAP kinase phosphatase-1.

In future, the entry of newer immunosuppressants and biological molecules into clinical practice may bypass the problem of corticosteroid insensitivity. The development of truly dissociated corticosteroids may overcome corticosteroid insensitivity by providing greater steroid potency with fewer side-effects. Finally, it may also be possible in future to restore corticosteroid sensitivity by two rather different strategies. First, the development of novel therapeutic agents may successfully reverse the molecular abnormalities involved. Second, the removal of environmental triggers and modification of behavioural factors may be equally instrumental in restoring steroid sensitivity in this difficult group of patients.

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Internal Medicine Journal **40** (2010) 335–341

ORIGINAL ARTICLE

Attitudes of physicians and public to pharmaceutical industry 'gifts'

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Key words
ethics, medical ethics, drug industry, bioethics, medical economics.

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Received 6 October 2009; accepted 1 March 2010.

doi:10.1111/j.1445-5994.2010.02233.x

Abstract

Background: Few studies have reported the attitudes of both individual doctors and members of the public toward the appropriateness of 'gifts' from pharmaceutical companies.
Aims: To investigate the attitudes of both doctors and members of the public toward the appropriateness of receiving particular 'gifts' from pharmaceutical companies, and to consider whether public acceptability is a suitable criterion for determining the ethical appropriateness of 'gifts'.
Methods: A survey questionnaire of medical specialists in Australia and a survey questionnaire of members of the public itemised 23 'gifts' (valued between AU$10 and AU$2500) and asked whether or not each was appropriate.
Results: Both medical specialists and members of the public believe certain 'gifts' from pharmaceutical companies are appropriate but not others. There was a tendency for members of the public to be more permissive than medical specialists.
Conclusion: Although some professional guidelines place importance on the attitudes of the general public to 'gift' giving, and other guidelines give importance to a need for transparency and public accountability, we question whether public acceptability is a suitable criterion for determining the ethical appropriateness of 'gifts'. We suggest that more weight be given to the need for independence of clinical decision making, with empirical evidence indicating that even small 'gifts' can bias clinicians' judgments, and to important values such as the primacy of patient welfare, autonomy and social justice. We conclude that it is time to eliminate giving and receiving of promotional items between the pharmaceutical industry and members of health professions.

Introduction

Interaction between physicians and the pharmaceutical industry has attracted widespread attention because of concern that it may subvert the goals of medicine and medical research, cause harm to patients, and increase the cost of healthcare.[1–5] Of the many forms of interaction that may occur, the giving of gifts to health professionals has been the focus of particular concern.[6–16] In part this is because gift giving is the most obvious interaction between physicians and the pharmaceutical industry and in part because of the concern that it may lead to conflicts of interest and compromise clinical judgement. Public and professional concern about the impact of such 'gifts' on physicians' prescribing practices has led to the development of ethical codes and guidelines.[17–25] These typically offer guidance rather than proscriptive rules and recommend restricting food and

Funding: This study was supported by a grant from the National Health and Medical Research Council of Australia, Canberra.
Conflict of interest: None for any of the authors, although Author 2 acknowledges participation as investigator in industry sponsored clinical trials including recruiting patients.

entertainment to modest levels, 'gifts' to items of low value, and advise doctors not to allow 'gifts' to influence their prescribing habits.[17–25] Some commentators have noted that the term 'gift' is misleading in that 'gifts' are more accurately termed 'marketing wares'[11] (or at least 'promotional aids'[22]) that are effective in influencing prescribers.[1,9–11] There are increasing calls for the elimination of 'gifts' entirely[11,16] with the consequence that some professional,[24] pharmaceutical industry[25] and institutional[5] guidelines have advised against[24,25] or prohibited[5,18] 'gift' giving or receiving. However, most guidelines still leave the determination of the appropriateness of a specific gift to individual physicians.[17,19–21,24]

Although there have been studies of patients' views,[8,14,15] the basis upon which individual doctors make decisions about the moral acceptability of 'gifts' and the degree to which these concur with public attitudes to gift giving has rarely been systematically examined[8] and has never been examined in the Australian context. This is particularly significant given that transparency and public accountability are core components of some guidelines on preventing conflicts of interest (including those of the Royal Australasian College of Physicians[24] and the Australian Medical Association[18]) and that other guidelines (e.g. those of the American College of Physicians and American Society of Internal Medicine[20,21]) suggest that physicians should gauge the acceptability of any gift from the pharmaceutical industry according to what patients or the public would think about the arrangement.

As part of a larger study investigating the relationship between the pharmaceutical industry and medical specialists, we undertook to describe the attitudes of medical specialists and the public to the receipt of 'gifts' from the pharmaceutical industry in order to examine more systematically whether the attitudes of either may be used as a reference point against which the ethical appropriateness of accepting gifts can be judged.

Methods

Data were collected through two surveys using self-report questionnaires designed specifically for each group. These surveys and the study methods were approved by the Human Research Ethics Committees of the University of Newcastle, Australia. Details of the medical specialist survey (including population sampling and methods) have been reported elsewhere.[3,12] Briefly, the medical specialist questionnaire consisted of 46 questions on all aspects of the relationship with pharmaceutical companies, including the frequency and nature of interactions and the frequency, type and value of 'gifts' offered and received and the appropriateness of 'gifts' offered. In particular we asked respondents to rate the appropriateness of a range of 23 'gifts' that medical practitioners may be offered by industry representatives (Table 1). These 'gifts' included items (such as pens, computers) or activities (such as dinner, expenses to attend a conference) and ranged in monetary value from A$10 to A$2500. Respondents were asked to indicate the extent to which they considered each gift 'appropriate' by choosing a response on a Likert scale.

The questionnaire for members of the public had a total of 20 questions seeking information on: the extent of their knowledge of the relationships between medical specialists and pharmaceutical companies; any concerns they may have about that relationship; their views on whether regulation of 'gifts' was needed; their attitudes to pharmaceutical company sponsored research; and personal demographics, including their level of education, health status, recent visits to a doctor, receipt of free medication and participation in research trials. As in the medical specialist survey, public respondents were asked to rate the appropriateness of the (same) range of 23 'gifts' that medical practitioners may be offered by industry representatives.

Differences between medical professionals and the general public (such as lack of familiarity among the general public with the physician–industry relationship, the nature of gifts that might be offered to doctors, experience with responding to survey instruments using Likert scales) necessitated some differences in the presentation of the question regarding gift appropriateness. Medical specialists were asked to indicate their level of agreement on a 5-point Likert scale (*strongly agree*, *agree*, *neither agree nor disagree*, *disagree*, *strongly disagree*) that receiving each of 23 hypothetical gifts was appropriate. Members of the public were asked to indicate the appropriateness of doctors receiving each of the 23 gifts on a simpler 4-point Likert scale (*Always appropriate to accept*; *Sometimes appropriate to accept*; *Never appropriate to accept*; *Not sure*).

For both medical specialists and the general public, 13 hypothetical 'gifts' were listed, from the full list of 23 'gifts', in each of two versions of the questionnaire (Forms A and B). This was done to reduce response fatigue. Three items ('patient information leaflets', 'dinner for doctor and partner to socialise with other doctors', and 'free samples of a new medicine') were common to both Forms. The 13 items in each version of the questionnaire were presented in random order and participants were assigned at random to receive Form A or B.

Results

The medical specialists' questionnaire was mailed to 2253 listed specialists,[3,12] of whom 133 were found to be

Table 1 Hypothetical 'gifts' from a pharmaceutical company to doctors as presented in Questionnaires Forms A & B in order of value†

1. Patient information leaflets on new drug (value $10) (both Forms)
2. Two boxes of chocolates for doctor and surgery staff (value $10) (Form B)
3. Small flashlight (value $10) (Form B)
4. Ticket to movies (value $15) (Form B)
5. Pens for the surgery (value $10). Plain without promotional logos–to be used by doctor and the receptionists. (Form B)
6. Pens with the name of a new drug printed on them (value $10). Doctor and receptionists will use. (Form A)
7. Two appointment books (value $10) to be used to track appointments for all doctors in surgery. (Form A)
8. Two movie tickets for doctor and partner (value $25). (Form A)
9. Sample packs of new medicine (value $100). (both Forms)
10. Set of electric scales (value $100) to be used by all doctors and nurse in surgery, to measure their patients' weight. (Form B)
11. Stethoscope (value $100). (Form B)
12. Two tickets to theatre for doctor and partner (value $100). (Form B)
13. Ticket to football grand final (value $100). (Form A)
14. Dinner at a city restaurant for doctor and partner (value $100)–with presentation about a new drug. (Form A)
15. Lunch for doctor and all surgery staff (value $100)–with presentation about a new drug. (Form B)
16. Dinner at a city restaurant (value $100) for doctor and partner to allow local doctors to meet and socialise. (Both forms)
17. Lunch for doctor and surgery staff (value $100). (Form A)
18. Conference including conference fees, accommodation, and airfares (value $1000). (Form B)
19. Trip for doctor and partner to attend a conference including conference fees, accommodation and airfares (value $1200). Partner will not attend conference. (Form A)
20. New refrigerator for surgery (value $2000) for use in staff lunchroom. (Form B)
21. New laptop computer (value $2500) for use at home. (Form A)
22. Computer (value $2500) for use by doctor to write prescriptions and keep patients' notes. (Form A)
23. Spirometer (value $2500) to be used by all of doctors in surgery. (Form A-Medical Specialist' Questionnaire only)
24. An electrocardiogram machine to monitor patents' heart rhythms (value $2500) (Form A-General Public Questionnaire only)

†All $ values = Australian dollars.

ineligible (deceased, emigrated or retired). A total of 832 (447 Form A, 376 Form B) questionnaires was completed and returned, giving an overall response rate of 39%. The respondents were similar to the original sample in terms of geographic location and clinical specialty. The average age was 49.9 (SD 10.6) years and 79% were male. Medical specialists (but not members of the public) were asked if they were aware of published guidelines on interactions with the pharmaceutical industry. There were 546 medical specialist (66%) who stated they were aware, and 321 (38%) who specified one or more particular guidelines, including those of the Royal Australasian College of Physicians (n = 254); other specialist colleges (n = 47); Australian Medical Association (n = 19); Medicines Australia – pharmaceutical industry guidelines (n = 15); governmental guidelines (n = 10); hospital or other institutional guidelines (n = 9); USA, UK, or other international guidelines (n = 7).

The public survey was mailed to 3000 people over the age of 18 years randomly sampled from the electoral roll of the Hunter region of New South Wales. Of these, 108 were returned as undeliverable, and 757 questionnaires were completed and returned (382 Form A, 375 Form B) giving an overall response rate of 26%. The average age of respondents was 52.2 (SD 16.2) years; the majority (59%) was female; and 20% had a university degree or were currently attending a university. By comparison with the wider population in New South Wales, these respondents tended to be older, better educated, and more likely to be female.[26] On χ^2 and Bayes factor tests there was no statistical difference between answers to the three 'hypothetical gifts' that were common to both Form A and Form B in either the general public or the medical specialist questionnaires.

Table 2 provides a comparison of the responses of the public and medical specialists by the proportions judging each nominated gift appropriate or otherwise and also shows the ranking of each gift from most to least appropriate. The proportions of members of the public who 'always' or 'sometimes' considered it appropriate to accept each of the 'gifts' ranged from a low of 15% (for two movie tickets) to a high of 96% (for patient information leaflets on drugs). Near unanimity was reached on the appropriateness of accepting two 'gifts' (patient information leaflets and drug samples), large majorities (70% or more) judged 17 'gifts' as clearly appropriate or inappropriate, while for six 'gifts' there was no clear agreement as to the appropriateness of these 'gifts' in that a third to two-thirds of respondents differed in their judgements of appropriateness.

The proportions of medical specialists who 'strongly agreed' and 'agreed' that it was appropriate to accept the

Table 2 Percentage of members of general public and medical specialists agreeing it is appropriate to accept nominated 'gifts' from industry†

	% of general public agree 'sometimes' + 'always' appropriate	General public Rank	% of medical specialists 'agree' + 'strongly agree' appropriate	Medical specialists Rank
Patient information leaflets ($10)	96	1	63	2
Drug samples ($100)	92	2	75	1
Appointment books ($10)	86	3	48	7
Flashlight to examine patients ($10)	85	4	50	5=
Lunch for doctor and staff‡ ($100)	83	5§	25	15§
Pens with logo ($10)	82	6	60	3=
Spirometer/ECG machine¶ ($2500)	80	7=§	26	14§
Stethoscope ($100)	80	7=§	33	12§
Pens no logo ($10)	77	9§	60	3=§
Conference with partner ($1200)	76	10§	20	17§
Conference doctor only ($1000)	75	11	40	9
Lunch and lecture with staff ($100)	66	12	35	11
Dinner and lecture with partner ($100)	60	13§	44	8§
Chocolates ($10)	54	14	36	10
Electric scales for patients ($100)	35	15§	50	5=§
Computer for surgery ($2500)	34	16=§	8	21=§
Dinner with partner social ($100)	34	16=	28	13
Theatre tickets with partner ($100)	30	18	13	20
Football ticket ($100)	28	19	17	18=
Refrigerator for staff room ($2000)	24	20	8	21=
Movie ticket ($15)	23	21	17	18=
Laptop for home ($2500)	18	22	4	23
Two movie tickets ($25)	15	23§	21	16§

†All $ values = Australian dollars. ‡Purpose not specified. §Ranking where there is a difference of five or more places between general public and medical specialists. ¶Medical specialists judged appropriateness of spirometer where as general public judged appropriateness of ECG machine. ECG, electrocardiogram.

various suggested 'gifts' ranged from 4% (laptop for home) to 75% (drug samples). Among medical specialists near unanimity was reached on the inappropriateness of accepting a laptop for personal use, a computer or a refrigerator for the surgery. Large majorities (70% or more) judged 10 other 'gifts' as clearly appropriate or inappropriate while for 13 'gifts' there was no clear agreement as to their appropriateness in that a third to two-thirds of respondents differed in their judgements.

For public respondents, patient information leaflets, drug samples and appointment books were ranked as the most appropriate 'gifts' for practitioners to accept and movie tickets and a laptop computer for home use as the least appropriate. For medical specialists, drug samples, patient information leaflets and pens were ranked as the most appropriate 'gifts' to accept while a computer and refrigerator for the surgery and a laptop computer for home use were ranked as the least appropriate. For nine of the nominated 'gifts', there was a substantial difference in ranking between medical specialists and the public with a difference of five or more places between their rankings. These are indicated, in each case, by a section mark (§) in Table 2. Of these nine, there were four 'gifts' in which there was both a five (or more) point difference in ranking and a difference of approximately 50% (47–58%) in the proportions of those finding the gift appropriate between members of the public and medical specialists. These four were: lunch for doctor and staff; spirometer/electrocardiogram machine; conference with partner; and stethoscope.

Discussion

The results of our study make it clear that both medical specialists and members of the public believe that it is acceptable for doctors to accept certain 'gifts' but not others. While consensus on the appropriateness (or otherwise) of some 'gifts' exists within and between groups there also exists some divergence on some of those 'gifts'. Overall, public respondents appeared to be more permissive about doctors accepting 'gifts' from pharmaceutical companies than do medical specialist respondents. There were four 'gifts' in which there was both a five (or more) point difference in ranking between members of the public and medical specialists and a difference of approximately 50% in the proportions of those finding the gift appropriate between the two groups. For each of these four 'gifts' (lunch for doctor and staff, spirometer/ECG

machine, conference with partner, and stethoscope) it was the public that was more accepting.

Public respondents appear to have judged the acceptability of 'gifts' according to a perception of their (more or less direct) relevance to medical practice. This conclusion is based on the observation that 'gifts' of equipment that have a parallel domestic use (e.g. electric scales, refrigerator, laptop computer) were judged appropriate by much smaller proportions of public respondents than 'gifts' of unambiguously clinical items, such as stethoscopes. Medical specialists, on the other hand, appear to have considered a wide range of factors, including the value of the gift, its relevance to patient care, and whether or not the gift extended to others (staff or partners). The items that 50% (or more) of medical specialists agreed were appropriate were either very low cost (pens valued at A$10, patient information leaflets valued at A$10) or relatively low cost and directly relevant to patient care (drug samples valued at A$100, and electric scales valued at A$100). Medical specialists were less accepting of moderate cost and expensive 'gifts' even when the equipment was specific to medicine (stethoscope and spirometer). Neither medical specialists nor members of the public were supportive of any 'gifts' that were clearly not relevant to medicine (laptop computer, tickets to theatre, sporting events) even when the cost of these was minimal (movie tickets).

It is worth noting however that a minority of medical specialists in our study considered 'gifts' appropriate that were not acceptable within the current guidelines.[27] For example, a small percentage agreed that it is appropriate to accept: a laptop computer for home use; a computer for the surgery; theatre tickets including partner; a ticket to a football grand final; and a trip with partner to attend a conference. This information should be of concern to the relevant colleges in their attempts to establish standards for ethical relationships between medical practitioners and industry.

A number of qualifications need to be made to our findings. First, given an overall response rate of 39% for medical specialists and 26% for members of the general public (a difficulty shared with other mail surveys[28]), we are unable to rule out a 'response bias'. It is possible that those with a particular interest in the relationship between pharmaceutical companies and the medical profession were more inclined to respond and their answers may differ from those of the wider populations from which they were drawn. In addition, our public sample was drawn from the Hunter area in New South Wales and it is possible that this region is not representative of the Australian population although we have no reason for believing that views about gifts to doctors are atypical in this area. As this survey was based on self-reports we also cannot be certain that answers given by medical specialists, regarding the acceptability of 'gifts', reflected their behaviour. We have also indicated (above) a caution in comparing two different datasets when the questions put to members of the public were not identical in form to the questions put to medical specialists and there were differences in the response scales. While the overall trends identified by the two groups may be compared, any direct comparison between the two groups in relation to any particular item must be made with caution. Although we have made some comparisons between the two groups, we have confined our specific comments to those items for which there were large differences in the rankings ($\geq$5 places) and large differences between the two groups in the proportions ($\geq$47%) of those judging the gift to be appropriate.

The major findings from this study are similar to those of Gibbons *et al*.[8] which found that both medical specialists and members of the public accept that some low or moderate cost items of clear and direct benefit to patients (e.g. drug samples and patient information leaflets) are appropriate. However, unlike the Gibbons study, we found a greater tendency for members of the public, rather than physicians, to regard 'gifts' as appropriate. In our study a high proportion of members of the public regarded items of direct relevance to medicine to be appropriate 'gifts', including an expensive item of equipment (ECG machine valued at A$2500).

The reason for this tendency for the public to be more accepting of some 'gifts' in our study is unclear. Possible explanations include differences between the public and medical specialists in awareness of the issues surrounding pharmaceutical industry influence on prescribing, a growing awareness among medical specialists of the potential for 'gifts' to bias doctors' judgements, and differences in awareness of ethical guidelines that advise against receiving 'gifts' of this kind. It may also be the case that the Australian public has a greater degree of trust in the capacity of physicians to act always in the best interest of their patients and to make decisions unbiased by 'gifts' from pharmaceutical companies than physicians have towards themselves and their colleagues. Whatever the explanation, we found that the majority of medical specialists in our study were more in line with current ethical guidelines and less inclined to regard 'gifts' from the pharmaceutical industry as appropriate than members of the general public.

There is a broader question, however, which is raised by this study. This is the question of whether public acceptability is a suitable criterion for determining the ethical appropriateness of 'gifts'. While we do not suggest that public acceptance is irrelevant we would be very

concerned if these findings were taken to suggest that a more liberal attitude to gift giving by pharmaceutical companies is indicated. In our view the ethical appropriateness of giving and receiving 'gifts' cannot be determined simply by reference to the prevailing attitudes of either the profession or the public. It is well understood within moral philosophy that consensus on an issue is not determinative of its moral worth. Popular support for racist policies for example does not make them morally justifiable. Similarly, a finding that 80% of the general public would consider it appropriate for a doctor to accept a gift of an ECG machine does not determine its *ethical* appropriateness. In our view judgements about the ethical appropriateness of giving and receiving 'gifts' should give more weight to important values (such as the primacy of patient welfare, autonomy, and social justice[5]), the need for independence of clinical decision-making, and empirical evidence indicating that even small 'gifts' can bias clinicians' judgements.[1,8–10] For all these reasons we consider that any notion that a commitment to transparency and public accountability[18,24] is sufficient to prevent conflicts of interest, or that the real or perceived attitudes of the general public to 'gift' giving may be used as a standard against which a doctor should gauge the acceptability of a gift,[19] is both simplistic and flawed. The finding of our own study, that medical specialists and members of the public regard some 'gifts' as appropriate, has to be weighed against the strong case *against* allowing any 'gifts' as promotional items for doctors.[5,11,16,18]

Our results reveal a relatively liberal public and professional approach to the receipt of some 'gifts' by the medical profession. Those attitudes are at odds with evidence (cited above) that harm may result from these activities. On this basis, and in keeping with other commentators,[11,16] we are persuaded that it is time to eliminate giving and receiving of promotional items between the pharmaceutical industry and members of the health professions.

Acknowledgements

We are grateful to the Australian medical specialists and to the members of the public who took part in our survey questionnaires.

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Internal Medicine Journal **40** (2010) 342–346

ORIGINAL ARTICLE

Acidosis in the hospital setting: is metformin a common precipitant?

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Key words
acidosis, metformin, lactic acidosis, type 2 diabetes.

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Received 30 September 2008; accepted 26 February 2009.

doi:10.1111/j.1445-5994.2009.01959.x

Abstract

Background: Acidosis is commonly seen in the acute hospital setting, and carries a high mortality. Metformin has been associated with lactic acidosis, but it is unclear how frequently this is a cause of acidosis in hospitalized inpatients. The aim of this study is to explore the underlying comorbidities and acute precipitants of acidosis in the hospital setting, including the relationship between type 2 diabetes (T2DM) and metformin use.

Methods: Retrospective review. Cases of acidosis were identified using the hospital discharge code for acidosis for a 3-month period: October–December 2005.

Results: A total of 101 episodes of acidosis were identified: 29% had isolated respiratory acidosis, 31% had metabolic acidosis and 40% had a mixed respiratory and metabolic acidosis. There were 28 cases of confirmed lactic acidosis. Twenty-nine patients had T2DM, but only five of the subjects with T2DM had lactic acidosis; two were on metformin. The major risk factors for development of lactic acidosis were hepatic impairment (OR 33.8, $P = 0.01$), severe left ventricular dysfunction (OR 25.3, $P = 0.074$) and impaired renal function (OR 9.7, $P = 0.09$), but not metformin use.

Conclusion: Most cases of metabolic and lactic acidosis in the hospital setting occur in patients not taking metformin. Hepatic, renal and cardiac dysfunction are more important predictors for the development of acidosis.

Introduction

Metformin is a biguanide hypoglycaemic agent, a group of medications that also includes phenformin and buformin. There are well-recognized benefits of metformin in the management of type 2 diabetes (T2DM). These include weight loss, reduction in all cause mortality, cardiovascular events and diabetes-related complications or death. The UKPDS[1] compared intensive metformin treatment with conventional management and demonstrated a 32% risk reduction in all diabetic endpoints, as well as an overall 36% reduction in all cause mortality. More recently, Evans *et al.* demonstrated a 1.43 relative mortality risk for newly diagnosed diabetics treated with sulphonylurea monotherapy compared with those on metformin monotherapy,[2] confirming that metformin should be first-line therapy. This is further strengthened by recent reports of adverse cardiovascular[3] and skeletal[4] events in patients treated with thiazolidinediones.

The main serious adverse event with metformin use is the development of lactic acidosis,[5] which may occur because of metformin accumulation predominantly in the setting of renal impairment.[6,7] The mechanism may relate to reduced excretion of metformin and increased metabolism of glucose to lactate in intestinal mucosa.[8] The Fremantle Diabetes Study showed an increase in

Funding: None.
Conflict of interest: None.

fasting lactic acid levels in community dwelling patients with T2DM treated with metformin compared with sulphonylureas, but no episodes of symptomatic lactic acidosis were identified.[9] A recent review of hospital admissions with lactic acidosis in this population estimated an incidence of 57/100 000 in those patients taking metformin; however, in all five cases an additional risk factor was present.[10] This is consistent with previous reports that, in most symptomatic cases of metformin-associated lactic acidosis, there is a precipitating acute event with resultant dehydration or renal impairment, rather than an accumulation of metformin in the setting of chronic illness.[11,12] Retrospective analysis estimated the event rate for lactic acidosis in the US at 9.7–16.9/100 000 patient-years prior to the introduction of metformin in 1995, which is indistinguishable from the rate of lactic acidosis after 1995.[13,14] A Cochrane review on the subject found the upper limit for the true incidence of metformin-associated lactic acidosis to be 6.3 cases per 100 000 patient-years, as compared with that in the non-metformin group of 7.8 cases per 100 000 patient-years.[15] These studies imply that the risk of lactic acidosis in patients with diabetes on metformin may be no higher than that for patients with diabetes alone.

Controversy exists regarding the validity of the current contraindications to the use of metformin.[16–18] For example, there have been multiple reports that indicate when metformin is used in patients with the current contraindications, not only has there been no increase in the incidence of lactic acidosis, but also improved control of diabetes. A Scottish retrospective cohort study reviewed 1847 patients with T2DM on metformin, and found that in 24% there were contraindications to its use. Despite this, there was only one episode of lactic acidosis in 4600 patient-years.[19] Similarly, Calabrese *et al.* identified 263 patients in a retrospective analysis,[20] of whom 27% had at least one absolute contraindication to metformin use, and in only 25% of these was metformin discontinued, yet no episodes of lactic acidosis were recorded.

Overall, the evidence suggests that despite a significant proportion of subjects taking metformin outside current guidelines, there has been no documented increase in cases of lactic acidosis. We have therefore reviewed this issue from an alternative perspective – that of acute illness – with the aim to explore the underlying comorbidities and acute precipitants of acidosis in the hospital setting, including the relationship between T2DM and metformin use.

Methods

All cases of acidosis in a tertiary hospital setting over a 3-month period were reviewed. Hospital discharge coding for acidosis was used to identify cases in the period of 1 October to 31 December 2005, a total of 102 patients. Audit of coding accuracy has indicated that this is consistently above 90%. Ethics approval was obtained prior to examination of case notes by a single reviewer and all information recorded by the reviewer was de-identified. Records were available for all patients and one patient was excluded as no evidence of acidosis could be found in either the inpatient notes or pathology results. Classification of acidosis was determined from arterial blood gas on admission to either the hospital or the intensive care unit. Acidosis was defined as a pH <7.35. Lactic acidosis was defined by an elevation in lactate to greater than 4 mmol/L, in association with a metabolic or mixed acidosis. A lactate between 4 and 6 mmol/L was present in three patients who had a pure respiratory acidosis on blood gases, and these three cases were considered not to have lactic acidosis. To obtain an estimate of metformin use in hospital inpatients at the time of the study, the number of patients discharged on metformin over the corresponding period was obtained from Pharmacy records. Although it is possible that the prescription of metformin on discharge may not accurately indicate actual metformin use in the community or on admission, its prescription on discharge indicates an ongoing use or commencement in the hospital setting. Therefore, a rate of in hospital use (which is the setting for our study) at least provides a denominator to calculate metformin-associated complications, such as acidosis.

Laboratory analysis

Formal arterial blood gas assay was performed in the laboratory on a Siemens 865 blood gas analyser using an amperometric electrochemical cell, with the measurement electrode containing lactate oxidase. Adequacy of compensation was determined using formulae previously described.[21] Routine biochemistry was carried out on an Olympus AU2700 automated biochemistry analyser (Olympus Corporation, Tokyo, Japan) by enzymatic assay using lactate oxidase and peroxidase, with bichromatic measurement of the absorbance change because of quinoneimine production. Renal function was assessed on the basis of calculated estimated glomerular filtration rate (eGFR)[22] as this was provided in the subjects records. Impaired renal function was defined as an eGFR < 30 mL/min/1.73 m^2. Left ventricular dysfunction was defined as an ejection fraction <30% on echocardiography or documentation of treated congestive cardiac failure. Impaired hepatic function was defined as alanine transaminase, gammaglutamyl transferase (ALT/GGT) more than twice the upper limit of the laboratory normal range or documentation of chronic liver disease.

Table 1 Patient characteristics

Variable	%
Age average (range)	66.4 years (29–100)
Age >65 years	64
Female	36
Type 2 diabetes	29
eGFR >60	42
eGFR 30–59	40
eGFR <30	19
Congestive cardiac failure (moderate–severe)	24
Respiratory impairment	39
Hepatic impairment	10

eGFR, estimated glomerular filtration rate.

Statistical analysis

Data were analysed using STATA version 10 (Statacorp, College Station, TX, USA). Logistical regression analysis was used to determine the relationship between risk factors and the development of acidosis.

Results

Patient characteristics are outlined in Table 1. The subjects were generally of older age and had other major medical comorbidities. Multiple precipitants for the acidosis were identified, in many cases more than one, as shown in Table 2. Of the 101 episodes of acidosis identified, 29% had isolated respiratory acidosis, 31% had metabolic acidosis and 40% had a mixed respiratory and metabolic acidosis. Therefore, 71% of hospital inpatients in this cohort with acidosis had a metabolic component.

Table 2 Precipitants of acidosis by type

Precipitant	Respiratory acidosis	Metabolic acidosis	Mixed acidosis
AMI	1	2	8
CCF	0	0	4
V+D	1	3	4
Sepsis	7	13	10
Pneumonia	8	3	7
Urosepsis	0	6	2
COAD	4	0	2
Contrast	0	0	4
Surgery	17	11	22
CABG	11	5	12
ARF	1	9	4
VF arrest	1	1	4

AMI, acute myocardial infarction; ARF, acute renal failure; CABG, coronary artery bypass graft surgery; CCF, congestive cardiac failure; COAD, chronic obstructive airways disease; V+D, vomiting and diarrhoea; VF, ventricular fibrillation.

In patients with diabetes, the type of acidosis was evenly distributed with 11 cases of respiratory acidosis, 11 cases of mixed acidosis and 7 cases of metabolic acidosis. Ten of these diabetic patients with acidosis were taking metformin. In five, the acidosis was a pure respiratory acidosis and, in the remainder, only two had an elevated lactate.

Lactate of >4 mmol/L was present in 28 patients with metabolic or mixed acidosis. There were seven patients in whom lactate was not measured, although none of these patients was taking metformin. Of the 28 patients with confirmed lactic acidosis, five had diabetes, two of whom were on metformin. Therefore, metformin-associated lactic acidosis comprised 2% of all presentations with acidosis and 7% of cases of lactic acidosis in this tertiary hospital series. During the time period of this study, 377 patients received metformin as part of their discharge medications, giving a rate of metformin-associated lactic acidosis of 530/100 000 (95% CI 81–1684) patient-years in this inpatient population.

Using logistic regression analysis the most important risk factors for development of acidosis were hepatic impairment (OR 33.8 $P = 0.01$), severe left ventricular dysfunction (OR 25.3 $P = 0.074$) and eGFR <30 (OR 9.7 $P = 0.09$); in each of these cases the confidence intervals are wide. Diabetes was not a significant risk factor for the development of lactic acidosis, in fact lactic acidosis was less common in patients with T2DM (OR −2.09, $P = 0.039$)

The overall mortality for patients in the study was 23%. Mortality varied with type of acidosis, being 39% in those with proven lactic acidosis, although this did not achieve statistical significance ($P = 0.527$). Both patients with metformin-associated lactic acidosis survived to discharge.

Discussion

This study demonstrates that most cases of metabolic and lactic acidosis in the hospital setting occur in patients not taking metformin, and that hepatic, renal and cardiac dysfunctions are important predictors for the development of acidosis. Our data showed a stronger association with hepatic dysfunction than renal or heart disease, but it is likely that with greater numbers all three may have reached statistical significance. While larger studies are needed to help fully identify the relative contribution of metformin in cases of lactic acidosis, our study is consistent with the current evidence that lactic acidosis is precipitated by acute illness or organ dysfunction, rather than accumulation of metformin in the setting of outpatients with stable chronic illness.

The patients in this study were elderly, with an average age of 66.4 years, and had a high rate of coexisting renal,

hepatic, cardiac and respiratory impairment. There were multiple precipitants identified for the development of acidosis. Overall, the mortality in this study was high at 23%, which reflects that the development of acidosis is an end-result of severe illness. The mortality for patients with lactic acidosis of 39% is consistent with that in previous reports.[6,23]

In our subpopulation of patients with T2DM, the type of acidosis was evenly distributed, and 5 of 29 patients had elevated lactate. Using logistic regression analysis, diabetes was not a significant risk factor for the development of lactic acidosis in a mixed medical and surgical patient group. In fact, diabetes was associated with a lower risk of lactic acidosis in this population. Possible explanations include inadequate reporting of diet controlled T2DM, the high number of episodes of lactic acidosis precipitated by surgery or small sample size. Other limitations of the study include the retrospective nature of the data and the issues around case identification. It is recognized that eGFR may not approximate actual GFR at the extremes of renal function, especially in obesity, and is not validated in the diabetic or hospitalized population.[24,25]

The calculated rate of metformin-associated lactic acidosis of 530/100 000 (95% CI 81–1684) patient-years in our inpatient population is significantly higher than in previous reports,[10,12–15] and is likely to relate to the selection of an inpatient rather than community population, the presence of an acute precipitating event, the high rate of comorbid conditions and the advanced age in our cohort.

Lactic acidosis is generally associated with a high mortality, because it results from severe tissue hypoperfusion and end-organ dysfunction. In contrast, true metformin-associated lactic acidosis in the absence of other precipitating factors may have a low mortality as reported by Lalau and Race.[26] The mortality for lactic acidosis in patients on metformin in our study was zero, although there were only two patients in this group. The main limitation of this study is the small sample size, so a statistically significant association of metformin use and lactic acidosis may have been missed. The strength of this audit is that all cases of acidosis are examined, allowing recognition of the importance of acute precipitating factors and underlying comorbidities in the development of acidosis.

Conclusion

In conclusion, while acidosis in general and lactic acidosis in particular is associated with a high mortality in the acute tertiary hospital setting, the relative contribution of metformin is small. The broader literature supports the re-evaluation of current contra-indications for the use of metformin, particularly in patients with mild to moderate stable renal impairment and controlled congestive cardiac failure. Our data demonstrate that most cases of metabolic and lactic acidosis in the hospital setting occur in patients not taking metformin. Severe hepatic and renal impairment (eGFR < 30 mL/min) and left ventricular dysfunction appear to be more important predictors for the development of acidosis than diabetes or metformin use.

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ORIGINAL ARTICLE

Atrial fibrillation and the risk of death in patients with heart failure: a literature-based meta-analysis

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Key words
heart failure, atrial fibrillation, prognosis, meta-analysis.

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Received 27 December 2008; accepted 24 March 2009.

doi:10.1111/j.1445-5994.2009.01991.x

Abstract

Background: Heart failure (HF) and atrial fibrillation (AF) are common, associated with significant morbidity and mortality, and frequently coexist. It is uncertain from published data if the presence of AF in patients with HF is associated with an incremental adverse outcome. The aim of this study was to combine the results of all studies investigating prognosis for patients with HF and AF compared with those in sinus rhythm (SR) to asses the mortality risk associated with this arrhythmia.

Methods: Electronic databases were searched (Biological Abstracts, Current Contents, EMBASE, Medline, Medline In-progress, PubMed and Scopus), to 31 December 2006, using the key words *congestive heart failure*, *heart failure*, *ventricular dysfunction*, *atrial fibrillation*, *atrial flutter*, *sinus rhythm*, *prognosis*, *outcome*, *death* and *hospitalization*. Bibliographies of retrieved publications were hand searched. Studies were eligible if they included a HF population and if outcomes were reported by cardiac rhythm (AF or SR). Studies were reviewed by predetermined protocol (including quality assessment). Data were pooled using a random effects model.

Results: Twenty studies were included (from 3380 initially identified) representing 32946 patients (10819 deaths). Nine randomized controlled trials (RCT) were included. The prevalence of AF was 15%, crude mortality rates were 46% (AF) and 33% (SR). The odds ratio for death was 1.33 (95% confidence interval (CI) 1.12–1.59) for AF compared with SR. Eleven observational studies were included. The prevalence of AF was 23%, crude mortality rates were 38% (AF) and 25% (SR). The odds ratio for death was 1.57 (95% CI 1.20–2.05) for AF compared with SR.

Conclusion: This meta-analysis demonstrates that AF is associated with worse outcomes for patients with HF compared with those with SR. Further research is required to determine whether the adverse outcome associated with AF is related to the arrhythmia itself, or to variables, such as HF severity, patient age and comorbidity.

Funding: This study did not receive any external funding. Several investigators received personal funding (Jithendra Somaratne, Douglas Goodfellow Medical Research Fellowship from the Auckland Medical Research Foundation and the Green Lane Research and Education Fund; Katrina Poppe, National Heart Foundation of New Zealand PhD Scholarship; Gillian Whalley, National Heart Foundation of New Zealand Senior Fellowship). The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Conflict of interest: None.

Introduction

Heart failure (HF) is a common condition, contributing to significant impairment of quality of life, and is associated with high mortality and morbidity.[1,2] Atrial fibrillation (AF) is the most common arrhythmia in the general population and is associated with increased mortality and morbidity even when adjusted for multiple factors, such as age, hypertension and ischaemic heart disease.[3] AF commonly coexists with HF, and the prevalence of AF in patients with HF appears to increase as the severity of HF increases.[4] HF and AF share many of the same predisposing conditions, such as hypertension, coronary artery disease, valvular heart disease and diabetes. The presence of HF leads to electrical and structural changes within the left atrium, which predispose to the development and maintenance of AF.[5,6] In addition, recent data suggest that genetic polymorphisms may increase the likelihood of AF in HF patients.[7] AF may lead to adverse haemodynamic consequences, particularly important in patients with HF, such as abnormalities of diastolic function (including shortened diastole due to high heart rates and loss of atrial 'kick'), impaired left ventricular systolic function due to heart rate irregularity and loss of atrioventricular synchrony, and tachycardia associated ventricular impairment.[8]

Despite the known adverse effects of AF, it is uncertain from published data whether the presence of AF in the context of a diagnosis of HF is associated with an adverse outcome compared with patients with sinus rhythm (SR). Studies that have evaluated the prognostic effect of AF in HF populations are heterogeneous, with wide ranging inclusion criteria, markedly different sample size, and variable length of follow up.

The aim of this literature-based meta-analysis was to combine the results of all studies investigating the prognosis for patients with HF and coexisting AF, compared with those in SR to gain a more accurate assessment of the mortality risk associated with this arrhythmia. The hypothesis was that survival would be worse among patients with heart failure with AF compared with those with SR.

Methods

Search strategy

The strategy for database searching was developed by all authors and the initial literature search was carried out by AP using the following search terms: congestive heart failure OR HF.mp OR heart failure.mp OR ventricular dysfunction AND atrial fibrillation OR atrial flutter OR sinus rhythm AND prognosis OR outcome.mp OR mortality OR death OR morbidity OR hospitalization. Databases were searched from inception until December 2006. Online databases, including Biological Abstracts, Current Contents, EMBASE, Medline, Medline In-progress, PubMed and Scopus were searched using Ovid Technologies, Inc. (New York, NY, USA) software. Hand searching of reference lists of obtained articles and previously identified reviews was carried out. Abstracts, unpublished studies and articles published in languages other than English were not excluded. Authors of included studies were invited to provide details of any additional studies, unpublished data and ongoing trials. An initial pool of 3380 potential publications was identified.

Criteria for study inclusion

Each study was reviewed according to a predetermined protocol, which included information about patients' recruitment and follow up (prospective, retrospective, consecutive recruitment, exclusions and reason), comorbidity, loss to follow up and completeness of data. Randomized controlled trials (RCT) and observational studies were included in this analysis. The titles and abstracts of all studies identified from the search of online databases were initially screened by AP and CW. Studies were evaluated in more detail if they were HF populations and if rhythm (AF or SR) and outcome had been recorded. Any studies that clearly did not meet the selection criteria were discarded. Furthermore, studies that excluded patients on the basis of rhythm, or recruited only patients with AF or SR, were excluded. The abstracts of the remaining studies were then screened by two investigators (AP and CW). Studies were retained or excluded at this stage if they appeared to meet the prespecified study inclusion criteria. The full-text of all retained studies was obtained, citation lists were checked for additional studies, and the two reviewers (CW, AP) agreed on potential publications, in which patient outcome (mortality) was reported according to cardiac rhythm. The final inclusion of studies was determined when consensus was reached by both reviewers and other listed authors. Included studies were required to enrol HF patients with both AF and SR at baseline and to report outcome (death) according to cardiac rhythm.

Data extraction

Data were extracted from included studies and recorded in an electronic database. Data collected included: duration of follow up, number of patients with AF and SR at the start of the study, number of deaths in each group, mean age and gender. The corresponding or senior

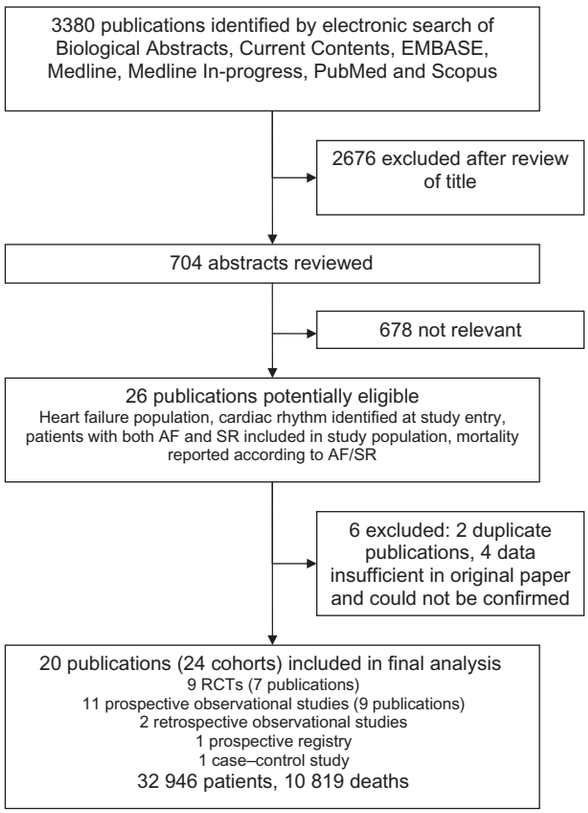

Figure 1 Review process for identification of suitable studies. AF, atrial fibrillation; RCT, randomized controlled trial; SR, sinus rhythm.

authors of all included studies were contacted by email and asked to confirm the data extracted or provide data where the paper's content was insufficient. In the case of potential duplicate publications clarification was sought from the authors and the largest single published dataset was used for the meta-analysis. At the same time, additional references to either published or unpublished studies were sought (Fig. 1).

Statistical methods

For all studies, patients were stratified according to cardiac rhythm (SR or AF). The number of patients and the number of events allocated to each group were recorded. The odds ratios (OR) comparing all-cause mortality in SR and AF were calculated for each study, then combined using a DerSimonian and Laird random effects model[9] to obtain a pooled OR for each of RCT and observational studies. Statistical heterogeneity (differences in the reported effects) and methodological heterogeneity (differences between studies according to characteristics of participants, interventions or outcome measures) were assessed using I^2 [10] and Cochran's Q statistic.[11] Funnel plots[12] were visually assessed for bias. Analyses were performed using the Cochrane Collaboration Program Review Manager v 4.2.1.[13]

This meta-analysis is of a clinically diverse patient population from differing study designs. Heterogeneity between included studies was expected as the search criteria were designed to include studies, which reported outcome stratified by the presence or absence of AF in patients with HF. These studies were not necessarily prospectively designed to evaluate the prognostic effect of AF in a HF population and therefore were expected to differ in methodology. It was decided *a priori* to address a primary source of heterogeneity by stratifying analysis by study design (RCT or observational). Further exploratory analysis of factors contributing to residual heterogeneity within strata was then investigated by sensitivity analysis of the mean I^2 value to assess the effects of study quality (assessed using the method of Hayden[14]), and potential confounders (pharmacotherapy vs non-pharmacotherapy RCT; studies from the pre-ACE (angiotensin converting enzyme) inhibitor era; very severe heart failure (pre-transplant cohorts); heart failure with preserved ejection fraction; studies with very long follow up).

All-cause mortality was the primary end-point. When available, pooled mean age and left ventricular ejection fraction (LVEF) were calculated within each category. Duration of follow up was variably reported between studies and is presented as reported in each publication.

Results

We identified 3380 publications from our literature search of published work. We excluded 2676 (Fig. 1) after review of the title, and a further 678 after review of the abstract. Thus, 26 potential publications were identified[15–40] involving 24 patient cohorts (in two studies there was patient overlap between other included studies[15,16] and thus these were excluded). Of these, 9 were RCT,[33–39] 11 prospective observational studies,[21,23,25,28–32,40] 2 retrospective observational studies,[24,26] 1 registry,[27] and 1 case-control study[22] (Table 1). Four studies were excluded as there was insufficient information in the original paper and further confirmation could not be obtained from the authors; these studies involved 2018 patients, representing 5.8% of potentially available patients.[17–20] Thus, 20 studies describing the association between the presence of AF or SR and mortality in patients with HF were included in this meta-analysis (32946 patients, 10819 deaths). Study data (number of patients and events) were confirmed by 12 of the 20 original authors.

Table 1 Characteristics of included studies

Study, year published	Origin	Data confirmed	Study design	HF population	Follow up (years)	AF (deaths/*n*)	SR (deaths/*n*)
Carson *et al.* (V-HeFT-I), 1993[39]	USA	Numbers in paper	Clinical trial	Male, chronic HF (Class II–III)	Mean 2.5	39/99	237/533
Carson *et al.* (V-HeFT-II), 1993[39]	USA	Numbers in paper	Clinical trial	Male, chronic HF Class II–III)	Mean 2.5	36/107	243/688
Dries *et al.* (SOLVD), 1998[38]	USA	Numbers in paper	Clinical trial	Chronic HF (Class I–II), EF <35%	4	144/419	1395/6098
Crijns *et al.* (PRIME-II), 2000[37]	Netherlands	Numbers in paper	Clinical trial	Chronic HF (Class III–IV), LV dysfunction (EF <35%)	Mean 0.97	50/84	153/325
Swedberg *et al.* (COMET), 2005[36]	Europe	Yes	Clinical trial	Chronic HF (Class II–IV), EF ≤35%	5	255/600	857/2429
Olsson *et al.* (CHARM), 2006[35]	USA/Europe	Yes	Clinical trial	Chronic HF (Class II–IV), EF≤40%	Median 3.14	248/670	1102/3906
Olsson(CHARM-P), 2006[35]	USA/Europe	Yes	Clinical trial	Chronic HF (Class II–IV), EF >40%	Median 3.14	117/478	364/2545
Pedersen *et al.* (Diamond), 2006[34]	Denmark	Numbers in paper	Clinical trial	Patients admitted with HF, EF ≤35%	10	634/818	1951/2661
Wasywich *et al.*, 2006[33]	New Zealand	Yes	Clinical trial	Patients admitted with HF	3	26/62	69/129
Convert, 1980[32]	France†	Yes	Prospective	Consecutive patients admitted with HF	Mean 3.37	6/32	38/100
Unverferth *et al.*, 1984[31]	USA	Yes	Prospective	Patients admitted with HF, EF <50%	1	8/12	16/57
Takarada *et al.*, 1993[30]	Japan	Numbers in paper	Prospective	Consecutive patients admitted with HF, FS <25%	Mean 3.8	3/36	31/111
Stevenson *et al.* 1, 1996[29]	USA	Numbers in paper	Prospective	Consecutive HF patients, transplant assessment, EF <40% (1985–1989)	2	45/73	129/286
Stevenson *et al.* 2, 1996[29]	USA	Numbers in paper	Prospective	Consecutive HF patients, transplant assessment, EF <40% (1990–1993)	2	41/93	75/298
Mahoney *et al.*, 1999[28]	USA	Numbers in paper	Prospective	Consecutive HF patients, transplant assessment, severe LV dysfunction	2	14/63	26/171
Aronow *et al.* EF <50%, 2001[40]	USA	Numbers in paper	Prospective	Chronic HF due to myocardial infarction, EF <50%	3.08	129/132	200/223
Aronow *et al.* EF >50%, 2001[40]	USA	Numbers in paper	Prospective	Chronic HF due to myocardial infarction, EF >50%	3.08	91/98	146/198
Baldasseroni *et al.* (In-CHF), 2002[27]	Italy	Yes	Prospective	Consecutive patients admitted with HF (Registry)	1	166/983	493/4534
Ahmed *et al.*, 2004[26]	USA	Yes	Retrospective	Medicare discharges with primary diagnosis of HF	4	166/233	439/711
Sosin *et al.*, 2004[25]	UK	Yes	Prospective	Patients admitted with HF	8	63/65	129/149
Koitabashi *et al.*, 2005[24]	Japan	Yes	Retrospective	Consecutive patients admitted with HF	2.83	31/188	45/239
Zysko *et al.*, 2005[23]	Poland†	Yes	Prospective	Consecutive patients admitted with HF	7	18/33	25/38
Wojtkowska *et al.*, 2006[22]	Poland	Yes	Case-control study	Consecutive men admitted with HF, EF <30%	3	33/60	26/60
Corell *et al.*, 2007[21]	Denmark	Yes	Prospective	Chronic HF	5.33	88/269	179/750

†Published in language other than English. AF, atrial fibrillation; EF, ejection fraction; FS, fractional shortening; HF, heart failure; LV, left ventricular; SR, sinus rhythm.

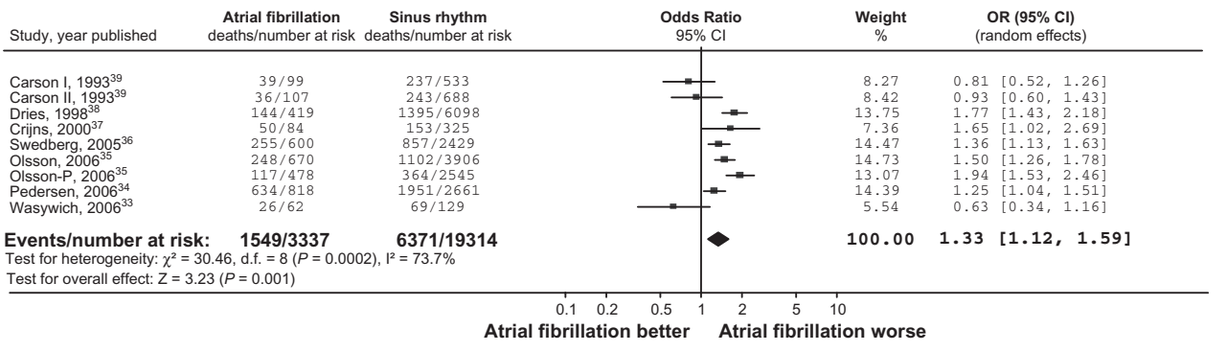

Figure 2 Meta-analysis of the effect of the presence of atrial fibrillation or sinus rhythm on mortality in patients with heart failure (randomized controlled trials). 95% CI, 95% confidence interval.

Randomized controlled trials

The RCT involved 22 651 patients: the prevalence of AF in this cohort was 15% (3337/22 651 patients); and 7920 (35%) patients died during follow up, which ranged from 1 to 10 years. Pooled mean age was 69 years for patients with AF and 64 years for those in SR. Pooled mean LVEF was 33% and 32% in patients with AF and SR respectively. Crude mortality rates were 46% in those with AF and 33% in those with SR. The overall OR for death was 1.33 (95% confidence interval (CI) 1.12–1.59) for those with AF compared with SR (Fig. 2). Significant heterogeneity was observed between these studies (I^2 = 73.7%, Cochran's Q statistic P = 0.0002). The asymmetry of the funnel plot suggests that bias may be present. The 'missing studies' are those that would favour SR, so if present, would support the findings of this meta-analysis (Fig. 3).

Observational studies

A total of 10 295 patients was included from observational studies: the prevalence of AF in this cohort was 23% (2370/10 275 patients); and 2899 (28%) patients died during follow up, which ranged from 1 to 8 years. Pooled mean age was 68 years for patients with AF and 75 years for those in SR. Pooled mean LVEF was 31% and 28% in patients with AF and SR respectively. Crude mortality rates were 38% in those with AF and 25% in

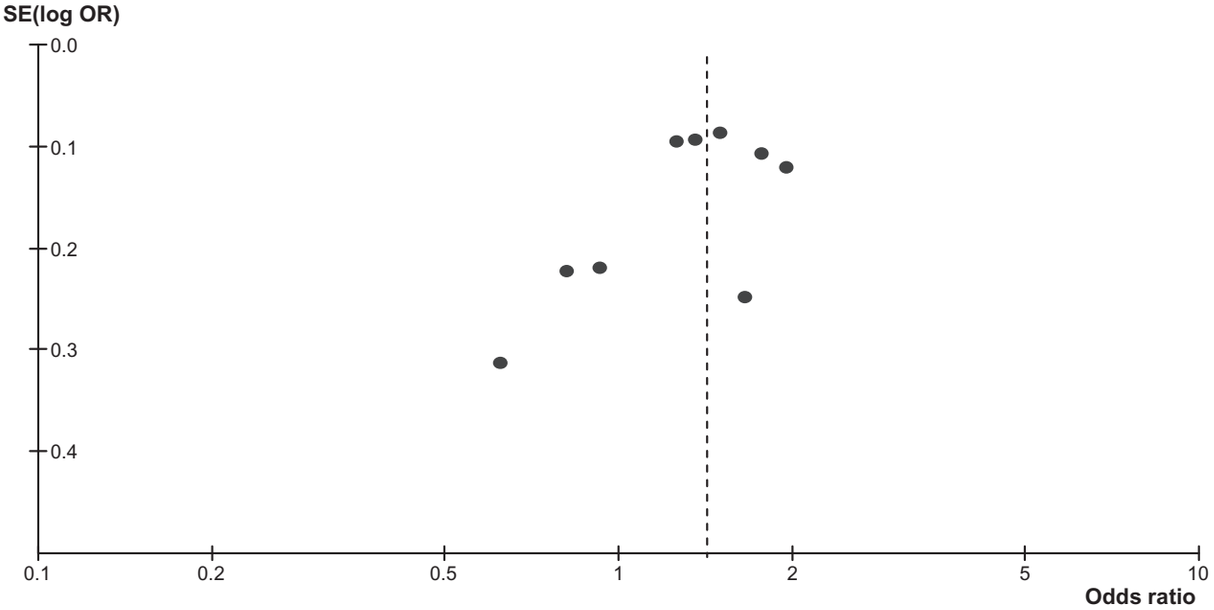

Figure 3 Funnel plot (randomized controlled trials). OR, odds ratio; SE, standard error.

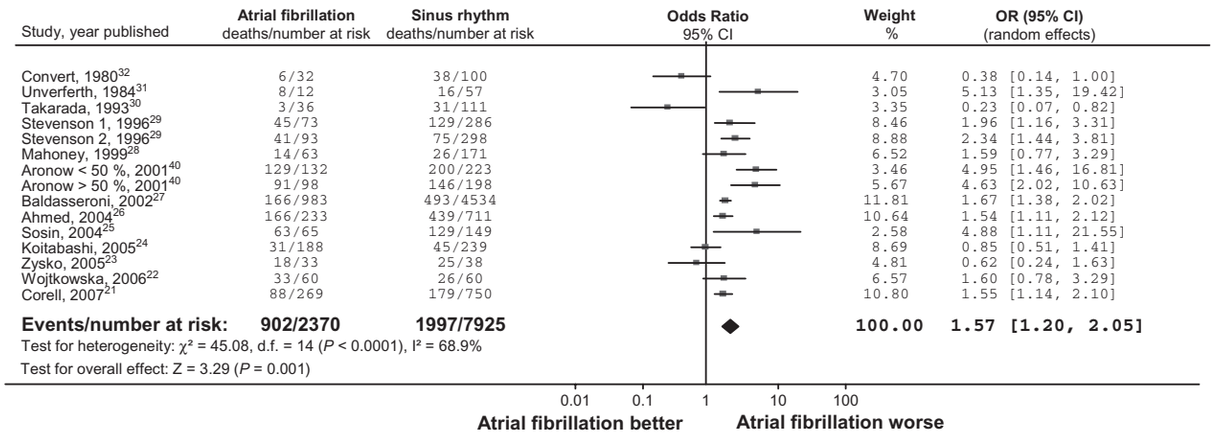

Figure 4 Meta-analysis of the effect of the presence of atrial fibrillation or sinus rhythm on mortality in patients with heart failure (observational studies). 95% CI, 95% confidence interval.

those with SR. The overall OR for death was 1.57 (95% CI 1.20–2.05) for those in AF compared with SR (Fig. 4). Significant heterogeneity was observed between these studies ($I^2 = 68.9\%$, Cochran's Q statistic $P < 0.0001$). The funnel plot does not suggest significant bias in the studies available for inclusion (Fig. 5).

Approach to heterogeneity

Significant residual heterogeneity remained within each of the RCT and observational analyses. The I^2 in the RCT analysis was 73.7%. No studies were identified as low quality. Exclusion of studies according to additional criteria specified above did not significantly reduce heterogeneity further (Table 2). The I^2 value in the analysis of observational studies was 68.9%. The greatest source of heterogeneity in the observational studies appears to relate to studies published before the ACE inhibitor era, exclusion of these studies[30–32] reduced the I^2 to 55.1%. Exclusion of the three studies identified as low quality[23,31,32] also significantly improved heterogeneity (I^2 reduced to 63.1%). Exclusion of other observational

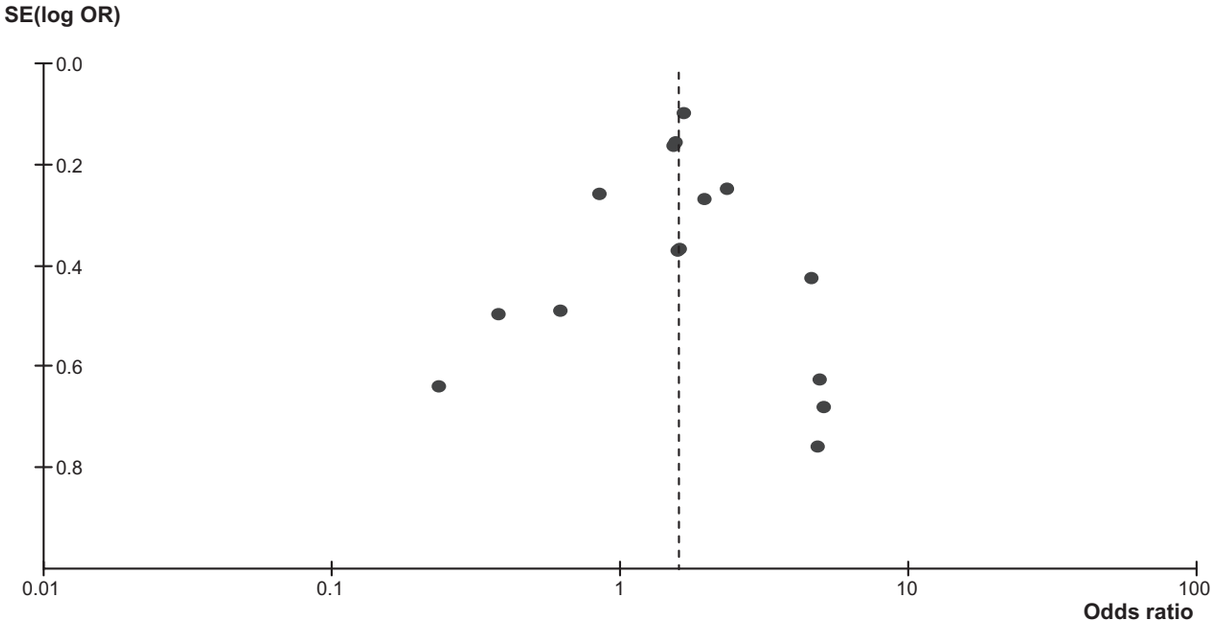

Figure 5 Funnel plot (observational studies). OR, odds ratio; SE, standard error.

Table 2 Sensitivity analysis of sources of heterogeneity

Reason for exclusion	I^2	OR (95% CI)
Randomized controlled trials	73.7	1.33 (1.12–1.59)
Non pharmacotherapy study[33]	70.1	1.4 (1.19–1.65)
Pre-ACE inhibitor era studies[39]	69.3	1.46 (1.24–1.73)
HF with preserved EF[35]	69.5	1.27 (1.06–1.15)
Prolonged follow up[34]	75.2	1.34 (1.09–1.64)
Observational studies	68.9	1.57 (1.20–2.05)
Pre-ACE inhibitor era studies[30–32]	55.1	1.7 (1.36–2.13)
Advanced HF studies[28,29]	73.7	1.46 (1.05–2.03)
HF with preserved EF[40]	66.4	1.47 (1.13–1.91)
Prolonged follow up[23,25]	69.4	1.59 (1.22–2.08)
Low quality studies[23,31,32]	63.1	1.65 (1.46, 1.86)

ACE, angiotensin converting enzyme; 95% CI, 95% confidence interval; EF, ejection fraction; HF, heart failure; OR, odds ratio.

studies according to additional specified criteria did not significantly change the I^2 (Table 2). Importantly, none of these approaches affected the direction or significance of the OR associated with AF.

Discussion

Previous individual studies have reported conflicting evidence of the prognostic impact of coexisting AF among patients with HF.[28,37,38,40–43] This literature-based meta-analysis, including 20 studies (representing 32 946 patients and 10 819 deaths), has shown that patients with HF and coexisting AF have higher total mortality than for patients with SR. The importance of this increase in odds of mortality is highlighted by the differences in the crude mortality rates of patients with AF and SR respectively (RCT 46.4% vs 33.0%, observational studies 38.1% vs 25.2%).

The association between HF and AF is well described: both conditions are common; prevalence increases with increasing age; and both share similar risk factors, such as ischaemic heart disease, hypertension and valvular heart disease. Data from the Framingham study show that the development of new HF in those with AF, or conversely the development of new AF in those with HF, is associated with increased mortality.[43] While this meta-analysis has provided evidence that AF is associated with higher mortality than SR in patients with HF the mechanisms underlying this higher mortality are uncertain. HF is a clinical syndrome and patients with HF have a wide range of underlying risk factors, coexisting diseases and cardiac abnormalities. There are many potential reasons why the presence of AF may worsen HF outcomes, such as abnormalities of diastolic function (including shortened diastole due to high heart rates and loss of atrial 'kick'), impaired left ventricular systolic function due to heart rate irregularity and loss of A-V synchrony, and tachycardia associated ventricular impairment.[8,44] In addition, the presence of AF significantly increases the risk of thromboembolic complications.[45] It is likely that different mechanisms will contribute to AF and subsequent poor outcome in different patients, despite all having the syndrome of HF.

Patients with AF in the RCT cohort were older, compared with those with SR; however, the reverse was true for the patients in the cohort of observational studies. This suggests that the increased mortality associated with AF is not likely to be simply related to patient age.

Previous studies have proposed that the effect of AF on prognosis in patients with HF may be different depending on the severity of HF.[46,47] While there is no universally accepted definition of severity, potential candidates include patient symptoms, hospital admission for HF, LVEF or 'advanced/stage D HF'.[48] Most RCT select HF patients on the basis of LVEF. Although EF is a crude measure of HF severity, within the current meta-analysis, pooled mean EF was similar in patients with AF and SR in both the RCT and observational study cohorts. Studies included in this meta-analysis included a wide range of HF severity, although most used low ejection fraction as a criterion for HF diagnosis.[22,28–30,34–38] In this analysis, the presence of AF in cohorts of advanced HF patients was associated with increased odds of death.[28,29] Conversely, studies that included outpatients with less severe disease suggest that the presence of AF is associated with a neutral effect[39] or increased mortality.[35,36,38] Similarly, the vast majority of studies enrolling patients at the time of hospital admission suggested that the presence of AF was associated with increased mortality[21,22,25–27,31,34,37] with only studies enrolling small numbers of patients suggesting a neutral or beneficial effect of AF on outcome.[23,30,32,33] The CHARM-preserved cohort provides insight into the effect of AF in patients with mild, moderate and severe HF who have relatively preserved ejection fraction. In this group of patients, the presence of AF was clearly associated with increased mortality.[35] This result is consistent with a smaller observational cohort with preserved EF[40] and with the results of a recently published study not included in our meta-analysis, although in this study, the adverse effect of AF on mortality was not independent of covariates.[50] These combined data suggest that the adverse prognostic effect of AF is not simply a function of patient age, HF severity or EF.

The overall adverse prognostic effect of AF in this meta-analysis (OR 1.33 in the RCT cohort, OR 1.57 in the observational study cohort) is very similar to that reported in unselected individuals from the Framingham population,[50] which reported a 1.5 (men)–1.9 (women) increase in mortality risk associated with the presence of AF after adjustment for multiple variables. The

recognition of this adverse prognostic effect of AF in the general population led to the 'rhythm control' approach to therapy, in the hope that the achievement and maintenance of SR in patients with AF would lead to an improvement in outcomes. The publication of the AFFIRM[51] and European[52] studies of rate control compared with rhythm control confirmed that the strategy of rhythm control in HF patients with AF did not improve their outcomes. Our data confirm that the presence of AF in patients with HF is associated with a similar increase in the odds of death compared with the general population, although this translates to a more significant increase in risk because of the poor prognosis of HF patients in general (crude mortality rates in our study increase from 33% to 46% (RCT) and 25% to 38% (observational studies) for HF patients in SR and AF respectively). The recent publication of the AF-CHF study[53] evaluated whether a rhythm control approach to AF in patients with HF was superior to rate control. The strategy of rhythm control did not improve outcomes (no difference in the rates of cardiovascular death) in this patient population. It is possible that the lack of superiority of a rhythm control approach is due in part to the adverse effects of antiarrhythmic drugs. To further evaluate whether return of SR is superior in patients with HF who have coexisting AF, a randomized study comparing catheter ablation of AF to a rate control strategy would be required.

Limitations

There are several limitations of this meta-analysis. One important factor is that most of the studies included in this meta-analysis were not designed to specifically address the prognostic effect of AF in patients with HF. All studies in the RCT cohort except one[33] were retrospective analyses of pharmacotherapy trials, which enrolled a HF population. These data are inherently limited by the selection bias, which occurs with recruitment for these studies. The observational cohort may provide a more 'real world' assessment of the prognostic effect of AF in HF patients. This dataset also included several studies, which were designed specifically to address the question posed by this meta-analysis (drawing patients from multiple sources: heart failure clinics,[21] hospital inpatients,[22,26] a heart failure registry[27] and pre-transplant populations).[28,29] The prognostic effect of AF was at least as important in the observational cohort. By design, the inclusion criteria of this study mean the question of the prognostic impact of the development of AF in patients with HF is not addressed by this study, although other published data suggest this is associated with an adverse prognosis.[54]

Heterogeneity is another important limitation of this meta-analysis and was expected. To explore reasons for heterogeneity, sensitivity analysis was undertaken. Exclusion of studies according to multiple criteria (study quality, pharmacotherapy vs non-pharmacotherapy RCT, studies from the pre-ACE inhibitor era, very severe heart failure (pre-transplant cohorts), heart failure with preserved ejection fraction, studies with very long follow up) attempted to address statistical heterogeneity and methodological heterogeneity. Attempts to address heterogeneity strengthened the results of this meta-analysis (Table 2).

By design, literature-based meta-analyses have many inherent limitations, including publication bias, duplication of published data and the inability to assess the independent impact of possible confounding factors. To minimize publication bias we contacted all corresponding authors of included studies and asked for any unpublished data. Examination of funnel plots does not suggest important publication bias. Duplication of patients in this meta-analysis is unlikely given the rigorous methodology adopted; two studies were excluded for this reason.[15,16] Although our study confirms that the presence of AF in patients with HF is associated with an adverse prognosis, we are unable to assess the impact that confounding factors, such as age, gender, aetiology of HF, severity of HF and duration of HF, may have on our results. Our data are unable to confirm that the presence of AF is independently associated with an adverse prognosis.

Conclusion

This meta-analysis, including all available data, has demonstrated that the presence of AF is associated with worse outcomes for patients with HF compared with those with SR. Further research is required to determine the specific factors associated with this worse outcome, and to subsequently design appropriate interventions to improve outcomes for patients with HF and AF.

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Internal Medicine Journal **40** (2010) 357–363

ORIGINAL ARTICLE

Exploring contrary trends in bladder cancer incidence, mortality and survival: implications for research and cancer control

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Key words
bladder cancer, incidence, mortality, survival trends.

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Received 30 October 2008; accepted 26 January2009.

doi:10.1111/j.1445-5994.2009.01980.x

Abstract

Aim: To investigate trends in bladder cancer incidence, mortality and survival, and cancer–control implications.

Methods: South Australian Registry data were used to calculate age-standardized incidence and mortality rates from 1980 to 2004. Sociodemographic predictors of invasive as opposed to *in situ* disease were examined. Determinants of disease-specific survival were investigated using Kaplan–Meier estimates and proportional hazards regression.

Results: Incidence rates for invasive cancers decreased by 21% between 1980–84 and 2000–04, similarly affecting men and women. Meanwhile increases occurred for combined *in situ* and invasive disease. While mortality rates decreased by approximately a third in men and women less than 70 years of age after the early 1990s, no changes were evident for older residents. The proportion of cancers found at an *in situ* stage was higher in younger ages and more recent diagnostic periods. Five-year survivals of invasive cases decreased from 64% for 1980–84 diagnoses to 58% for 1995–2004. Multivariable analysis showed that diagnostic period was not predictive of survival after age adjustment ($P = 0.719$), with lower survival relating to older age, transitional compared with papillary transitional cancers, female sex, indigenous status and a country as opposed to metropolitan residence.

Conclusions: Reductions in invasive disease incidence may be due to increased detection at an *in situ* stage. The decline in survival from invasive disease in more recent periods is explained by increased age at diagnosis. Poorer outcomes of invasive cases remain for women after adjusting for age, histology, indigenous status and residential location.

Introduction

Bladder cancer accounts for about 2% of invasive cancers and cancer deaths recorded by Australian cancer registries.[1] This corresponded to about 2230 newly diagnosed cancers and 870 cancer deaths in 2003.[1] The age-standardized incidence reduced by about 36% between 1983 and 2003, with similar reductions in men and women.[1] Meanwhile, reductions in mortality rates of approximately 18% took place, with more pronounced decreases in men than women.[1]

Trends in bladder cancer are difficult to interpret because of differences in classification and coding.[2–4] These differences probably account for the twofold to threefold variation in incidence recorded by Australian state and territory cancer registries, despite minor variations in mortality.[5] In the USA, incidence rates have changed little since the early 1980s, but these

Funding: None.
Conflict of interest: None.

data included *in situ* as well as invasive cancers.[3,6] Meanwhile, mortality reductions of about 13% occurred, affecting both sexes.[6]

In a study of 27 European countries, age-standardized bladder cancer mortality was found to be stable until the early 1990s, with reductions of about 14% then occurring in both sexes by the early 2000s.[7] Researchers hypothesized that decreases in smoking or occupational exposures were a plausible explanation for reductions in men, but not in women where it was thought that better control of urinary tract infections and possibly dietary improvements or other factors might have been involved.[7] In England and Wales, the pattern differed, in that incidence rates increased in both sexes between 1971 and 1998, while mortality rates decreased in men but not in women.[2]

Case survivals from bladder cancer are generally lower in women than men, which is contrary to differences seen by sex for many other cancers.[6,8,9] Five-year survivals were 71% for men with invasive bladder cancer in Australia in 1992–97, compared with a corresponding 65% for women.[8] Higher survivals also have been reported for men than women in England and Wales,[10] Europe more generally,[9] and the USA.[6]

USA Surveillance Epidemiology and End Results (SEER) data indicate that the male survival advantage is partly explained by more advanced stages of disease at diagnosis in female patients.[6] Specifically, 27% of staged female cancers were reported to have spread to the regional nodes or more distant sites by diagnosis, compared with 22% of male cases. In addition, for cases with regional spread, men had better outcomes, with 47% surviving 5 years compared with 40% for women.[6] These differences are contrary to patterns seen for many other cancers, where women show earlier stages and better survival.[6,8–13]

Unadjusted 5-year survivals from invasive bladder cancer, reported in New South Wales and South Australia over the past 20 years, have declined while survivals for most cancers increased.[12,13] This trend was not observed in USA SEER data, although these data covered *in situ* as well as invasive cancers.[6]

Because of differences in classification and coding, opportunities for benchmarking and evaluation of effects of public health interventions have been limited for bladder cancer.[2–4] Moreover, the reductions recorded in unadjusted survivals in Australia are at odds with the USA experience and warrant further investigation. [6,12,13]

South Australian Registry data have been collected for bladder cancer using standard coding practices, since around 1980.[11,13] Although differences in pathology practices and registry measurements cannot be excluded, it seems that data from a single registry may give a more accurate interpretation of trends than data from multiple registries where variable coding practices may have applied.[11,13] In addition, *in situ* cancer has been registered by the South Australian Registry since 1980, allowing an assessment of trends for combined *in situ* and invasive cancers, as practised in the USA.[6]

In this study, we investigate trends in incidence, mortality and survival, and differences in survival by sex, using data from the South Australian Cancer Registry.

Methods

Data collection

The Registry has received statutory notifications of invasive and *in situ* bladder cancers since 1977.[11,13] The Registry covers all regions of the State. Its procedures have been described previously.[11] Death data are collected through routine notifications, electronic searches of official State death records, the National Death Index at the Australian Institute of Health and Welfare, and from interstate registries.[11] Under-ascertainment has been checked through active follow up, and with deaths reported independently, and found to be minimal.[11,14]

The present study included 4114 invasive and 3414 *in situ* bladder cancers (International Classification of Diseases for Oncology, 3rd Edition, code C67 [ICDO3: C67]) diagnosed between 1980 and 2004. Data for the 1970s were excluded, because of uncertainty about consistency of coding.

Systemized Nomenclature of Medicine (SNOMED) II histological codes were used to group cases into four broad categories, that is invasive papillary transitional cell carcinomas (81 303), transitional cell carcinomas (81 202–81 243), squamous cell and related carcinomas (80 502–80 823) and remaining histology types.[15]

Sociodemographic descriptors included age at diagnosis; sex; region of residence, classified as 20 statistical subdivisions and as metropolitan or non-metropolitan;[11] country of birth (World Health Organization criteria);[16] indigenous status; and relative socioeconomic disadvantage, as inferred from residential postcode characteristics using the socio-economic indexes for areas; the index of relative socio-economic disadvantage (SEIFA).[17]

Statistical analyses

A de-identified file was extracted and analysed in-house under provisions of the South Australian Health Commission Act, using STATA 9.2 software.[18]

Mean annual incidence and mortality rates were determined for 4-year periods from 1980 to 2004, directly standardizing by 5-year age group (open-ended category

from 85 years) to the 2001 Australian reference population.[19] Ninety-five per cent confidence limits were calculated assuming a Poisson distribution, as described previously.[20] Rates were calculated for all ages combined and for age categories under 40 years and 40–49, 50–59, 60–69, 70–79 and 80 years or more respectively, to assist visualization of trends. Where confidence ranges did not overlap, differences were assumed to be non-random, although with multiple comparisons it is likely that some of these also occurred by chance.

Epidemiological characteristics of *in situ* and invasive cancers were investigated, initially using the Pearson chi-squared test for nominal variables (substituting the Fisher exact test when cell sizes were small) and the Mann–Whitney *U*-test (MW) for ordinal variables.[18,19] Epidemiological characteristics that gave the best-fitting model for predicting invasive as opposed to *in situ* disease also were explored using multiple logistic regression.[19] All sociodemographic variables were entered as predictors, with backwards elimination of those variables where the fit of the model did not reduce as a consequence ($P > 0.05$).[19] Assumptions underlying the analysis, including an absence of colinearity, were found to be satisfied.

Case survivals were calculated, with a date of censoring of live cases of 31 December 2004. Kaplan–Meier product-limit estimates of disease-specific survival were calculated, treating deaths from other causes and people still alive at the end of 2004 as censored observations.[18,19]

Multivariable Cox proportional hazards regression also was undertaken to assess sociodemographic and histological predictors of survival from bladder cancer.[18,19] The regression analysis used the same censoring criteria as for the Kaplan–Meier analyses. All predictor variables were entered into the analysis, with backwards elimination. Assumptions underlying the analysis, including proportionality and an absence of colinearity, were found to be satisfied.[19]

Disease-specific survival was preferred to relative survival in this study because life tables were not available for many population subgroups. Analyses have shown very similar survival estimates in South Australia and New South Wales, irrespective of whether relative survivals or disease-specific survivals were used. [12,21] More recently in South Australia, relative survival figures for invasive bladder cases diagnosed in 1982–2003 were calculated and found to be 58% at 5 years and 50% at 10 years,[13] which compared with corresponding Kaplan–Meier estimates of 59% and 51% respectively. For combined *in situ* and invasive bladder cancers, corresponding relative survivals and Kaplan–Meier estimates were 79% and 78%, respectively, at 5 years, and 74% for both methods at 10 years.

Results

Time trends in incidence and mortality

The annual incidence per 100 000 of invasive bladder cancer (95% confidence limits) reduced by 20.5% from 13.2 (12.3, 14.2) for both sexes combined in 1980–84 to 10.5 (9.8, 11.2) in 2000–04 (Table 1). Whereas a reduction was suggested for men, this was less apparent in women, although the annual mean incidence per 100 000 for 1990–2004 of 4.9 (4.5, 5.3) was still lower than the 1980–84 baseline value of 6.3 (5.5, 7.2) (Table 1). Reductions were more pronounced in the younger age groups, with reductions between 1980–84 and 2000–04 for both sexes combined of 62.8% for those under 50 years, 48.9% for 50–59 years, 30.2% for 60–69 years and 12.3% for 70–79 years, and with a 0.4% increase recorded for those aged 80 years or more.

The annual incidence per 100 000 of *in situ* and invasive cancers combined showed a converse trend, increasing 33.3% from 17.1 (16.0. 18.2) for both sexes combined in 1980–84 to 22.8 (21.8. 23.8) in 2000–04 (Table 1). Both sexes showed an increase. The increase was less pronounced in the age range under 70 years (13.1%) than in older ages (48.4%).

Mortality rates for all ages combined did not show a consistent trend, although the mean annual rate for 2000–04 tended to be lower than beforehand (Table 1). This was mostly due to a low 2000–04 figure for women, although with overlapping confidence ranges, this low figure could have occurred by chance.

A reduction in mortality was suggested for ages less than 70 years after the early 1990s, affecting men and women. A trend was not suggested between 1980–84 and 1990–94, but the annual mortality per 100 000 then decreased from 1.29 (1.14, 1.46) for 1980–94 to 1.21 (0.97, 1.50) for 1995–99 and 0.88 (0.68, 1.12) for 2000–04, comprising a 31.8% reduction. Meanwhile, a secular trend was not suggested for mortality rates in the age range of 70 years and over.

Comparison of sociodemographic characteristics of invasive and *in situ* lesions

In situ lesions tended to be diagnosed at a younger age than invasive cases (MW $P < 0.001$). The proportion of lesions that were *in situ* decreased from 73.1% for patients less than 40 years to 69.7% for 40–49 years, 53.8% for 50–59 years, 47.0% for 60–69 years, 43.1% for 70–79 years and 35.7% for those aged 80 years or more. *In situ* lesions also tended to be diagnosed in later diagnostic periods than invasive cases (MW $P < 0.001$). The percentage of lesions that were *in situ* increased from

Table 1 Mean annual age-standardized (Australia, 2001) incidence and mortality rates (95% confidence limits) for bladder cancer per 100 000 South Australians by sex and calendar year period†

		Year					
		1980–84	1985–89	1990–94	1995–99	2000–04	1980–2004
Incidence (invasive)	Men	(*n* = 530)	(*n* = 601)	(*n* = 590)	(*n* = 636)	(*n* = 677)	(*n* = 3034)
		22.8	22.6	19.5	19.0	17.8	20.3
		(20.9, 24.8)	(20.8, 24.5)	(18.0, 21.1)	(17.6, 20.5)	(16.5, 19.2)	(19.6, 21.0)
	Women	(*n* = 200)	(*n* = 203)	(*n* = 201)	(*n* = 216)	(*n* = 260)	(*n* = 1080)
		6.3	5.6	4.9	4.7	5.0	5.3
		(5.5, 7.2)	(4.9, 6.4)	(4.2, 5.6)	(4.1, 5.4)	(4.4, 5.6)	(5.0, 5.6)
	Total	(*n* = 730)	(*n* = 804)	(*n* = 791)	(*n* = 852)	(*n* = 937)	(*n* = 4114)
		13.2	12.6	11.0	10.7	10.5	11.6
		(12.3, 14.2)	(11.7, 13.5)	(10.2, 11.8)	(10.0, 11.4)	(9.8, 11.2)	(11.2, 12.0)
Incidence (invasive and *in situ*)	Men	(*n* = 695)	(*n* = 964)	(*n* = 1128)	(*n* = 1313)	(*n* = 1499)	(*n* = 5599)
		29.4	35.3	36.2	38.4	38.9	35.7
		(27.3, 31.7)	(33.1, 37.6)	(34.1, 38.4)	(36.4, 40.5)	(37.0, 40.9)	(34.8, 36.6)
	Women	(*n* = 262)	(*n* = 322)	(*n* = 382)	(*n* = 449)	(*n* = 514)	(*n* = 1929)
		8.3	9.0	9.5	10.1	10.3	9.4
		(7.3, 9.3)	(8.0, 10.0)	(8.6, 10.5)	(9.2, 11.1)	(9.4, 11.2)	(9.0, 9.8)
	Total	(*n* = 957)	(*n* = 1286)	(*n* = 1510)	(*n* = 1762)	(*n* = 2013)	(*n* = 7528)
		17.1	20.0	21.0	22.2	22.8	20.6
		(16.0, 18.2)	(18.9, 21.1)	(20.0, 22.1)	(21.2, 23.3)	(21.8, 23.8)	(20.1, 21.1)
Mortality	Men	(*n* = 182)	(*n* = 232)	(*n* = 230)	(*n* = 279)	(*n* = 315)	(*n* = 1238)
		9.2	9.5	8.5	8.9	9.0	9.0
		(7.9, 10.6)	(8.3, 10.8)	(7.4, 9.7)	(7.9, 10.0)	(8.0, 10.1)	(8.5, 9.5)
	Women	(*n* = 76)	(*n* = 89)	(*n* = 124)	(*n* = 116)	(*n* = 119)	(*n* = 524)
		2.5	2.5	3.0	2.5	2.2	2.5
		(2.0, 3.1)	(2.0, 3.1)	(2.5, 3.6)	(2.1, 3.0)	(1.8, 2.6)	(2.3, 2.7)
	Total	(*n* = 258)	(*n* = 321)	(*n* = 354)	(*n* = 395)	(*n* = 434)	(*n* = 1762)
		5.1	5.3	5.1	5.0	4.8	5.0
		(4.5, 5.8)	(4.7, 5.9)	(4.6, 5.7)	(4.5, 5.5)	(4.4, 5.3)	(4.8, 5.2)

†Data source: South Australian Cancer Registry.

23.7% in 1980–84 to 37.5% in 1985–89, 47.6% in 1990–94, 51.6% in 1995–99 and 53.5% in 2000–04. Differences between *in situ* and invasive cases were not found in relation to sex distribution (chi-squared $P = 0.171$) or place of residence, whether expressed as statistical subdivisions (chi-squared $P = 0.565$) or as metropolitan or country (chi-squared $P = 0.907$). Similarly, differences were not found by socioeconomic status (MW $P = 0.322$), indigenous status (Fisher exact test $P = 0.524$) or country of birth (chi-squared $P = 0.325$).

Multiple logistic regression indicated that age at diagnosis and diagnostic period was the variable most predictive of invasive as opposed to *in situ* stage, with the relative odds of an invasive stage increasing with age and decreasing in later diagnostic periods (Table 2). No other variable was found to increase model fit.

Table 2 Relative odds (95% confidence limits) of diagnosis with invasive compared with *in situ* bladder cancer at diagnosis: South Australian Cancer Registry, 1980–2004†

Predictors	Relative odds
Age at diagnosis (years)	
Under 50 (reference) (*n* = 432)	1.00
50–59 (*n* = 887)	2.14 (1.67, 2.75)
60–69 (*n* = 1928)	2.92 (2.32, 3.67)
70–79 (*n* = 2639)	3.71 (2.97, 4.65)
80+ (*n* = 1642)	5.34 (4.22, 6.75)
Diagnostic period:	
1980–84 (reference) (*n* = 957)	1.00
1985–89 (*n* = 1286)	0.49 (0.40, 0.59)
1990–94 (*n* = 1510)	0.32 (0.26, 0.38)
1995–99 (*n* = 1762)	0.26 (0.22, 0.31)
2000–04 (*n* = 2013)	0.23 (0.19, 0.27)

†Multivariable logistic regression analysis, entering age, diagnostic period, sex, region of residence, country of birth, indigenous status and SEIFA index of relative socioeconomic disadvantage and using backwards elimination to select variables giving the model of best fit (see text). Data source: South Australian Cancer Registry.

Survivals

Survival (±standard error) from invasive bladder cancer was 59.8% (±0.9) at 5 years from diagnosis during

Table 3 % survival (±SE) from bladder cancer in South Australia by diagnostic year and period from diagnosis: South Australian Cancer Registry, 1980–2004†

	Diagnostic year		Period from diagnosis (years)				*P*-value‡
			5	10	15	20	
Invasive and *in situ*	1980–1984 (*n* = 957)	100	72.9 (±1.5)	66.7 (±1.7)	63.5 (±1.8)	60.4 (±1.9)	
	1985–1989 (*n* = 1286)	100	76.1 (±1.3)	70.8 (±1.4)	67.8 (±1.5)	—	
	1990–1994 (*n* = 1510)	100	78.4 (±1.1)	74.7 (±1.2)	—	—	<0.001
	1995–2004 (*n* = 3775)	100	80.2 (±0.8)	—	—	—	
	Total (*n* = 7528)	100	77.9 (±0.5)	73.3 (±0.6)	70.2 (±0.8)	67.2 (±1.1)	—
Invasive	1980–1984 (*n* = 730)	100	64.2 (±1.9)	55.9 (±2.1)	51.7 (±2.2)	43.4 (±1.4)	
	1985–1989 (*n* = 804)	100	61.3 (±1.8)	52.7 (±2.0)	47.7 (±2.1)	—	0.027
	1990–1994 (*n* = 791)	100	57.9 (±1.9)	50.8 (±2.0)	—	—	
	1995–2004 (*n* = 1789)	100	57.8 (±1.4)	—	—	—	
	Total (*n* = 4114)	100	59.8 (±0.9)	52.0 (±1.0)	47.3 (±1.1)	43.4 (±1.4)	—

†Kaplan–Meier product-limit estimates. Date of censoring of live cases: 31 December 2004; ‡Derived from Cox proportional hazards regression, unadjusted for other variables. Data source: South Australian Cancer Registry.

1980–2004, with corresponding survivals of 62.0% (±1.0) for men and 53.3% (±1.7) for women. When *in situ* and invasive cancers were combined, the 5-year survival was 77.9% (±0.5), with the survivals of 79.3% (±0.6) for men and 73.9% (±1.1) for women.

Survivals increased with later diagnostic period for combined *in situ* and invasive cancers, with 5-year figures ranging from 72.9% (±1.5) for 1980–84 to 80.2% (±0.8) for 1995–2004 (Table 3). By comparison, survivals decreased for invasive cancers, with 5-year figures decreasing from 64.2% (±1.9) for 1980–84 to 57.8% (±1.4) for 1995–2004.

Multivariable proportional hazards regression indicated that survival from invasive bladder cancer did not change by period of diagnosis after adjusting for age at diagnosis ($P = 0.719$). This applied, irrespective of whether age was expressed as a continuous variable, or as dummy variables as shown in Table 4.

The only predictors of lower survival retained in the model were increasing age at diagnosis, female sex, transitional as opposed to papillary transitional histology, non-transitional cell type, indigenous status and a country as opposed to a metropolitan place of residence (Table 4). Neither socioeconomic status, country of birth, nor diagnostic period was found to improve model fit ($P > 0.200$) and were excluded from the final model.

When a corresponding regression analysis was undertaken for combined *in situ* and invasive cases, the results were similar with lower survival found with increasing age at diagnosis, female sex, non-transitional cell histology types, indigenous status and a country as opposed to a metropolitan place of residence. However, survival was better for cases diagnosed in 1995–2004 than beforehand ($P = 0.027$).

Discussion

In the USA, *in situ* and invasive cancers are reported collectively by the SEER programme to avoid bias from

Table 4 Relative risk (95% confidence limits) of death from bladder cancer among invasive cancer: South Australian Cancer Registry, 1980–2004†

Predictors	Relative risk
Age at diagnosis (years)	
Under 40 (reference) (*n* = 40)	1.00
40–49 (*n* = 87)	1.69 (0.72, 3.97)
50–59 (*n* = 410)	2.65 (1.24, 5.69)
60–69 (*n* = 1021)	3.31 (1.56, 7.01)
70–79 (*n* = 1501)	4.68 (2.21, 9.89)
80+ (*n* = 1055)	7.73 (3.65, 16.36)
Sex	
Male (reference) (*n* = 3033)	1.00
Female (*n* = 1081)	1.21 (1.08, 1.34)
Histological type	
Transitional cell (reference) (*n* = 2126)	1.00
Papillary transitional cell (*n* = 1657)	0.45 (0.41, 0.51)
Squamous cell and related (*n* = 86)	2.41 (1.85, 3.13)
Other (*n* = 153)	1.39 (1.11, 1.75)
Unknown (*n* = 92)	1.86 (1.40. 2.46)
Race	
Non-indigenous (*n* = 4108)	1.00
Indigenous (*n* = 6)	3.19 (1.32, 7.71)
Place of residence	
Metropolitan (*n* = 3138)	1.00
Country (*n* = 976)	1.31 (1.18, 1.47)

†Multivariable Cox proportional hazards regression, entering age, diagnostic period, sex, region of residence, country of birth, indigenous status and SEIFA index of relative socioeconomic disadvantage, and using backwards elimination to select variables giving the model of best fit (see text). Date of censoring of live cases: 31 December 2004. Data source: South Australian Cancer Registry.

differences in definition.[3,6] When this is done, SEER data do not show the reductions in incidence reported for invasive cancer by Australian registries and some European registries.[1,6,22] Indeed, a slight increase is suggested.[6]

The data presented in this study are confirmatory in not showing a decrease for combined *in situ* and invasive incidence. As in the USA,[6] an increase is indicated. However, as in Europe and Australia more generally, a decrease in invasive cancer incidence is indicated.[1,7]As suggested by some researchers, reductions in tobacco smoking and occupational exposures to carcinogens may have contributed,[2,7] but the similar scale of reduction in men and women suggests that other factors may be involved.[7] In South Australia, lung cancer mortality rates have reduced for men, but increased for women, which is consistent with differences in prior smoking trends by sex, but contrary to the trends seen for bladder cancer.[23]

An alternative hypothesis is that the underlying bladder cancer risk did not reduce in our population during 1980–2004. Indeed an increase may have occurred, reflected in the increased incidence of combined *in situ* and invasive disease. An explanation for the reduced incidence of invasive cancer could be the increased detection of bladder cancer when still at an *in situ* stage, particularly in the younger age groups. This and ongoing patient surveillance could have prevented progression of *in situ* to invasive disease, accounting for reduced numbers of invasive cancers, and fewer deaths in the age range less than 70 years, but leading to an increase in age at diagnosis of invasive cancers and a consequent reduction in survival.

This unfavourable survival trend for invasive cancers was eliminated when age was controlled in the model. Also, survivals for combined *in situ* and invasive lesions showed a progressive improvement during 1980–2004, which remained after adjusting for age, sex, place of residence and indigenous status. The extent to which this reflects true survival benefits, as opposed to lead time, length time, over-diagnosis and related factors, warrants further investigation.

The 5-year survival of 80% for combined *in situ* and invasive cancer in 1995–2004, based on the Kaplan–Meier analysis, equated with a marginally lower estimate of 79% when relative survival was substituted. Comparisons with USA SEER relative survival data for combined *in situ* and invasive cancer show similar 5-year results, in that the SEER figure was 81% for 1996–2003.[6]

In our population, there was little evidence of a secular reduction in bladder cancer mortality for all ages combined, although a reduction of 32% was indicated in the age range under 70 years for the period since the early 1990s, which hopefully will extend to older age groups. This is consistent with the finding of a greater proportion of *in situ* bladder cancer in this younger age range.

Along with other researchers, we suspect that the higher case fatality in women than men reflects the more advanced stages at diagnosis, as demonstrated by the USA SEER data.[6] Because of anatomical differences, haematuria may not be noticed as readily by women. In addition, women may attribute it on some occasions to menstrual bleeding or it may be assumed to be a result of bladder infection. Although speculative, it is also possible that increased awareness in men of prostate cancer has increased their likelihood of responding promptly to urology symptoms, including haematuria.

USA data also point to poorer outcomes for women than men for bladder cancers overall, and for those diagnosed with regional spread of disease.[6] Further research is needed to determine whether these findings apply in Australia and if so, the explanations for them. We are unable to address these matters further, as stage of invasive cancer is not recorded in the Registry.

Our data confirm other findings of poorer survivals in old patients.[6,8,10] The extent to which this disparity could be reduced is uncertain, as higher levels of comorbidity and frailty in the aged could impose compromises to treatment plans. The poorer outcomes for indigenous patients, although based on very small numbers, were statistically significant ($P < 0.050$) and consistent with previous study findings for other cancers where poorer outcomes have been associated with later stages at diagnosis and less complete care.[24–26]

The poorer survivals for country than metropolitan patients may reflect less ready access to specialist diagnostic and treatment services in country areas. Further research may be warranted to find means of increasing service access and availability in country areas.

The higher survivals for papillary transitional compared with transitional cell and other cell types observed in this study confirm other but not all findings.[27,28]

Conclusions

Reductions in invasive disease incidence and increased age at diagnosis may be due to earlier detection of lesions at an *in situ* stage and at a younger age. Although survival from invasive disease has reduced, this is explained by increased age at diagnosis. Poorer case outcomes remain in women after adjusting for age, histology, indigenous status and place of residence, which warrant further investigation and remedial attention, including earlier diagnosis.

Acknowledgements

Staff members of the South Australian Cancer Registry are thanked for the care taken over so many years in the collection of data used in this study.

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Internal Medicine Journal **40** (2010) 364–371

ORIGINAL ARTICLE

Acute care costs of patients admitted for management of chronic obstructive pulmonary disease exacerbations: contribution of disease severity, infection and chronic heart failure

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Key words
chronic obstructive pulmonary disease, cost of illness, chronic heart failure.

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Received 3 August 2008; accepted 15 December 2009.

doi:10.1111/j.1445-5994.2010.02195.x

Abstract

Background: In 2003, chronic obstructive pulmonary disease (COPD) accounted for 46% of the burden of chronic respiratory disease in the Australian community. In the 65–74-year-old age group, COPD was the sixth leading cause of disability for men and the seventh for women.
Aims: To measure the influence of disease severity, COPD phenotype and comorbidities on acute health service utilization and direct acute care costs in patients admitted with COPD.
Methods: Prospective cohort study of 80 patients admitted to the Royal Melbourne Hospital in 2001–2002 for an exacerbation of COPD. Patients were followed for 12 months and data were collected on acute care utilization. Direct hospital costs were derived using Transition II, an activity-based costing system. Individual patient costs were then modelled to ascertain which patient factors influenced total direct hospital costs.
Results: Direct costs were calculated for 225 episodes of care, the median cost per admission was AU$3124 (interquartile range $1393 to $5045). The median direct cost of acute care management per patient per year was AU$7273 (interquartile range $3957 to $14 448). In a multivariate analysis using linear regression modelling, factors predictive of higher annual costs were increasing age ($P = 0.041$), use of domiciliary oxygen ($P = 0.008$) and the presence of chronic heart failure ($P = 0.006$).
Conclusion: This model has identified a number of patient factors that predict higher acute care costs and awareness of these can be used for service planning to meet the needs of patients admitted with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic systemic inflammatory disease associated with considerable morbidity and consequent cost burden.[1–6] Clinical presentation usually occurs during the fifth and sixth decades of life, when respiratory symptoms begin to affect daily activities. Once diagnosed, the disease progresses over two or three decades, resulting in significant physical as well as psychological disability. Based on death certification, current estimates of COPD-related mortality are likely to be underestimated, particularly because sudden cardiac deaths and deaths secondary to pneumonia may be attributable to underlying COPD.[7]

Funding: None.
Conflict of interest: None.

The chronic systemic inflammation associated with COPD has been linked to increased risk of ongoing chronic lung damage, cardiovascular disease, mortality risk and muscle wasting.[2–6] Amplification of the inflammatory process associated with acute exacerbations of COPD (AECOPD) may in part explain the association between AECOPD and the increased risk of acute myocardial infarction and deterioration of chronic heart failure (CHF) in these patients.[8,9]

Acute health costs

COPD is a leading contributor to death, disability and the economic burden of disease in Australia and internationally.[10] With the population ageing, it is clear that COPD will continue to contribute to this economic burden for some years to come. Much of the economic cost of COPD is attributable to the direct cost of managing AECOPD, particularly those resulting in hospitalization.[11] In Australia during the years 1993–1994, hospitalization was estimated to account for 37% of the total direct cost of managing COPD.[12]

The cost of COPD management increases as disease severity increases, mainly as a result of more frequent acute care admissions.[11–16] In a review of the economic burden of COPD in the USA, Foster *et al*. found that direct cost estimates per patient lay between US$2700 and US$5900 annually, with inpatient hospitalization accounting for up to 70% of all direct costs.[11] Hilleman *et al*.[13] found that healthcare utilization and costs were highly correlated with disease severity. The COPD phenotype may also influence cost. For example, patients who have frequent AECOPD may have more frequent admissions and therefore higher acute care costs.[16,17]

Ambulatory care sensitive conditions

COPD is now recognized as being an ambulatory care sensitive condition amenable to chronic disease management strategies.[18] Overall, COPD is the second commonest cause of potentially preventable admission in Australia, with a rate of 282.6 admissions per 100 000 population. As COPD is a highly prevalent condition and the predominant cost of COPD management results from utilization of acute care services, small decreases in patient admission rates can result in large potential cost savings at a population level. Efforts to reduce inpatient admissions for COPD have centred around three approaches: (i) disease prevention (smoking cessation, influenza immunization),[19] (ii) optimization of patient management according to evidence-based clinical practice guidelines (e.g. pulmonary rehabilitation & smoking cessation programmes and domiciliary oxygen therapy) and (iii) rapid treatment of AECOPD.[20]

To develop appropriate and targeted disease management programmes for ambulatory care sensitive conditions, it is important to have accurate information about factors predisposing patients to frequent acute care admissions. These factors are likely to include disease-specific issues, such as COPD severity, susceptibility to infection and comorbid disease. They also comprise issues relating to healthcare service delivery, including access to pulmonary rehabilitation and community-based supportive services, as well as socioeconomic factors.

Aim

The current study was undertaken to measure the influence of disease severity, COPD phenotype and comorbidities on acute health service utilization and direct acute care costs in patients at risk of admission to acute care for management of an exacerbation of COPD.

Methods

Study design

A prospective cohort of 80 patients were selected from 390 presenting to the Royal Melbourne Hospital between July 2001 and June 2002 with AECOPD. Patients were recruited within 4 weeks of discharge of their index admission (defined as the first admission during the study period). Inclusion criteria were diagnosis of COPD according to Global Initiative for Obstructive Lung Disease (GOLD), criteria stage 2—4,[20] smoking history of greater than or equal to 10 pack-years, age greater than 40 years and willingness to give informed consent. At recruitment spirometry was carried out, the Modified Medical Research Council Dyspnoea Scale was recorded[21] and the 6-min walking distance calculated.[22] COPD severity was defined according to GOLD guidelines criteria.[20,23]

Cost data

Detailed data for the costing for each inpatient admission were obtained by medical record review. Data included were: length of stay, admission unit and destinations, reason for admission, medical interventions and pharmacological management. Acute care costs (both emergency and inpatient services) were estimated using Transition II software, an activity-based costing system, to model the actual costs of delivering acute inpatient care. Direct cost categories modelled using this software system included: hotel costs (accommodation, food, etc.), investigations

(radiology and pathology), and the cost of medical, nursing and allied health time.

Medication costs

Costs of pharmaceuticals were derived using two methods. First, using Transition II the cost of pharmaceuticals was derived at a ward level, and second to measure the actual cost of treating COPD exacerbations, the actual medications prescribed for each patient were collated. The cost of medications was calculated using the actual cost of 'imprest stock items' supplied by the hospital pharmacy to the ward and published Pharmaceutical Benefits Scheme costs for non-ward stock items.

Statistical analysis

Summary data are presented for patient demographics and cost components. Summary cost data (median and interquartile range (IQR)) are given per episode of care (admission or emergency presentation) and annual per patient cost. Summary measures of costs are presented as median, IQR and range as the data were right-skewed (Fig. 1).

To evaluate the representativeness of the study cohort, the characteristics of the study cohort were compared with all patients who presented to Royal Melbourne Hospital with AECOPD in 2001–2002 using Wilcoxon signed-rank tests for non-parametric data and linear regression.

Linear regression analysis was used to determine the effect of patient factors (sex, age, comorbidities, COPD disease severity and subtype) on acute health service utilization rates and total annual acute healthcare costs per patient. Continuous variables were log-transformed before regression analysis to attain a normal distribution. Backwards linear regression was used to develop multivariable prediction models for factors that predict total annual presentation rates and total annual bed-days in acute care. Univariate variables were retained in the model if the regression coefficient was greater than one and the *P*-value less than 0.05. To assess that the natural log of these variables gave a normal (Gaussian) distribution, χ^2 tests were carried out. All statistical analyses were carried out using STATA version 8.2 (StataCorp. LP, College Station, TX, USA).[24]

Results

Total admissions to acute care during the study period

During the study period 1 July 2001 to 30 June 2002, 390 patients, aged 50 years or older, presented to Melbourne Health with a primary discharge diagnosis of COPD, of these 72 (18%) were emergency department admissions only. For the 318 patients who had multi-day index admissions, the median length of stay was 5 days (IQR 2–7), minimum 2 and maximum 61 days. The median age of patients at the index admission was 74 years (IQR 66–80), and 60% were male. Comparing the patients recruited to the costing study ($n = 80$) with all ($n = 238$) patients admitted for COPD during the study period, the two groups were well matched for median age and sex. The median number of comorbidities recorded on the administrative dataset was 3 for each group ($P = 0.221$). Median length of stay per admission for the study group was 4 days (IQR 3–6) versus the comparison group 5 days (IQR 2–8) ($P = 0.520$). During the follow-up period, however, study patients had more frequent COPD-related multi-day admissions per unit time (incident rate ratio 1.63 [95% confidence interval (CI), 1.34–

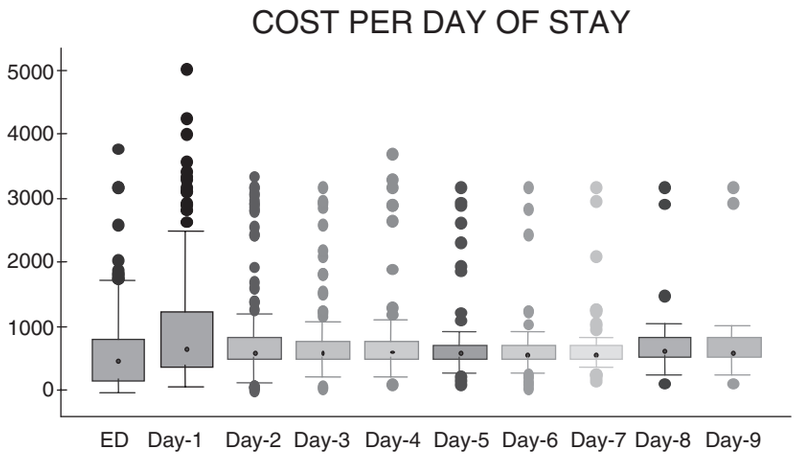

Figure 1 Median, interquartile range and range of costs per day of admission.

1.99], $P < 0.001$). Indicating that the study sample included a small number of patients with very frequent hospital presentations (≥5 per year), these patients were included in the analysis so that the characteristics of this high healthcare utilization group could be further explored.

Participants in the costing study

Eighty patients were included in the study, median age 73 years (range 54–88), 59% were male and 58% were born in Australia. Patient baseline characteristics are listed in Table 1. Sixty-nine per cent of participants had chronic bronchitis, including 8% who had bronchiectasis and an additional 19% who had concomitant asthma. A history of cardiac and vascular diseases was common in the cohort, including angina (19, 24%), past history of acute myocardial infection (22, 28%), cardiac arrhythmias (17, 21%), chronic heart failure (27, 34%), peripheral vascular disease (5, 6%) and cerebral vascular disease (6, 7%).

Acute healthcare costs

Detailed cost data were obtained for 225 presentations to acute care, of these 40 (18%) were managed by emergency department services only, while 185 (82%) required inpatient admission. The mean length of stay in acute care (emergency or inpatient admission) for those requiring admission was 6.43 days (range less than 24 h to 60 days). The median number of hospital presentations per patient per year was 2 (range 1–13), median bed-days used per patient per year was 11 (IQR 6–19, range 1–85). Thirty-eight per cent of patients presented once, 20% twice, 18% three times, 20% four to nine times and 5% 10–13 times over 12 months.

The median cost per emergency presentation was AU$382 (IQR $194 to $814), and the median cost of an inpatient admission was $3124 (IQR $1393 to $5045). The median cost of the first inpatient admission day (including admissions to short stay units, medical assessment and planning) was AUS$725 (IQR $396 to $1391) per presentation. Subsequent admissions days (days 3–7) had a daily median cost of AUS$568 to $646 (IQR AUS$556 to $815). Increased costs on the first day of admission related to diagnostic services, including chest X-ray, pathology and lung function testing, along with expert clinical assessment (medical staff costs, physiotherapy and allied health).

Table 1 Characteristics of study participants

$N = 80$	
Age†	73 years (54–88)
Sex (male : female)	47:33
Pack-years smoking†	49 (10–130)
Current smoker	17 (21%)
FEV_1 (l)‡	1.00 (0.68–1.42)
FEV_1/FVC ratio‡	51% (38 to 61%).
GOLD severity	Stage 2 25 (32%)
	Stage 3 31 (39%)
	Stage 4 24 (30%)
Chronic bronchitis	55 (69%)
Domiciliary oxygen	22 (28%)
MRC Dyspnoea Scale	Grade-1 2 (3%)
	Grade-2 7 (9%)
	Grade-3 19 (24%)
	Grade-4 30 (38%),
	Grade-5 22 (28%).

†Data presented as mean and range. ‡Data presented as median and interquartile range. D_{LCO}, diffusion lung carbon monoxide; FEV_1 (L), forced expiratory volume in 1 s; FEV_1/FVC ratio, FEV_1 to forced vital capacity ratio; GOLD, Global Initiative for Obstructive Lung Disease; MRC, Medical Research Council.

Cost according to type of service provided

The median inpatient bed cost per inpatient admission (includes both hotel costs and cost of nursing staff) was AU$3124 (IQR $1368 to $5045). Staffing costs per episode of care (emergency department or inpatient) were: pharmacy staff AU$117 ($47 to $261), medical staff AU$441 (IQR $160 to $1109) and allied health staff AU$12 (IQR $0 to $163). The median cost of pathology tests per episode of care was AU$121 ($47 to $261), and radiology AU$53 (IQR $49 to $99). During the 12-month follow up, there were nine episodes of care (for eight patients) that resulted in intensive care unit (ICU) admission (median length of stay 5 days (IQR 1–12 days)) (with seven requiring invasive ventilation) and five episodes (for five patients) that required coronary care unit admission (median length of stay 1.5 days). The median costs per stay, respectively, were AUS$8265 (IQR $3848 to $11 069) and AUS$382 (range $382 to $854). The total median cost per admission increased to AUS$18 842 ($13 295 to $25 154) if ICU care was required, with the ICU component of care accounting for 45% (range 37–51%) of the total admission cost.

Cost of medications for exacerbations of COPD

Medication costs were available for 225 episodes of care. Total hospital medication costs included both inpatient medication costs and the cost of discharge medication supplied to the patient for use over the first week post discharge. The median cost of supplying all medications per episode was AUS$108 (IQR $55 to $156), the median

Table 2 Annual per patient costs of acute care services

	Median [IQR] total cost/ patient/year†	Median [IQR] bed-days/ patient/year	Range/total bed-days/ patient/year	No. of hospital presentations/patient/year
Total patients	$7273 [$3956–$14 449]	11 [6–19]	<1 to 85	2 [1–3] Range 1–13
GOLD-2 (*n* = 25)	$5786 [$4147–$10 551]	8.5 [5–14]	1–61	2 [1–3] Range 1–6
GOLD-3 (*n* = 31)	$7074 [$3008–$13 837]	10 [5–19]	2–85	2 [1–5] Range 1–13
GOLD-4 (*n* = 24)	$13 014 [$5602–$24 341]	17 [8–30.5]	1–75	2.5 [1–5] Range 1–13
Age < 70 yrs (*n* = 25)	$6559 [$2323–$21 078]	7.5 [4–20]	1–52	2 [1–4] Range 1–9
70–79 yrs (*n* = 42)	$7507 [$4040–$19 504]	12.5 [6–23]	2–85	2 [1–3] Range 1–13
≥80 yrs (*n* = 13)	$8048 [$4822–$12 376]	10.5 [7–15]	2–40	2 [1–3] Range 1–6
Chronic bronchitis				
Yes (*n* = 55)	$10 164 [$4254–$19 504]	13.5 [6–24]	2–85	2 [1–4] Range 1–13
No (*n* = 25)	$4909 [$2671–$7940]	6.0 [4–13]	1–52	2 [1–2.5] Range 1–9

†Costs are presented in Australian dollars. GOLD, Global Initiative for Obstructive Lung Disease; IQR, interquartile range.

cost of inpatient medications was AUS$68 (IQR $26 to $108) and discharge medications was AUS$38 (IQR $23 to $61).

All patients were prescribed inhaled corticosteroids as maintenance therapy, and long-acting beta-2 agonists were not used as this therapy was not approved for use in COPD in 2001. The majority of episodes were treated with systemic corticosteroids, 90 admissions were treated with intravenous hydrocortisone at a median cost of AUS$5.34 (IQR $1.79 to $10.74) per admission and all inpatient admissions received oral corticosteroid therapy at a median cost of AUS$1.76 (IQR $0.91 to $3.61). Intravenous antibiotics were used to treat 119 episodes of care, at a median cost per episode of AUS$15.75 (IQR $5.27 to $26.35). The most commonly used intravenous antibiotics were: cephalosporins prescribed in 57 episodes at median cost of $17.04 (IQR $5.27 to $26.35) per episode, macrolides used in 21 episodes with a median cost of $27.96 (IQR $9.32 to $55.92) per episode and penicillins used in 55 episodes with a median cost of $11.95 (IQR $3.2 to $29.25) per episode. Oral antibiotics were used for 188 episodes, at a median cost of AUS$13.13 (IQR $3.08 to $30.01).

Annual per patient cost of acute care management

The median annual cost of acute care services (emergency and inpatient admission) per patient per year was AUS$7273 (IQR $3957 to $14 448). The median annual costs increased as COPD severity category increased: GOLD-2 AUS$5786/year, GOLD-3 AUS$7074/year and GOLD-4 AUS$13 014/year (Table 2). Patients who used long-term domiciliary oxygen had higher annual acute care costs compared with those who did not ($P = 0.050$). Patients with chronic bronchitis had higher median annual costs than those without, independent of disease severity (chronic bronchitis AUS$10 164 per year vs. no chronic bronchitis AUS$4909 per year ($P = 0.014$).

The major factor predictive of annual costs was total annual bed-days in acute care (coefficient 1.04 [95%CI 0.93–1.15], $P < 0.001$). Fifty-eight per cent of patients presented to acute care one to two times per year accounting for 31% of annual acute care costs, while 25% of patients presented four or more times per year accounting for 65% of overall acute care costs.

Patient factors predictive of annual bed-days and costs

A model was developed to determine which patient factors were predictive of total annual bed-days. Patient factors included in the model were: age, sex, diagnosis of chronic bronchitis, GOLD severity grade, FEV_1 per cent predicted, use of domiciliary oxygen and Charlson Co-morbidity score and diagnosis of CHF. In the univariate analysis, the following factors were significant: male 6.64 [95%CI 0.69–13.96] ($P = 0.075$), chronic bronchitis 8.82 [95%CI 0.81–16.83] ($P = 0.031$), domiciliary oxygen use 12.47 [95%CI 3.76–21.17] ($P = 0.006$), GOLD severity 5.20 [95%CI 0.87–9.54] ($P = 0.019$) and CHF 9.50 [95%CI 1.64–17.37] ($P = 0.019$).

In the multivariate model obtained using backwards stepwise linear regression, the model which explained the highest amount of the variance in total annual bed-days included: domiciliary oxygen use, chronic bronchitis and CHF; however, this model explained only 14% of the variance in total bed-days between patients (Table 3, Model-1). A second model was developed to identify which patient factors predicted annual hospital presentation rates. In this model, the use of domiciliary oxygen, CHF and decade of age were statistically significant predictors of presentation rate, although the lower limits of the 95%CI was less than 1, this model explained 17% of

Table 3 Linear regression models to predict acute healthcare utilization

$n = 78$	*F*-statistic	R^2	Adjusted R^2
Model-1: Patient factors predictive of total annual bed-days in acute care†			
Total bed-days/patient/year	5.33	0.18	0.144
	Coefficient	95%CI	*P* value
Domiciliary oxygen	10.67	2.06 to 19.28	$P = 0.016$
Chronic bronchitis	7.23	–0.60 to 15.05	$P = 0.070$
Chronic heart failure	6.33	–1.46 to 14.12	$P = 0.109$
Constant	7.00	0.35 to 13.65	$P = 0.039$
$n = 78$	*F*-statistic	R^2	Adjusted R^2
Model-2: Patient factors and acute care presentation rate per year‡			
Total acute hospital presentations/patient/year	6.16	0.1998	0.167
	Coefficient	95%CI	*P* value
Domiciliary oxygen	1.80	0.49 to 3.11	$P = 0.008$
Chronic heart failure	1.623	0.47 to 2.78	$P = 0.006$
Age (group decades)	–0.79	–1.54 to –0.03	$P = 0.041$
Constant	4.12	1.99 to 6.24	$P < 0.001$

†Linear regression model total annual bed-days per patient was the dependent variable. ‡Linear regression model total acute care presentations per patient per year was the dependent variable. 95%CI, 95% confidence interval.

the variance in annual presentation rates (Table 3, Model-2).

Discussion

This study of acute healthcare costs, for persons presenting to an Australian metropolitan teaching hospital due to an exacerbation of COPD, shows that costs of illness are related to concomitant diagnosis of chronic bronchitis; severity of COPD as classified using GOLD criteria;[20,23] and frequency of healthcare utilization. Furthermore, this study shows that comorbid cardiac failure and the use of home oxygen (a marker of underlying disease severity) are predictors of both total annual bed-days in acute care and acute care presentation rate per year. Chronic bronchitis only contributed to the explanatory model for total annual bed-days in acute care, and increasing age contributed only to the model explaining acute care presentation rate per year. These models indicate that there are differences between the factors that determine overall length of stay in acute care and the frequency of attendances. Higher bed-days reflect more complex disease and the presence of unstable comorbidities. In contrast, frequent attendances were associated with increasing age.

The costs of hospitalization were determined using a proprietary activity-based clinical costing system (Transition II), which allocates costs to the individual patient on the basis of aggregate cost per patient at the ward level. This approach has the advantage that it captures actual costs associated with different components of care delivery rather than costs derived from payments to healthcare providers; it is truly a clinical costing system and is not reflective of prices for individual therapy components. The generalizability of the findings based on this costing method is difficult to determine as the costs are derived from a patient cohort based in only one hospital, the findings therefore need to be treated with caution. Nonetheless, the range of values for the costs of illness and the relationship between cost of acute care and severity of illness is consistent with previously reported findings.[13,15,16]

Patients presenting to the Royal Melbourne Hospital in 2001–2002 were not referred from alternative service providers, rather they were admitted from their usual place of residence. They did not have access to alternative home treatment programmes that might otherwise have contributed to the management of patients with milder forms of AECOPD of underlying disease of milder severity. There is no evidence to suggest that the patients were subject to some form of admission or referral basis which would otherwise predispose to a biased estimate of costs of hospitalization. Similarly, no analysis of the impact of seasonality upon cost of admission was undertaken although it is possible that seasonal variation in length of stay was present as this has been observed for other patient groups in Victorian hospitals. The patients were managed according to evidence-based clinical practice guidelines developed at this institution. Medical staff were actively encouraged to follow management

algorithms that included: admission criteria and choice of antibiotics and encouragement to minimize the length of time intravenous therapies were used. No attempt has been made to analyse costs on the basis of adherence to guidelines or not.

This study gives cost estimates for high-acuity COPD patients who are identified as at risk of admission to acute care. The annual costs for these individuals will be higher than those found in a general non-hospitalized COPD population. In addition, there is no evidence to suggest that the costs of treatment for patients admitted for AECOPD to a metropolitan teaching hospital are representative of costs of treatment for a similar episode of care for patients admitted to non-teaching or non-metropolitan hospitals. Since this study was conducted there have been several changes in the management of COPD. Therapies such as tiotropium bromide and long-acting bronchodilators have now become standard maintenance therapy for COPD, and these treatments have been shown to impact upon readmission rates.[7,25] Non-invasive ventilation is now standard therapy for hypercapnic respiratory failure associated with AECOPD. The data from this study show that admission to ICU is associated with significantly increased costs of admissions. This gives an indication of the substantial cost savings that may be associated with avoidance of intensive care admission and invasive ventilation.

In concordance with previous studies, expenditures were disproportionally distributed with a small group of frequent attendees accounting for a substantial proportion of the total costs.[26] The finding that the use of home oxygen and the presence of chronic bronchitis and cardiac failure are important predictors of healthcare costs and resource utilization provides the basis for future research studies. No attempt was made to adjust for the effect of home oxygen use upon costs independent of disease severity, as it seems likely that this relationship is confounded by indication for use of home oxygen in the first place. These studies could determine whether community-based interventions which focus on such patients can result in improved outcomes and reduced acute hospital use.[27] These disease management programmes would need to focus on community management of exacerbations of COPD and CHF, patients requiring long-term domiciliary oxygen and provision of greater community supports for those with severe end-stage disease. Such research could subsequently inform policy when aiming to develop targeted programmes as part of a chronic disease management model. This study was conducted before the initiation of government-sponsored disease management programmes (Hospital Admission Risk Programs) in Victoria, Australia, and pulmonary rehabilitation and community programmes for the management of exacerbation of COPD were not available at our centre.

Conclusion

This study of direct costs of acute hospitalization for a cohort of patients admitted to a metropolitan teaching hospital shows an important finding of higher costs associated with age, the presence of chronic bronchitis, congestive cardiac failure and the use of home oxygen, the latter potentially a marker of COPD disease severity, as well as with greater healthcare resource utilization as reflected in a requirement for ICU treatment and total length of stay per annum. The data presented provide useful baseline comparison data for future studies evaluating the impact of disease management initiatives on healthcare utilization and the associated direct costs of inpatient management.

Acknowledgement

Funding for this study was received from Asthma and Allergy Research Institute at the Sir Charles Gairdner Hospital, Perth.

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Internal Medicine Journal **40** (2010) 372–380

BRIEF COMMUNICATIONS

Acute chest syndrome in sickle cell disease

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Key words
sickle cell disease, acute chest syndrome, inhaled nitric oxide, intensive care.

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Received 7 October 2008; accepted 1 December 2008.

doi:10.1111/j.1445-5994.2010.02129.x

Abstract

Acute chest syndrome is a common cause of death among patients with sickle cell disease, and an unfamiliar condition to most Australian medical practitioners. We present a case of acute chest syndrome successfully treated with inhaled nitric oxide and exchange transfusion. In the discussion we review current and future management options of acute chest syndrome.

A 33-year-old Middle Eastern man presented to our emergency department with chest, shoulder and abdominal pain following a visit to a wildlife park with his family. He recognized his symptoms as a sickle cell painful crisis having had two to three previous episodes associated with fasting or exertion since coming to Australia 2 years ago. Previous investigations at our hospital had confirmed his genotype was most likely a homozygous for sickle cell anaemia (HbSS) with alpha thalassaemia trait (HbS solubility +ve, HbS level not recorded, HbF 19.8%, HbA_2 2.1%, mean corpuscular volume 66, mild iron deficiency).

In the course of 24 h, despite aggressive rehydration with 6 L intravenous crystalloid and high-dose morphine patient-controlled analgesia, he had persistent tachycardia, hypertension and rigors. He was febrile up to 38.5°C. His chest X-ray revealed a progressive interstitial infiltrate but no consolidation. He was treated empirically with timentin and received a total of 60 mg frusemide intravenously. He developed worsening hypoxic respiratory failure (PaO_2 47, saturation 88%, non-rebreath mask 15 L) and was transferred to our intensive care unit (ICU).

On admission to ICU he was diaphoretic with a respiratory rate of 40–50 breaths per minute. He maintained adequate oxygenation on non-invasive ventilation (BiPAP 15/8, FiO_2 0.8, PaO_2 122, $PaCO_2$ 34, pH 7.41, saturation 100%) but his chest X-ray had worsened (Fig. 1). Investigations revealed a consumptive coagulopathy with haemolysis (haemoglobin 74, platelet counts 17, international normalized ratio 2.0, D-dimer 32, lactate dehydrogenase unrecordably high), mild hepatic enzymosis and oliguric renal impairment (urea 9.0, creatine 142). A sepsis screen revealed Gram-negative bacilli in his sputum but no growth on culture, a transthoracic echocardiogram revealed normal left ventricular function and moderate–severe right ventricular dilatation with mild pulmonary hypertension (estimated right ventricular systolic pressure 58), and an abdominal ultrasound revealed a normal liver, gallbladder and renal tract. These findings were most consistent with an acute chest syndrome secondary to a vaso-occlusive crisis, likely related to dehydration from the previous day's activities.

He was commenced on intravenous frusemide and glyceryl trinitrate infusions and underwent a three-unit exchange transfusion, but became fatigued and was

Funding: None.
Conflict of interest: None.

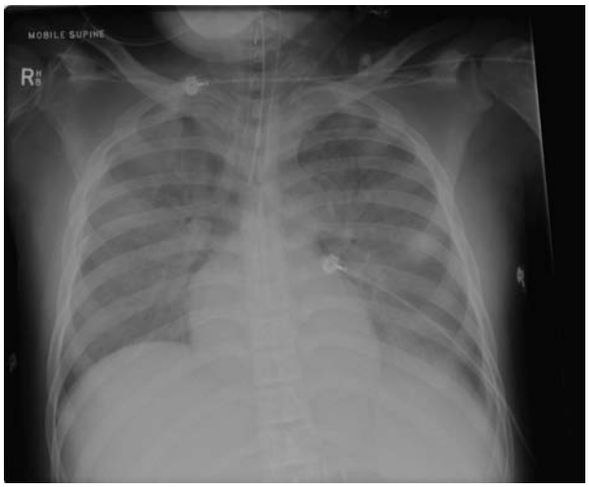

Figure 1 Chest X-ray showing acute respiratory distress syndrome.

intubated uneventfully. He received lung-protective ventilation (6 mL/kg, respiratory rate 18–24, $P_{peak} < 35$) and was paralysed with a vecuronium infusion titrated to a train-of-four of one to two twitches. Despite these measures, his oxygenation worsened (PaO_2 66, $PaCO_2$ 35, FiO_2 1.0, PaO_2/FiO_2 ratio 66, aA gradient 603). Inhaled nitric oxide was initiated at 10 p.p.m. in an effort to improve his oxygenation, prevent further sickling, and reduce his pulmonary pressures. This was effective and weaned after 5 days without complications (nitrogen dioxide <1 p.p.m., metHb < 3.0). He was mechanically ventilated for 14 days, re-intubated twice for blocked endotracheal tubes because of blood clots and required continuous veno-venous haemodiafiltration for a total of 14 days.

Management of his acute chest syndrome involved a further five-unit exchange transfusion after which his HbS fraction reduced from 75.4% on admission to 8.6% following this transfusion. It remained at less than 8.0% throughout the rest of his ICU admission without need for further exchange transfusions, although he received multiple blood and blood product transfusions because of ongoing coagulopathy, thrombocytopenia and generalized ooze from venepuncture sites. He had no major haemorrhagic events. Folic acid supplementation was given. No doubt as a result of all these transfusions he developed allo-immunization with anti-K and anti-Jkb antibodies (already having anti-C and anti-e antibodies). His renal function returned to normal and he made a full recovery from his acute chest crisis. He was discharged on oral hydroxyurea 500 mg daily after a 5-week hospital admission. Shortly after discharge he underwent an uneventful urgent laparoscopic cholecystectomy for cholecystitis, which was likely precipitated by pigment stones formed after haemolysis.[1] Neurological complications are also common in acute chest crisis. He has some residual facial pain but a normal magnetic resonance imaging brain. He remains well and has returned to his studies. His latest bloods revealed HbS 66% and HbF 30% indicating a good response to the hydroxyurea.

Sickle cell disease results from a substitution of valine for glutamic acid on the sixth codon of the beta-globulin gene.[2] Sickle cell disease has a number of genotypes, most commonly sickle cell anaemia (HbSS) and compound heterozygotes HbSC and HbS thalassaemia. The resulting sickle haemoglobin forms stiff polymers when deoxygenated,[3] which occlude vascular beds and shorten red cell lifespan. Factors that pre-dispose to polymerization include slow flow, high haematocrit, low pH and low oxygen tension, conditions that are present in the spleen resulting in chronic ischaemia and necrosis. In health, the polymers usually fall apart in the lungs and the cells revert to their normal flexible shape. Patients with sickle cell disease are prone to vaso-occlusive crises. Often these attacks are unprovoked but can be precipitated by infection, extreme temperatures, physical or emotional stress, hypoxia, acidosis and polycythaemia. The severity of these crises directly correlates to the proportion of abnormal haemoglobin.[4] During polymerization the sickle cells increase density because of potassium efflux.[5–8] Vaso-occlusion results from a complex interaction of the sickle cells with endothelial cells and the constituents of plasma resulting in aggregation and adherence of sickle cells in the micro-circulation impairing end-organ perfusion. This results in a range of manifestations, but the acute chest syndrome is the most likely to require ICU admission (Table 1).[9]

The causes of the acute chest syndrome are infection, pulmonary infarction and fat embolism. Seventy-five per cent of patients who develop an acute chest syndrome have been admitted with a painful crisis. The prodromal attack lasts an average of 2.5 days before developing respiratory symptoms. The diagnosis of acute chest syndrome is a triad of fever, respiratory distress and new interstitial infiltrates on chest X-ray (Table 2). The average length of hospitalization is more than 10 days. Factors that are associated with longer admissions include older age, pain in arms and legs at presentation, fever, low platelet count at diagnosis, extensive radiographic changes, transfusion and respiratory failure. Adult patients fair worse than paediatric patients. Those ≥20 years old have a 9% mortality compared with those aged <20 years who have a 2% mortality.[10] Management of acute chest syndrome includes therapies to reduce the HbS proportion, supportive care, and agents that ameliorate the sickling process. Consideration should also be given to long-term strategies to prevent further episodes.

Table 1 Complications of sickle cell disease

Vaso-occlusion-related
• Painful crisis
• Acute chest syndrome
• Abdominal painful crisis
• Priapism
• Hypersplenism
Vasculopathy
• Dactylitis
• Stroke
• Leg ulceration
• Osteonecrosis
• Spontaneous abortion
• Proliferative retinopathy
• Renal insufficiency
Complications of haemolysis
• Anaemia
• Cholecystitis
• Liver disease
Infectious complications
• Acute splenic sequestration
• Aplastic crisis
• Septicaemia
• Osteomyelitis

Table 2 Definition of acute chest syndrome

New pulmonary infiltrates with chest pain
Temperature >38.5°C
Tachypnoea, wheezing or cough

The mainstay of any acute sickle cell crisis including the acute chest syndrome is simple or exchange transfusion to reduce the HbS fraction (aiming for <30%). Transfusion has a number of actions – dilution of HbS, suppressing erythropoietin-induced HbS production, correction of anaemia, increasing oxygen-carrying capacity and increasing the lifespan of red cell.[11] Although there have been no comparative trials between simple and exchange transfusions, they both improve oxygenation to a similar degree.[10] Several case series suggest transfusion rapidly improves oxygenation and the clinical course of acute chest syndrome.[12,13] A rule-of-thumb is to use simple transfusions for mild hypoxia and an exchange transfusion for moderate to severe hypoxia. Given this population can be transfusion-dependent, it is important to consider the potentially preventable long-term risks associated with transfusion that include transmitted infection, haemosiderosis and allo-immunization. Allo-immunization occurs in up to 20–30% of patients with sickle cell disease requiring transfusion. This can be significantly reduced by phenotypic cross-matching blood units.[14] Our patient received a total of 29 units of packed red cells, 12 units of pooled platelets and 5 units of fresh frozen plasma during his hospital admission, so it is not surprising that he developed two clinically significant antibodies.

Supportive therapies include mechanical ventilation, bronchodilators, folic acid supplementation and antibiotics. In the National Acute Chest Syndrome Study Group, 13% of the 531 patients (69 patients) required mechanically ventilation for a mean duration of 4.6 days. Of these, 81% (56 patients) recovered, which is significantly better than other forms of acute respiratory distress syndrome (ARDS).[15] Up to 60% of patients have evidence of bronchospasm and inhaled bronchodilators are effective therapy if there is audible wheeze.[10] Folic acid supplementation 1 mg daily to prevent megaloblastic anaemia has been standard care since 1967[16] although its necessity is still contested.[17]

Broad-spectrum antibiotics including atypical coverage should be given. The most common respiratory pathogens in patients with acute chest syndrome include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and respiratory syncytial virus. However, the organisms implicated in infection-related deaths during an acute chest crisis include *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophilus influenzae*, legionella, cytomegalovirus, *Staphylococcus aureus* and chlamydia.[10] Patients with sickle cell disease are functionally asplenic, and as a result are susceptible to overwhelming infections with encapsulated organisms especially pneumococcus and haemophilus. These infections are the leading cause of death in patients with sickle cell disease, particularly children. However, mortality from these two organisms has been reduced considerably since the introduction of routine childhood immunization in 1975.[18]

Inhaled nitric oxide is an attractive therapy in an acute chest crisis. First, it improves oxygenation as has been shown in ARDS.[19] Although inhaled nitric oxide use does not improve mortality in ARDS, most patients with ARDS die from multi-organ failure not from hypoxia.[20] Nitric oxide may be of greater benefit for sickle cell patients as it will help break the hypoxia-polymerization cycle. Once our patient's profound hypoxia improved after institution of inhaled nitric oxide, his HbS percentage remained stable and his haemolysis markers all improved suggesting his acute sickling process had resolved. Admittedly, this improvement may have been confounded by a concomitant exchange transfusion.

Second, similar to other acute hypoxic events, a chest crisis is associated with pulmonary hypertension[21] which is an independent risk factor for death in sickle cell disease.[22] Our patient had mild pulmonary hypertension and we did not measure the response to nitric oxide administration as our clinical end-point was improvement in

oxygenation. A follow-up transthoracic echo would have been interesting but was not clinically indicated because of his overall improvement. Despite documented benefits in adult oxygenation and pulmonary arterial pressures, neonatal pulmonary hypertension remains the only proven indication for inhaled nitric oxide.[19]

Third, it is known that in an acute chest crisis there is abnormal nitric oxide regulation of vascular tone, adhesion, platelet activation and inflammation.[23–26] *In vitro* studies have shown that inhaled nitric oxide downregulates the adhesion molecule vascular cell adhesion molecule-1,[27] and may or may not increase oxygen affinity of sickle erythrocytes.[28,29] So the beneficial effects of inhaled nitric oxide may not be confined to improving oxygenation and pulmonary vasodilation. This hypothesis is supported by the use of inhaled nitric oxide reducing pain scores during vaso-occlusive crisis in spontaneously breathing patients without clinically significant hypoxia or acute chest crisis.[30]

A small number of paediatric case reports support the use of inhaled nitric oxide in an acute chest crisis showing improvements in oxygenation and reduced pulmonary pressures.[31,32] Our patient received inhaled nitric oxide at 10 p.p.m. or less for 5 days without any complications and although ongoing coagulopathy was an issue we do not believe that the nitric oxide was contributory. Indeed there is a suggestion that the platelet effects may be beneficial.

In conclusion, this report stresses some of the important issues faced when managing a patient with sickle cell disease and an acute chest syndrome, including the use of exchange transfusion and inhaled nitric oxide in ICU. Because of migration patterns it is likely that the prevalence of sickle cell disease in our communities will increase and awareness of how to manage an acute crisis will become increasingly relevant.

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Leucocytoclastic and renal vasculitis in a patient with autoimmune pancreatitis: new associations

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Key words
autoimmune pancreatitis, leucocytoclastic vasculitis, renal vasculitis, pancreatic mass.

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Received 7 May 2009; accepted 22 August 2009.

doi:10.1111/j.1445-5994.2010.02175.x

Abstract

Autoimmune pancreatitis (AIP) is an uncommon condition which comprises diffuse or discrete pancreatic enlargement and irregular pancreatic duct strictures of autoimmune origin leading to pain or obstructive jaundice associated with extra-pancreatic manifestations. It is characterized by an elevated IgG, especially IgG4, level. We illustrate the first described case of a patient with AIP in association with leucocytoclastic and renal vasculitis.

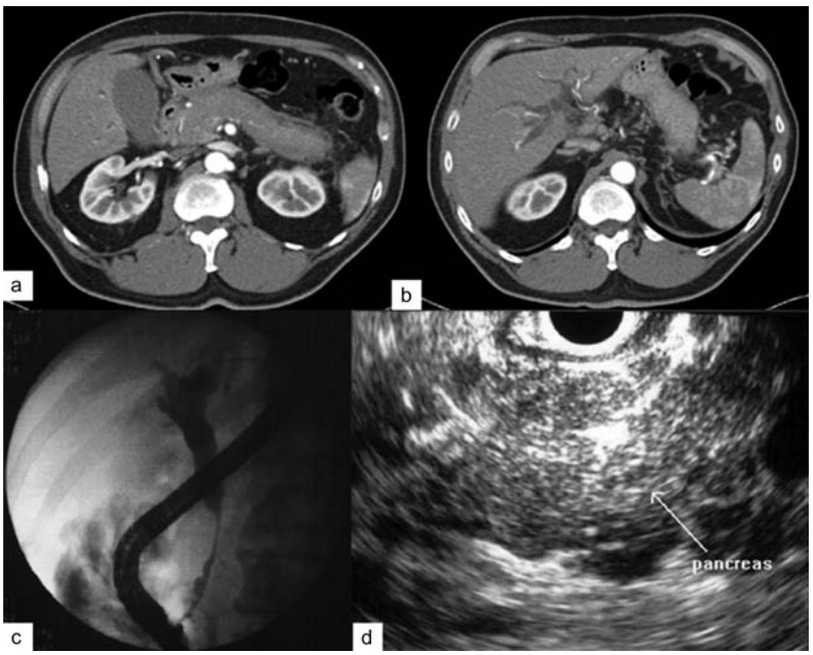

Figure 1 Computed tomographic images showing (a) diffuse pancreatic enlargement with the suggestion of a mass in the head of pancreas and (b) dilatation of intrahepatic bile ducts. (c) Endoscopic retrograde cholangiopancreatography showing a 3-cm bile duct stricture. (d) Endoscopic ultrasound images of enlarged pancreatic parenchyma.

A 69-year-old man of Malaysian Chinese origin with a past history of hepatitis B and stage IIA (T3N0M0) sigmoid cancer resected in 2003 was referred following the development of painless obstructive jaundice for 2 weeks.

Blood tests showed bilirubin 160 μmol/L, alkaline phosphatase (ALP) 156, gamma glutamyl transpeptidase (GGT) 379, alanine aminotransferase (ALT) 204, albumin 40 g/L, lipase 315 U/L and normal Ca 19-9 and carcinoembryonic antigen (CEA). Hepatitis screen showed positive HBsAg and HBeAb. Abdominal ultrasound and computed tomography (CT) scan showed no definite gall stones, normal liver, with dilated extra- and intra-hepatic ducts, including a 1.4-cm common bile duct (Fig. 1a,b). The pancreatic head was bulky, measuring 4 cm in diameter, suggestive of a mass lesion.

An endoscopic retrograde cholangiopancreatography (ERCP) (9 July 2008) showed a 3-cm stricture in the common bile duct with dilatation of the extra- and intrahepatic biliary tree (Fig. 1c). A 10 French 9-cm biliary stent was inserted with gradual improvement in liver biochemistry. Brushings of the bile duct stricture showed no evidence of malignancy.

Subsequent endoscopic ultrasound (EUS) (1 August 2008) showed a diffusely hypoechoic and swollen pancreas with no discrete mass lesion (Fig. 1d). Fine needle aspirates of the pancreas showed atypia but no malignancy, and microscopy and cultures (including for acid fast bacilli) were negative.

Over the next 4 weeks, worsening cholestatic liver biochemistry (ALP 255, GGT 304, ALT 54, Bili 14) led to a repeat abdominal CT scan and EUS (29 September 2008), once again showing a bulky pancreatic head and a 1.8 × 0.7 cm lymph node, with non-malignant fine needle aspirate (FNA) cytology.

Concurrently, the patient developed a purpuric rash over both lower legs up to the mid calves, as well as bilaterally swollen and tender parotid and submandibular glands. His renal function deteriorated, with creatinine rising to 136 μmol/L from a previous baseline of 90 μmol/L. Microscopic examination of his urine showed $>1000 \times 10^6$ erythrocytes per litre, with trace protein, no casts, no leucocytes and negative culture. A normocytic anaemia (haemoglobin 100 g/L) and elevation of inflammatory markers (C-reactive protein 83, erythrocyte sedimentation rate 129) was noted.

Immunoglobulin (Ig) levels showed elevated IgG level of 33.3 g/L (normal range 7.0–16.0), with elevation of all fractions IgG1 15.9 g/L (3.8–9.3), IgG2 7.7 g/L (2.4–7.0), IgG3 2.26 g/L (0.22–1.76) and IgG4 5.84 g/L (0.04–0.86). IgA and IgM levels were within the normal range.

A full autoimmune screen was conducted, which showed a mildly elevated antinuclear antibody (ANA) titre of 160, negative extractable nuclear antigen,

Funding: None.
Conflict of interest: None.

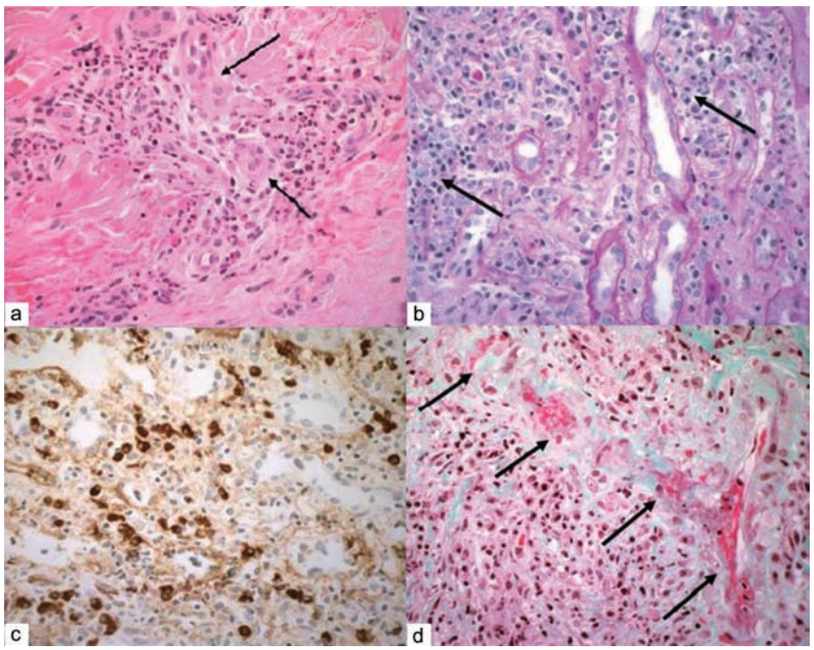

Figure 2 (a) Skin biopsy showing early or resolving leucocytoclastic vasculitis. Perivascular infiltrate of neutrophil polymorphs and eosinophils with focal leucocytoclasis in the superficial dermis, with swelling of blood vessel walls without necrosis. Haematoxylin and eosin stain. (b–d) Kidney biopsy. (b) Dense expansile interstitial infiltrate composed predominantly of plasma cells and eosinophils (arrows). Periodic acid Schiff stain. (c) Most of the plasma cells are IgG4-positive. Immunoperoxidase stain. (d) Extensive fibrinoid necrosis/necrotising vasculitis within small vessel (arrows). Aldehyde fuchsin Gomori stain. All original magnification ×400.

rheumatoid factor (RF), antineutrophil cytoplasmic antibodies, serum protein electrophoresis and anti-streptococcal antibodies. C3 (0.50, normal range 0.90–1.80) and C4 (<0.02, normal range 0.16–0.47) were both low. Cryoglobulins were negative. Anticardiolipin antibody titres were slightly elevated. Mumps virus serology showed positive IgG, but negative IgM antibodies.

A biopsy of his rash (Fig. 2a) showed features in keeping with leucocytoclastic vasculitits. The patient then went on to have a renal biopsy (Fig. 2b–d), which showed moderately severe tubulointerstitial nephritis (TIN) with expansile infiltrate containing numerous IgG4-positive plasma cells. Occasional arterioles showed focal fibrinoid necrosis. No significant glomerular pathology was detected on light microscopy, but electron microscopy showed 'immune-type' deposits within Bowman's capsule. The appearances were consistent with IgG4-related TIN and renal small vessel vasculitis.

A diagnosis of autoimmune pancreatitis (AIP) was hence made, and the patient was commenced on prednisolone 50 mg daily with gradual tapering of the dose. He improved clinically with resolution of his inflammatory markers, and renal function and liver biochemistry returning to baseline.

Further evaluation of his hepatitis B showed HBeAb to be positive, with a hepatitis B virus DNA titre of 53×10^6 copies. Entecavir was hence commenced.

His biliary stent was removed with good biliary flow re-established. To date, he is clinically well, and his pancreas has returned to normal size on repeat CT scan.

AIP is an uncommon but increasingly recognized condition, the precise prevalence of which is as yet uncertain. Most cases have been reported in Japan, with a prevalence of 6% reported in a study of 521 patients with chronic pancreatitis.[1] A similar incidence has been observed in retrospective pathological reviews of pancreatic resections for benign disease at the Mayo Clinic where 27 of 254 specimens had features resembling AIP, and in an Italian multicentre study that identified autoimmunity as a risk factor in 23 of 383 patients with chronic pancreatitis.[2] Cases have also been recognized in Korea.[3] The mean age of diagnosis is over 55 years, with men being affected two to five times as commonly as women.[4]

Diagnostic criteria for AIP have been developed and are based on typical clinical, laboratory, imaging and histopathological features.[5–7]

Clinical features are reflective of the underlying structures involved, with mild abdominal pain (but usually without acute attacks of pancreatitis), or obstructive jaundice due to primary bile duct stricturing or compression secondary to mass effect from the inflamed pancreas.

Laboratory features include cholestatic liver biochemistry with mild elevation of amylase and lipase, as well as increased levels of serum immunoglobulins, particularly the IgG4 fraction of IgG. Diagnostic levels of IgG $\geq$18.0 g/L and IgG4 $\geq$1.35 g/L have been proposed,[5] with the latter showing a sensitivity of 95% and specificity of 97% in distinguishing AIP from pancreatic cancer.[8]

The levels of the patient in this report were above this range (IgG 33.3 g/L and IgG4 5.84 g/L respectively). Autoantibodies, including ANA (65%), antilactoferrin antibody (75%), anticarbonic anhydrase II (55%) and RF (25%), have been described in this group of patients.[4] Our patient showed ANA positivity.

Imaging with CT or MRI typically reveals a diffusely enlarged pancreas characteristically with minimal stranding, calcification or peri-pancreatic fluid; with ERCP showing segmental or diffuse narrowing of the main pancreatic duct. Narrowing of the bile ducts, typically of the intra-pancreatic portion, but sometimes resembling primary sclerosing cholangitis or cholangiocarcinoma may also be seen. Enlargement of the pancreatic head may occasionally be mistaken for malignancy. A histopathological or cytological diagnosis in cases of obstructive jaundice and pancreatic mass is hence imperative, as illustrated in this paper.

Histological examination of the pancreas in AIP shows interlobular and occasionally intralobular fibrosis, with lymphoplasmacytic infiltration typically of IgG4-positive plasma cells.

Many extra-pancreatic lesions have been associated, including sclerosing cholangitis (60% in one series), sialadenitis (13%), TIN (7%), type 2 diabetes mellitus (43–68%), retroperitoneal fibrosis (9%), lymphadenitis (9%) and chronic thyroiditis (7%),[4] as well as ulcerative colitis and Crohn's disease (9%). IgG4-positive plasma cells are detected in many of these organs, suggesting a systemic autoimmune disorder. In the absence of demonstrable IgG4-positive plasma cells from pancreatic tissue in our patient, the renal biopsy provided this information. Notably, to our knowledge, both leucocytoclastic and renal small vessel vasculitis are yet to be described in association with AIP.

Another interesting observation in our patient is the concurrent hepatitis B infection. Although no formal association between AIP and hepatitis B has been described, there have been case reports describing the presence of HbsAg in pancreatic acinus epithelia and small ductules in cases of pancreatic carcinoma and chronic pancreatitis.[9–11] Indeed, a case report of AIP in a patient with chronic hepatitis B infection is also present.[12] This may need further study.

Treatment for AIP consists of steroid therapy. A response rate of 50–75% has been shown in case series, and although often dramatic, can take 1–4 months. The duration of steroid use has been typically 1–4 years, with 25% patients requiring a second course.[13,14] Strictures can respond to steroid therapy, although complicated strictures or cholangitis may occasionally require endoscopic or percutaneous transhepatic drainage. Surgery may be indicated in refractory cases, particularly to exclude malignancy. Ursodeoxycholic acid, immunomodulators, including 6-mercaptopurine, and the anti-CD20 monoclonal antibody rituximab have also been reported to benefit in refractory cases.[15,16]

In summary, AIP is an important clinical entity characterized by mild abdominal pain or obstructive jaundice in association with inflammatory pancreatic mass and elevation of serum IgG4. As appearances of the pancreas in AIP may mimic carcinoma and result in unnecessary surgery, it is imperative that histopathological confirmation of malignancy should be obtained, if possible, in all cases in patients with obstructive jaundice before treatment. We believe this is the first report of leucocytoclastic and renal vasculitis in association with AIP and these associations may help us to diagnose patients with AIP in the future.

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HISTORY IN MEDICINE

Lasthénie de Ferjol syndrome: a rare disease with fascinating history

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Key words
iron deficiency anaemia, factitious disorder, Lasthénie de Ferjol, Jean Bernard.

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Received 8 September 2009; accepted 13 October 2009.

doi:10.1111/j.1445-5994.2009.02154.x

Abstract

In our paper, we present the fascinating story of Lasthénie de Ferjol syndrome. A rare self-induced iron deficiency anaemia caused by surreptitious blood-letting. The French haematologist Jean Bernard first described the syndrome and named it after the heroine of Barbey d' Aurevilly's novel *The Story without a Name*. This factitious anaemia presents a great challenge for physicians even today, both in diagnosis and in therapy.

Introduction

In 1967 the eminent French haematologist Jean Bernard described the syndrome of Lasthénie de Ferjol, a recurrent iron deficiency anaemia provoked by repeated episodes of self-induced blood-letting. He named the disease after the heroine of Barbey d' Aurevilly's novel *The Story without a Name*.

The origin of the syndrome's name

Barbey d' Aurevilly (1808–1889) (Fig. 1), a French novelist[1] specializing in mystery tales that explored hidden motivation, published in 1882 his novel entitled *The Story without a Name*.[2] It is actually one of the rare cases in literature where the author clearly describes, for the first time, a disease that physicians would discover and study a century later. Inspired from a true story, he narrated in detail the tragic destiny of Lasthénie de Ferjol, a 16-year-old beautiful girl.

At the end of the 18th century, the young Lasthénie lived with her mother the Baroness de Ferjol and their old servant Agatha in a reclusive life in their castle close to Forez, in Normandy, France, until a Capuchin priest enters their life. He takes up residence in the Ferjol household for the duration of the Lent sermons and disappears before completing them. Soon afterwards Mme de Ferjol discovers that her daughter is expecting a child and to her questions about the name of the father she claims to be innocent and cannot explain her pregnancy. Suddenly, Lasthénie falls ill, loses weight, becomes weak, pale, looking like 'a putrefying mummy' and she withdraws into total silence; finally, she delivers a stillborn child and dies. After her death, Mme de Ferjol puts out Lasthénie's corset and she discovers 18 needles stuck into her heart, placed there one by one after the birth of her child, displaying self-mutilating behaviour (provoking bouts of anaemia) with lethal results. The story ended when the priest Riculf repented and retired to a monastery where he revealed the truth before his death: he had raped Lasthénie while she was in a trance-like state of somnambulism.[3]

First description of the syndrome

In the 1960s in St Louis Hospital in Paris, the Professor of Haematology and academician Jean Bernard (Fig. 2) used to hospitalize women suffering from hypochromic–

microcytic anaemia of unknown aetiology that did not improve with medical treatment.[4]

Patients were usually women aged 20–40 years, working in the medical or paramedical field with a history of untreated anaemia, multiple prior hospitalizations and frequent office visits to physicians. They had symptoms of the anaemia itself (easy fatiguability, tachycardia, palpitations, dyspnoea on exertion), skin and mucosal changes (smooth tongue, brittle nails, cheilosis) and pica. The anaemia was a severe hypochromic–microcytic one, with haemoglobin concentration as low as 50–60 g/L with low serum ferritin and iron levels and increased total iron binding capacity.

The case confused the attending doctors for almost 2 years until they observed that the patients worsened after having stayed alone overnight. In their rooms they discovered syringes, injection needles and bottles filled with blood and it was assumed that they were performing self blood-letting. Between 1960 and 1979 they had 30 similar cases. Jean Bernard and his collaborators named the disease 'Lasthénie de Ferjol syndrome' inspired by the story of Barbey d'Aurevilly's heroine.[5]

Psychiatric approach – treatment

The Lasthénie de Ferjol syndrome is an anaemia that belongs to the group of factitious disorders; psychiatric conditions in which the individual presents with an illness that is deliberately produced or falsified. The syndrome is difficult to diagnose because of the permanent disorder appearing inside the therapeutic relationship.

On a behavioural level this trouble is defined by the necessity of the illness and of appearing to be sick and by the need to challenge doctors. A borderline personality disorder seems particularly to apply to these patients who are characterized by unstable interpersonal relationships, rage, impulsivity, self-mutilation and/or suicide attempts.[6] To establish the diagnosis, except for a severe, treatment – refractory iron deficiency anaemia of unknown aetiology, the patient has to fulfil the criteria established by the Diagnostic and Statistical Manual of Mental Disorders 4th Edition, Text Revision:

- Intentional production or feigning of physical or psychological signs and symptoms
- Motivation to the behaviour to assume the sick role
- Absence of external incentives for the behaviour (e.g. economic gain, avoiding legal responsibility).[7]

The early detection of the syndrome is essential not only for appropriate treatment, but also for establishing a prognosis. Hospitalization for the anaemia may be needed, psychotherapy should always be offered and in severe cases the use of selective serotonin reuptake inhibitors or antipsychotic drugs may be beneficial.[8] Family therapy will help the family members in better understanding the syndrome and subsequently helping the patient. Close monitoring even with closed-circuit video cameras will assist in the prevention of self-injuries.

Conclusion

Lasthénie de Ferjol syndrome remains a very rare illness extremely challenging for haematologists, psychiatrists and general practitioners and should always be suspected in young women with medical training and severe iron deficiency anaemia not responding to treatment.

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IMAGES IN MEDICINE

Anaplastic thyroid carcinoma

A 44-year-old woman presented to our hospital after noticing an enlarging mass in her neck for the previous 2 months. She complained of pain, orthopnoea, stridor, hoarseness and weight loss. Physical examination revealed a solid mass with ill-defined borders and intrathoracic extension. Pulses were present in the right arm, but absent in the left arm and both legs. A chest X-ray and magnetic resonance imaging with angiography were ordered, revealing an intrathoracic mass arising from the thyroid gland (Fig. 1). Fine needle aspiration of the mass showed an anaplastic thyroid carcinoma. The patient was discharged home with palliative measures, and she died a few days later.

Anaplastic thyroid carcinoma is a rare and very aggressive tumour that accounts for 1–2% of all thyroid cancers.[1] It usually presents in women in the sixth or seventh decades of life and is characterized by a rapidly enlarging neck mass. Symptoms are related to the compression of adjacent structures and include dyspnoea, stridor, dysphagia and hoarseness.[2] Invasion of vascular structures is uncommon. Most patients have metastases at the time of diagnosis, with the most common sites being regional lymph nodes and the lungs. Treatment is highly unsatisfactory and mean survival after diagnosis ranges from 3 to 8 months.[3]

Received 24 June 2009; accepted 29 June 2009.

doi:10.1111/j.1445-5994.2010.02219.x

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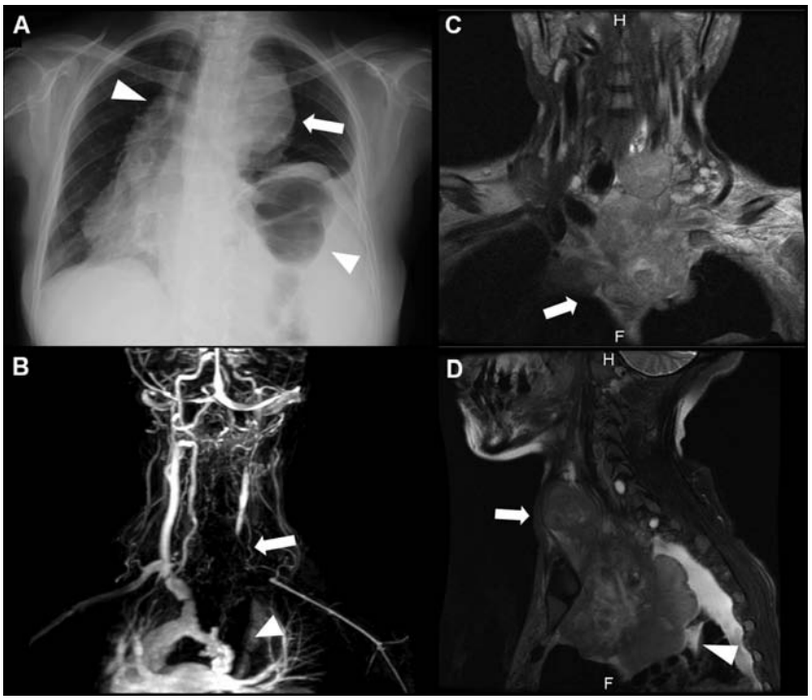

Figure 1 Chest X-ray (A) revealed a mass (arrow) that displaced the heart and trachea, with elevation of the left hemidiaphragm (arrowheads). Magnetic resonance imaging revealed a tumour arising from the thyroid gland with invasion of the mediastinum (C and D, arrows) and the left hemithorax (D, arrowhead). Magnetic resonance angiography showed an interruption of the left carotid artery (B, arrow) and the aortic arch (B, arrowhead).

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IMAGES IN MEDICINE

Giant renal angiomyolipomatosis in association with pulmonary lymphangiomyomatosis

A 51-year-old woman was admitted to hospital with a 2-year history of intermittent exertional dyspnoea. High-resolution computed tomography (CT) of the lungs showed bilateral diffuse cystic changes with a maximal diameter of 15 mm (Fig. 1). Abdominal CT showed bilateral renal fat-density masses (massive in the right kidney) consistent with angiomyolipomas (Fig. 2), and a non-obstructing calculus in the right renal pelvis. Pulmonary function tests show decreased forced expiratory volume in 1 s. These findings were consistent with giant renal angiomyolipomas in association with pulmonary lymphangioleiomyomatosis (LAM), and raised the possibility of tuberous sclerosis. Family history and clinical signs of tuberous sclerosis were absent and cerebral magnetic resonance imaging was normal.

LAM is a rare multisystem disorder that mainly affects the lungs but can also involve the kidneys (with renal angiomyolipomas representing the most important extrapulmonary complication of LAM), the lymphatic system, liver, uterus and pancreas. It occurs mainly in women of childbearing age with a mean age of 34 years, although the diagnosis is sometimes made in postmenopausal women. Men are rarely affected. There is no familial tendency. The disorder is histologically characterized by a diffuse proliferation of atypical smooth muscle cells (LAM cells) in the alveoli and cystic destruction of the normal lung parenchyma. The most common presenting symptoms are exertional dyspnoea, chronic cough and pneumothorax. CT shows numerous thin-walled cysts throughout the lungs.[1–3] Renal angiomyolipomas are characterized by the presence of mature fat, smooth muscle and blood vessels. The most frequent clinical

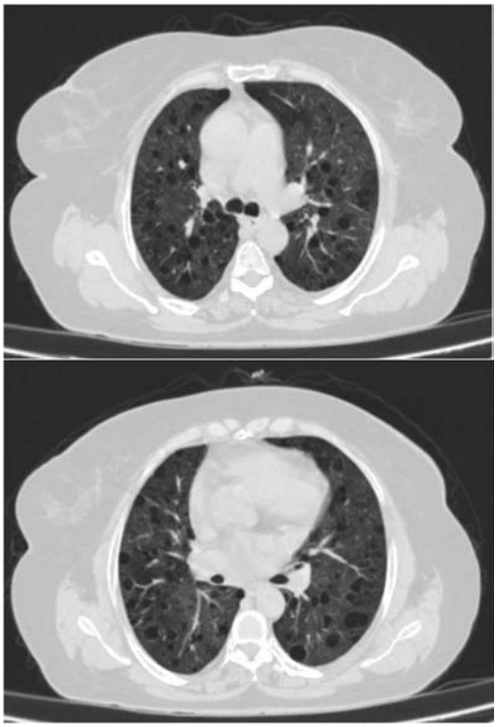

Figure 1 High-resolution computed tomography scans of the lungs showing widespread thin-walled bilateral cysts in a background of normal parenchyma.

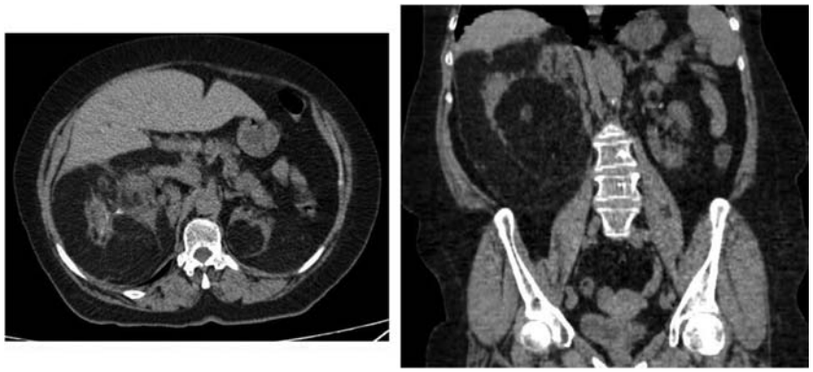

Figure 2 Axial and reformatted coronal abdominal computed tomography images of renal angiomyolipomas.

symptoms include flank pain, retroperitoneal bleeding, haematuria, and symptoms of pyelonephritis. The demonstration of intratumoural fat with negative attenuation values on CT is virtually pathognomonic of angiomyolipomas.[1,4] No effective treatment currently exists for this progressive disorder. The prevalence of LAM is probably underestimated based on its clinical latency and the absence of specific laboratory tests.[3]

Received 26 June 2009; accepted 13 August 2009.

doi:10.1111/j.1445-5994.2010.02218.x

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Clinical-scientific notes

Ventriculo-atrial shunt induced severe pulmonary arterial hypertension: a time for routine screening?

A 44-year-old woman with spina bifida and ventriculo-atrial (V-A) shunt presented with dyspnoea over 2 days and was found to be hypoxic. Computed tomography pulmonary angiography (Fig. 1) showed bilateral massive pulmonary emboli within the main pulmonary arteries and an isolated 1.7-cm short catheter in the right pulmonary artery (RPA), patchy ground glass appearance in both lung fields, thought to be secondary to an *in situ* chronic thromboembolic pulmonary arterial process and/or de novo pulmonary arteriolar hyperplasia. She was subsequently thrombolysed with tenecteplase. Baseline echocardiography showed a grossly dilated right heart with marked impairment in right ventricular function, severe pulmonary hypertension (PH) with an estimated mean pulmonary artery pressure of 70 mmHg. Duplex scanning failed to show evidence of a peripheral source of venous thromboembolism. Thrombophilic screen was negative.

She was anticoagulated, and her right heart failure was treated with combination diuretic therapy. An empiric combination therapy of oral sildenafil (25 mg t.i.d.) and bosentan (125 mg b.i.d.) was prescribed in an effort to reduce her pulmonary vascular resistance. A failed attempt at removal of V-A shunt led to a new ventriculo-peritoneal shunt being inserted, leaving the caudal portion of V-A shunt within the RPA.

There are several possible complications associated with V-A shunt implantation which include shunt dysfunction, shunt infection and *in situ* PH with associated thromboembolism, although the latter process is much less clinically reported and poorly understood.[1] Post-mortem studies of patients with V-A shunt implantation have estimated the prevalence of thromboembolic phenomenon to be of the order of 60%,[2] with pathological evidence of PH being 6.9%;[2] however, clinically diagnosis is only established in 0.4% and 0.3% respectively.[2,3]

The development of *in situ* PH within the V-A shunt population is thought to result from either *de novo* development of thrombus with subsequent thromboembolism, or a locally altered thrombogenic environment within the pulmonary arterial vasculature. It is thought that the reaction of endothelium to proteins such as thromboplastin from cerebrospinal fluid may alter the local environment thus rendering the pulmonary vasculature more thrombogeneic, resulting in increased platelet aggregation and subsequent vascular thrombosis.[2,4] The mechanism for thromboembolism in these patients cannot be completely explained by the presence of a foreign body in their right atrium, as patients with pacemaker leads do not have the same incidence of thromboembolism and PH.[5]

Medical therapies including anticoagulation is recommended for this cohort. Although currently not considered to be proven therapy within the V-A shunt PH population, the off-label use of pulmonary vasodilator therapies may be of benefit, including bosentan, an endothelin-receptor antagonist; sildenafil, a selective inhibitor of type 5 phosphodiesterase; and prostacyclin analogues (i.e. inhaled iloprost).[6]

In summary, despite a dearth of case reports in the literature describing the association between V-A shunts and *in situ* pulmonary thromboembolism and PH, we advocate a strong case for the routine clinical, electrocardiographic and echocardiographic screening of all

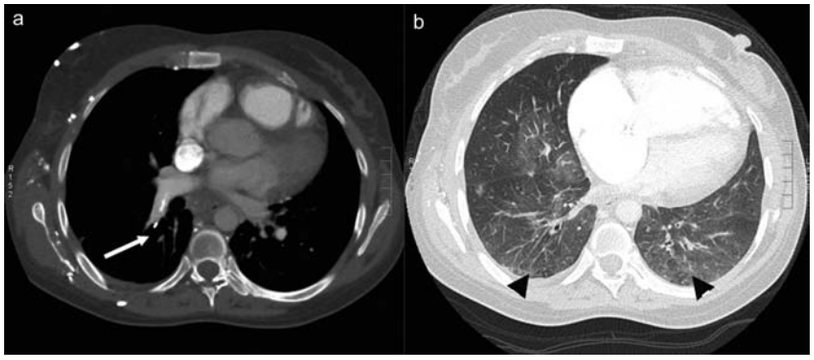

Figure 1 (a) Helical slice through mediastinal window of computed tomography (CT) chest showing dislodgement of ventriculo-atrial shunt tube caudally in the right pulmonary artery. (b) Helical slice through lung windows of CT chest showing arrows that point to mosaic pattern of lung attenuation suggestive in this case of vascular lung disease beyond the third-generation bronchial tree.

patients with V-A shunt implantation. A high index of clinical suspicion for the presence of thromboembolism and PH should exist in patients with an implanted V-A shunt presenting with respiratory symptoms.

Received 10 June 2009; accepted 1 September 2009.

doi:10.1111/j.1445-5994.2010.02178.x

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Successful rituximab therapy in the treatment of refractory cold haemagglutinin disease with long-term disease control

Cold agglutinin disease (CAD) is a rare disorder characterized by autoimmune haemolytic anaemia (AIHA), mediated by cold-reactive autoantibodies that bind to erythrocyte carbohydrate antigens, causing haemagglutination and complement-mediated haemolysis.[1] CAD is understood to be a B-cell disorder usually resistant to treatment with immunosuppressive therapy with splenectomy used, usually ineffectively, as a second-line therapy.[1,2]

Rituximab is a monoclonal antibody that is specific for the CD20 antigen, expressed on the surface of B lymphocytes and used in immune-mediated disorders.[3–5]

We describe three different cases of CAD treated with rituximab at our institution. Two patients had primary refractory severe CAD with a nadir haemoglobin (Hb) of 52 and 43 g/L and a third patient with chronic CAD (CCAD) and a nadir Hb of 100 g/L. All patients presented with AIHA, high cold agglutinin titre, high lactate dehydrogenase, positive direct antiglobulin test and low haptoglobin (Table 1). Bone marrow biopsy was carried out in all patients and showed normal results without evidence of B-cell clonality as shown by the cell marker studies.

The first patient, a 65-year-old man, presented in February 2007 with Hb of 70 g/L (Normal (N.) 140–180). He failed initial treatment with steroids with a further drop in Hb (56 g/L). Thereafter, treatment with intravenous

Table 1 Patient characteristics

	Case 1	Case 2	Case 3
Age at diagnosis (years), sex	65, male	48, male	76, male
Lowest Hb (N. 140–180 g/L)	52	43	101
Max LDH (N. 123–243 U/L)	406	613	218
Max reticulocyte count (N. 10–100)	186	664	120
Lowest haptoglobin (N. 0.40–2.10 g/L)	<0.06	< 0.06	0.2
Max. bilirubin level (N. <17 μmol/L)	1112	74	16
Max cold agglutinin titre	1:1024	1:256	>1:2048
Computed tomographic scan of chest, abdomen and pelvis	NAD	Mild hepatosplenomegaly, no lymphadenopathy	NAD
Bone marrow biopsy	Marked erythropoiesis	Marked erythropoiesis	Erythroid hyperplasia
Previous treatments	Prednisolone/azathioprine Intravenous immunoglobulin Vincristine	Prednisolone Vincristine Cyclophosphamide	Plasmapheresis Prednisolone
Concomitant infection/underlying diseases	Moraxella catarrhalis	Acute Epstein–Barr virus infection	Autoimmune disease with Raynaud's phenomenon
Rituximab dose (mg/m^2)	6 × 375	4 × 375	4 × 375
Current Hb (N. 140–180 g/L)	134	145	122
Follow up post rituximab (months)	24	36	35

Hb, haemoglobin; LDH, lactate dehydrogenase; N., normal; NAD, no abnormality detected.

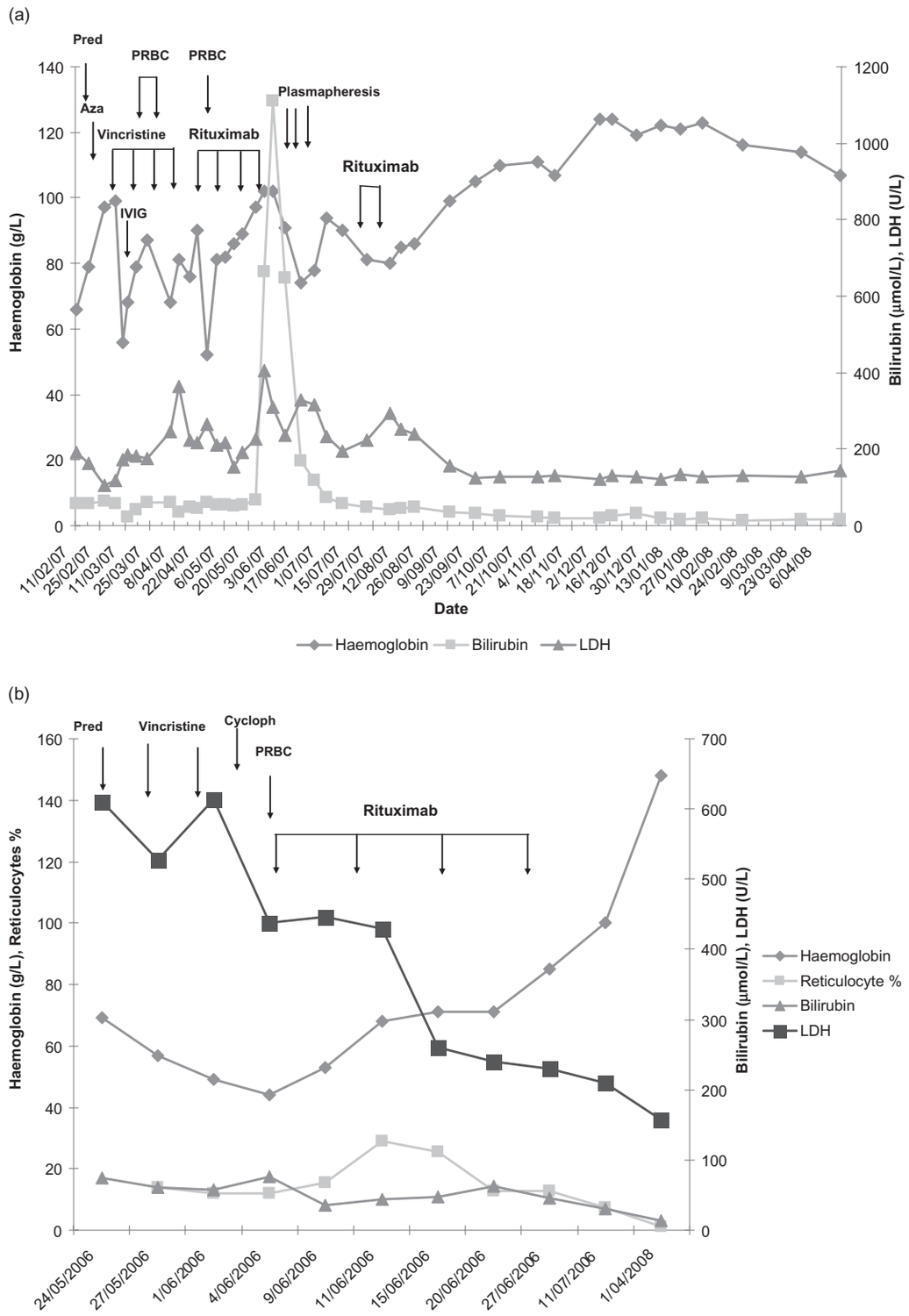

Figure 1 The effect of different therapies on haemoglobin, bilirubin, reticulocyte count and lactate dehydrogenase (LDH) in (a) patient 1 and (b) patient 2 as well as the responses after commencement of rituximab monotherapy. Aza, azathioprine; Cycloph, cyclophosphamide; IVIG, intravenous immunoglobulin; PRBC, packed red blood cells; Pred, prednisolone.

immunoglobulin (IVIG) 1 g/kg and vincristine (2 mg IV weekly for four doses), was commenced with Hb improvement to 87 g/L. Four weeks later, he had a further relapse with an Hb of 52 g/L. Thereafter, treatment with rituximab was commenced initially with four doses of 375 mg/m^2 IV weekly. However, the patient developed marked hyperbilirubinaemia of max 1112 μmol/L (N. < 24) secondary to a concomitant oral antibiotic (amoxicillin and clavulanic acid) and or antimycotic (fluconazole) treatment that required three plasmaphereses to resolve (Fig. 1a). Therefore, two extra doses of rituximab 375 mg/m^2 IV weekly were given after plasmapheresis to maintain the drug–plasma levels. Currently, 24 months after rituximab, he presents with an Hb of 134 g/L without further therapy.

The second patient, a 48-year-old man, presented in April 2006, with jaundice, fever, fatigue and myalgia. Computed tomographic scan showed hepatosplenomegaly, but no lymphadenopathy. The patient has severe anaemia with an Hb of 69 g/L and cold agglutinin titre of 1:256. Epstein–Barr virus immunoglobulin M was positive, consistent with a recent infection. He failed to respond initially to prednisolone and subsequently to cyclophosphamide and vincristine, with Hb falling to 43 g/L (Fig. 1b). He was subsequently commenced on rituximab (375 mg/m^2/week/4 weeks). He showed substantial improvement and recovery, with normalization of his Hb level currently to 145 g/L without evidence of haemolysis after 36 months post rituximab.

The last patient, a 76-year-old man, first presented in May 2005, with CCAD associated with Raynaud's phenomenon and acrocyanosis. Because of continuous worsening of anaemia (Hb 100 g/L) despite initial plasmapheresis and subsequent prednisolone therapy, he was commenced 1 year later on rituximab 375 mg/m^2 IV weekly for four doses. Currently after 35 months follow up post rituximab therapy, he presented with an Hb of 122 g/L and no active haemolysis without immunosuppresive treatment.

It is worth noting that both patients with acute CAD have had severe life-threatening drop of Hb levels despite different immunosuppressive treatment with several immunomodulating agents, including vincristine, cyclophosphamide, azathioprine, prednisolone and IVIG therapy. Therefore, it is highly unlikely that a resistant CAD will spontaneously resolve without a specific treatment, especially in this refractory setting to the immunotherapy. Additionally, these therapies while not consistently effective present an increased risk of infection that may complicate the treatment course and adversely affect overall outcome.

In our series, rituximab played a significant role in patients with CAD and refractory AIHA, particularly in the long-term control of the disease. This confirms the immediate effect of rituximab in inducing remission of CAD.[6,7] None of the patients proceeded with splenectomy. Furthermore, rituximab successfully achieved long-term control of the disease without maintenance therapy unlike other reports.[8]

Received 15 April 2009; accepted 4 November 2009.

doi:10.1111/j.1445-5994.2010.02173.x

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General correspondence

Evaluation and clinical improvement requires responsiveness, scientific method, audit and due process applicable to all

Performance is not the same as audit. Inability, using clinical indicators, to 'drive' improvement in clinical practice was attributed to the lack of a computerized data collection system, by Brand *et al.*[1] The fact that they set out to test whether improved clinical effectiveness and safety occurred instead of access and efficiency, which are clinical concerns, does not have anything to do with the fact that theirs is, to make the most of it, a two-part study to determine whether a data collection system is better than no data collection system, and phase three, which they have not addressed, is likely to be whether a palm-held interactive Internet connecting and data storage device, 'pod', is better than no 'pod'.

Wielding the big stick to 'drive' improvement does not work. If anything can be salvaged from an anecdotal uncontrolled hospital-based activity, the report of Brand *et al.*[1] shows the need to include 'responsiveness' into performance measurement as recommended by the World Health Organization, in its June 2000 assessment of medical systems around the world.[2,3]

To make their efforts worthwhile, Brand *et al.*[1] need to control for the lack of responsiveness in the design of their study (phase four), by thinking scientifically not bureaucratically, by leading not by herding. By introducing the concept of localized controlled trials, educating doctors to be leaders of teams and others to be team members not opportunists; by encouraging and supporting objective evaluation; by introducing competition; by creating incentive rather than disincentive; by encouraging brainstorming and innovation; by providing opportunities to present the findings in public and presentations and awards; by creating opportunities of responsiveness as a hallmark and awarding the participants when new discoveries are made; by engaging students, and above all by engaging patients to determine treatment goals as well as to assess treatment outcomes, beyond morbidity and mortality data; by providing scientific protocols, not disastrous ones; by accepting criticism as an essential element of the growth process as another performance measure, is food for thought, responsiveness and action.

The fifth phase and most challenging relates to fig. 2,[1] which exemplifies the notion that flow is unidirectional in the evaluation process. Interestingly, there needs to be feedback. It is easier to assume the role of know all, much harder to accept the need to know, much harder to be evaluated than to issue decrees, build power bases and delegate than to participate. It is even harder to see the wood from the trees when idealism or delusion takes over.

Scientific method, audit and due process which are open to constructive criticism, whereby decisions themselves are evaluated as 'good' or 'bad', are required to drive change for improvement. This is a process that is wanting in 'bureaucratic' medicine and the reason why it is necessary to ask 'do existing indicators measure what they purport to measure?'[4]

If generally accepted, 'outcome responsive evaluation' provides the basis for driving improved performance in health[2,3,5] and decision-making in law[5–8] for the benefit of all.

Received 25 August 2009; accepted 3 September 2009.

doi:10.1111/j.1445-5994.2010.02179.x

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Reply

We agree with Myers[1] about the need for clinical leadership in measuring performance and driving improvement. The General Medical Indicator Program was

conceived by clinicians, designed by clinicians, implemented and evaluated by clinicians. This was not a 'big stick', management-driven project.

We also agree that performance is not synonymous with audit, the former being an outcome of clinical practice and the latter being one of a number of methods whereby performance can be measured. We suggest that by measuring performance we can better understand our practice and target areas for improvement. The WHO report, referenced by Myers, focuses on health system improvement at the level of government. In contrast we are measuring one aspect of healthcare provider clinical performance, namely implementation of evidence into practice. We have clearly defined this perspective and the purpose for which the indicators were developed. As Myers suggest, prioritization is a key element of improvement and our clinicians contributed to this process using a set of priority criteria. We accept that in 'handing over' this prioritization to clinicians that the breadth of quality domains under which individual indicators fall is limited (mainly to appropriateness, effectiveness and safety) and we may be criticized for not including team-based and patient-perceived priorities (access and responsiveness) within our indicator set. We acknowledged this limitation in the paper, explaining our aim to focus specifically in the first instance on processes of care immediately within the control of medical clinicians.

We agree that the study design should be appropriate to the question raised. It would have been inappropriate to test each indicator within a randomised controlled trial, given the evidence base already published about effectiveness of therapeutic interventions, such as use of ACE-I, beta blockers and rehabilitation for chronic heart failure. As clearly stated, our main aim was to assess feasibility of implementation of the indicator set. Failure to implement evidence into practice using interventions, such as clinical practice guidelines, may be due, not to the inadequacy of the guideline recommendations, but to failure to implement effectively. Therefore, before performing an expensive but definitive (scientific) study to assess effectiveness of the indicator set as a measure of performance to target improvement, a preliminary feasibility study was considered to be essential. The feasibility study used appropriate evidence-based implementation strategies and programme evaluation methods. Furthermore, the results outlined in the paper justified this approach and provide other clinicians with important information about barriers and enablers to use of an indicator set for quality improvement purposes.

We have been open in our cautious approach to using these performance measurement tools. We recognize the limitations of indicators as measures of performance and the perverse ways in which they can be applied.

We suggest that planning for improving health outcomes needs to be considered at multiple levels (clinician and patients, management and funding provider as well as government) and using multiple strategies according to the issue of interest, evidence about effective interventions and contextual factors influencing implementation of those interventions. Finally, we also agree there is no room for idealism, delusion, but plenty of room for constructive criticism and learning as we participate in various ways in this challenging era of health reform.

Received 14 January 2010; accepted 20 January 2010.

doi:10.1111/j.1445-5994.2010.02191.x

C. Brand,[1,2,3] S. K. L. Lam,[4] C. Roberts,[1] A. Gorelik,[1] B. Amatya,[1] D. Smallwood[5] and D. Russell[6]

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Reference

1 Myers J. Evaluation and clinical improvement requires responsiveness, scientific method, audit and due process applicable to all. *Intern Med J* 2010; **40**: 390.

Erratum

The authors would like to draw the reader's attention to an error in the following article:

S Lindstrom, V Nagalingam, S Boyd, M Safe, S McBrearty, S Deshpande, H Newnham. The 2009 Melbourne Heat Wave and Medical Presentations: Much More of the Same. *Intern Med J* 2010; **40** (s1): 134. (Abstract number P245)

In the Results section in the Abstract (number P245), the adjusted incidence rate ratio for acute myocardial infarction should read IRR 4.3, and not IRR 3.83 as currently stated.

The authors apologize for this error and any confusion it may have caused.

Erratum

The publisher would like to draw the reader's attention to important errors in the Conflict of Interest and Funding statements which were published in the following article:

Davis WA, Knuiman MW, Davis TME. An Australian cardiovascular risk equation for type 2 diabetes: The Fremantle Diabetes Study. *Intern Med J* 2010; **40**: 286–92.

The errors occurred during proof mark up. The declarations should have read:

Conflict of Interest: None.

Funding: The present study was funded by an unrestricted educational grant from Merck, Sharp and Dhome, Australia and The Raine Foundation, University of Western Australia.

The publisher apologizes for these errors and any confusion caused.

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IMJ.PI.NOV09

VOLUME 40 ISSUE 5 MAY 2010

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