MEASUREMENT OF FAECAL CALPROTECTIN LEVEL IN INFLAMMATORY BOWEL DISEASE

Farhat Saadi, Jayantha Arnold

The newly available surrogate marker tests for inflammatory bowel disease have the potential to make it easier to distinguish between functional and organic diseases of the gut and predict or confirm relapse in known patients with inflammatory bowel disease. A study conducted in the University of Padova by Barabino et al in 2009 [1] compared a number of non-invasive tests for diagnosing intestinal inflammation in children with spondyloarthopathies. Forty-two children study IBD or rheumatologic manifestations associated with gastrointestinal symptoms, investigated by 99mTechnetium-HMPAO labeled white cell scanning, abdominal ultrasound, ESR, faecal occult blood and faecal alpha 1-antitrypsin. 99mTechnetium-HMPAO labeled white cell scanning was shown to be the most sensitive (85%) and specific (100%) in detecting gut inflammation.

Many studies have been carried out in this area, all aimed at enhancing the sensitivity and accuracy of the new tests which can diagnose diseases more competently. One of the new tests is measurement of faecal calprotectin in gastrointestinal disease, in this article we have focus on the role of fecal calprotectin in inflammatory bowel disease as a biomarker of disease activity. Some leukocyte proteins, such as lactoferrin and calprotectin, are more stable and have greater resistance to degradation and can be used as surrogate markers to detect the presence of leukocytes in stools.

Faecal calprotectin, a novel biomarker of inflammation of the bowel, may play a role in detecting intestinal pathology, reducing the need for endoscopy in some patients, and may also provide good prognostic information. Calprotectin is a calcium binding protein, composed of one light chain and two heavy chains, formed mainly from the turnover of cytosolic portion of neutrophils, monocytes and macrophages (CD14+), but is not present in T or B lymphocytes [2]. It has antimicrobial activity by inhibiting the growth of pathogens through competition for zinc, it also has an anti tumour activity by inducing apoptosis of certain tumour cells.

Calprotectin can be detected in plasma, stool, cerebrospinal fluid, sputum, amniotic fluid, pleural and synovial fluid and its level found to be significantly elevated in stool and to a lesser extent in plasma when there is bowel inflammation as in inflammatory bowel disease. Although calprotectin
and lactoferrin are very sensitive markers to detect inflammation in the gastrointestinal tract increased levels are also found in patients with colorectal cancer, with non-steroidal anti-inflammatory drug usage, infections and polyps [3]. Inflammatory bowel disease is characterised by multiple relapsing and remitting attacks of diarrhea with or without blood in stools, and abdominal pain. Crohn’s disease can affect any part of gastrointestinal tract and Ulcerative colitis usually affects the Colon. The annual incidence of the Crohn’s disease is approximately 4-10 per 100,000 while that of Ulcerative colitis is 6-15/100,000, females are affected more than males.

The pathogenic causes are still not fully understood but several factors play a role in its pathogenesis including genetic predisposition, infections, nutritional factors, smoking and immunological factors. There is elevation of inflammatory markers like CRP and anaemia as a response to the chronic course of the disease and for definitive diagnosis patients require invasive procedures such as colonoscopy or flexible sigmoidoscopy and mucosal biopsy. The current inflammatory markers of the disease are non-specific and are elevated in other diseases also such as chronic infections, tumours and non-intestinal inflammatory conditions.

Measurement of faecal calprotectin can be used:

- As a non-invasive marker of the inflammatory bowel disease activity.
- To assess the response to therapy.
- As a predictor of disease relapse and as a confirmatory test for relapse.
- To distinguish inflammatory bowel disease from functional bowel disease i.e. irritable bowel disease as the level of fecal calprotectin is not elevated in irritable bowel disease.
- As a non-invasive, investigation compared to endoscopy and also for following up the patient.

Calprotectin is measured by a single step enzyme linked immunosorbant assay (ELISA) using antibodies against six epitopes found on the calprotectin molecule, fecal calprotectin can be measured in a single stool sample, rather than a 24-hour or four day stool collection, only 5 grams of faeces is required to be collected (a cut off .150 g/g is used to determine intestinal inflammation). Calprotectin is very stable due to calcium binding, and specimens can be stored for up to 7 days at room temperature before being
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processed. This allows specimens from other centers to be sent to a reference laboratory [2].

<table>
<thead>
<tr>
<th>Molecular weight</th>
<th>36 kDa protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular course</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Physiological role</td>
<td>Host defense</td>
</tr>
<tr>
<td>Type of sample</td>
<td>Fecal</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>0.5-50</td>
</tr>
<tr>
<td>Active IBD*</td>
<td>500-50,000</td>
</tr>
<tr>
<td>Non active IBD</td>
<td>50-500</td>
</tr>
<tr>
<td>IBS**</td>
<td>1-150</td>
</tr>
</tbody>
</table>

*IBD: Inflammatory Bowel Disease
**IBS irritable Bowel Syndrome

Many studies have been conducted to determine the clinical significance of fecal calprotectin in inflammatory bowel disease. While fecal calprotectin is a very sensitive measure of intestinal inflammation, it is not specific for the detection of the cause of inflammation [2]. A recent study used BÜHLMANN Calprotectin ELISA (monoclonal) at the University Hospital Basel, Switzerland, to measure calprotectin level in a total of 405 symptomatic patients, a sensitivity of 84% and specificity of 95% was found [5]. The result support findings by Tibble et al. 2000, where 81 asymptomatic patients were included and followed up for 1 year. It was reported that at 50 mg/l the test has a sensitivity of 90% and specificity 83% for predicting relapses [6].

In another study where 49 patients were included and 151 of their 220 first degree relatives investigated for the presence of bowel inflammation using fecal calprotectin test, it was found that 49% of relatives had intestinal inflammation [7]. Faecal calprotectin has also been investigated in colorectal cancer. A study suggested that fecal calprotectin has a negative predictive value for colorectal neoplasia (99%), making it possibly useful in investigating patients suspected to have colorectal malignancy [8].

A prospective multi centre study in Italy has raised some doubt on the value of faecal calprotectin in identifying patients with Inflammatory bowel disease. A result of > 50 mg/l was found only in 81% of patients who showed inflammatory lesions at colonoscopy. A normal faecal calprotectin value was reassuringly found in all patients with diarrhea with normal colonoscopic findings.

Measurement of fecal calprotectin is a new emerging test which should complement procedures such as colonoscopy and flexible sigmoidoscopy for detecting and monitoring inflammatory bowel disease. Stool markers of gastrointestinal inflammation such as lactoferrin and, more recently, calprotectin, are of considerable research interest and are likely to enter clinical practice after validation in larger trials [9].
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WRITTEN COMMUNICATION BETWEEN GENERAL PRACTITIONERS AND HOSPITALS, AN ANALYSIS

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ABSTRACT

Communication between general practice and hospital doctors is essential for patient care. We conducted a retrospective study of patient referral letters and paired discharge summaries for all patients admitted to the hospital following referral by their general practitioner (GP) (n=773) between 1st November 2006 and 30th April 2007. Handwritten referrals were more likely to omit results of investigations ($X^2 = 7$, d.f. =1, $p=0.008$), a list of current medications ($X^2=12$, d.f. =1, $p=0.0005$), and past medical history ($X^2=76$, d.f. = 1, $p<0.0001$). Few of the handwritten discharge summaries included investigations requiring GP action ($X^2=4$, d.f. = 1, $p=0.04$). There were no examples of complete communication between GP and hospital doctor. This study highlights a number of issues surrounding written communication. Strategies such as electronic forms are still unsuccessful. It is vital that doctors involved be consulted during the development of these forms to ensure that they contain the information needed to improve the quality of patient care.

Key Words: communication, referral letters, discharge summaries, electronic data

Key Points

1. Communication between general practice and hospital care has long been problematic
2. Typed/electronic templates aid legibility but do not currently offer a unified system of communication
3. General practitioners and hospital doctors need to be involved in the development of future templates if the quality of patient care is to be improved.
INTRODUCTION

Communication between General Practitioners (GP) and hospitals is essential for a patient’s continuity of care management. The principle is enshrined in the GMC’s guidance document Good Medical Practice, which requires keeping colleagues well informed when sharing the care of patients.

Previous reports have highlighted the poor quality of written information between doctors, both on admission and on discharge. Whilst there are minor differences between admission and discharge notification the same failings can be identified, specifically relating to the legibility of written communication and to the absence of relevant important information. Recognition of these inadequacies has lead to the creation of guidelines for medical communication. The Scottish Intercollegiate Guidelines Network (SIGN) of the Royal Society of Physicians of Scotland has recommended a standard for admission letters and The Royal College of Physicians (RCP) has published a similar draft standard for discharge summaries. However neither of these guidelines have been adopted nationally.

As part of the drive to improve the quality of letters, there have been local attempts to standardise medical letters and attempts at the development of electronic records and discharge packages. Our hospital is part of a pilot scheme with Communicating for Health and uses Notification of Discharge software for discharges from 5 of its medical wards whilst paper discharge summaries persist in other wards. Notification of discharge software contains compulsory fields for diagnoses, allergies, problem list, management and investigations, medication and whether the patient lives alone.

The aim of the present study was to investigate the entire communication loop between primary care and our hospital and back to the referring primary care physician.

METHODS

The hospital admission software (Isoft v.3.1) was used to identify all patients admitted from their general practitioner (GP) as emergencies to the district hospital between 1st November 2006 and 30th April 2007. The notes were examined for the presence of both a referral letter and discharge communication. Notes were also examined for investigations and changes to medication.

Legibility of communication was assessed by one of the authors (KleD) and deemed to be acceptable if either every word was legible and/or the context of each sentence could be understood.

Adequacy of communication was assessed by comparison with the guidelines from the Royal Colleges (see above).
Furthermore, note was made of specific questions raised by the admission letter regarding the reason for referral and the corresponding discharge letter reviewed to assess whether these were specifically answered.

LOCAL VIEWS

An attempt was made to gain further insight into our local referral processes by interviewing a selection of the doctors most involved in the communication pathways. Interviews were carried out with local GPs (n=5) and senior house officers (SHOs, n=5). The GPs represented the practices that referred the most and the least, as well as three with ‘average’ referral numbers. The SHOs interviewed represented the specialties of medicine (2), surgery, and A&E (2), and were in post at the time of the study. Trauma and orthopaedics, gynaecological and urology were excluded due to the direct referral pathway used at our hospital, where such patients are admitted straight to their specialist unit following telephone referral. We chose SHOs, as they are the first point of contact for GP referrals. SHOs were asked to rank the SIGN criteria in their personal order of importance. Similarly GPs were asked to rank the areas highlighted by the Royal College of Physicians for good discharge summaries.

The study included 773 patients with complete information on GP A&E referral letter and corresponding discharge summaries.

STATISTICS

Statistical analysis was performed using SPSS statistical software (v 11.5-SPSS Inc. Chicago). Chi-square analysis was used to compare variables within the various handwritten and typed referrals. P values (Two tailed) of <0.05 was considered significant.

RESULTS

There were 9548 admissions in the hospital A&E between November 2006 and April 2007. Of these, 2100 (22.0%) patients were admitted via casualty following a referral from their local GP. The referral letter was missing from the records of 1218 (58%) patients and 109 (5%) lacked discharge summaries. Of the original referrals 773 (37%) had a paired GP referral letter and discharge summary and were available for this study (Figure 1).
a. Admission letters

Of the referral letters (n=773) 67% were handwritten with only one practice using a proforma template corresponding to the template standard recommended by SIGN. Of the 537 handwritten letters received, 519 were legible. Complete information was found in 54 (7%) referral letters using the SIGN recommendations (Table 1).

Table 1 – Completeness of information and legibility of GP referral letters (n=773)

<table>
<thead>
<tr>
<th>No. Content complete (%)</th>
<th>Handwritten</th>
<th>Typed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legible</td>
<td>519 (95%)</td>
<td>230 (100%)</td>
</tr>
<tr>
<td>Complete</td>
<td>42 (8%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Specific question</td>
<td>114 (21%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>History of presenting complaint (reason for referral)</td>
<td>445 (81%)</td>
<td>170 (74%)</td>
</tr>
<tr>
<td>Past medical history</td>
<td>247 (45%)</td>
<td>182 (79%)</td>
</tr>
<tr>
<td>Current and recent medication/clinical warnings</td>
<td>217 (40%)</td>
<td>122 (43%)</td>
</tr>
<tr>
<td>Additional relevant information (Social circumstances) to aid discharge planning</td>
<td>64 (12%)</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>Investigation results</td>
<td>85 (16%)</td>
<td>80 (35%)</td>
</tr>
<tr>
<td>Examination results</td>
<td>301 (55%)</td>
<td>140 (61%)</td>
</tr>
<tr>
<td>TOTALS</td>
<td>537 (100%)</td>
<td>230 (100%)</td>
</tr>
</tbody>
</table>

Of the remaining (n=719) letters all were incomplete and omitted at least one aspect considered important/essential by the aforementioned standards. The most common omission was the patient’s social circumstances (90.6%). Handwritten referrals were more likely to omit results of investigations ($X^2 = 7$, d.f. =1, $p=0.008$), a list of current medications ($X^2=12$, d.f. =1, $p=0.0005$), and past medical history ($X^2=76$, d.f. = 1, $p=<0.0001$).

b. SHO priorities for written communications

SHOs ranked presenting complaint, past medical history, current and recent medicines and clinical warnings as their top three priorities for admission letters. A total of 162 letters did not give the reason for referral, which was ranked most important by admitting SHOs (Table 2).
Table 2 – SHO ranking of six items suggested by SIGN as important for referral letters, and numbers (%) if each item omitted

<table>
<thead>
<tr>
<th>Item in rank order</th>
<th>Items omitted N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting complaint/reason for referral</td>
<td>162 (21%)</td>
</tr>
<tr>
<td>Past medical history</td>
<td>348 (45%)</td>
</tr>
<tr>
<td>Current and recent medication/clinical warnings</td>
<td>438 (56%)</td>
</tr>
<tr>
<td>Additional relevant information (Social history to aid discharge planning)</td>
<td>693 (89%)</td>
</tr>
<tr>
<td>Investigation results</td>
<td>612 (79%)</td>
</tr>
<tr>
<td>Examination findings</td>
<td>336 (43%)</td>
</tr>
</tbody>
</table>

A specific question was asked by 126 GPs (16%).

c. Discharge summaries

A total of 66% of discharge summaries were handwritten, 34% were electronic. The majority of the handwritten summaries (96%) were legible. On discharge 51% of the discharge diagnoses corresponded to the admitting GP’s diagnosis. Of the remainder 36% had a different diagnosis on discharge and

Table 3 – the completeness of information and legibility of discharge summaries at District hospital Hospital (n=773)

<table>
<thead>
<tr>
<th>No. Content complete (%)</th>
<th>Handwritten</th>
<th>Electronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legible</td>
<td>486 (96%)</td>
<td>263 (100%)</td>
</tr>
<tr>
<td>Complete</td>
<td>0</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Changes to current medicines</td>
<td>474 (94%)</td>
<td>257 (98%)</td>
</tr>
<tr>
<td>Reasons for changes or stopped/new medicines</td>
<td>390 (77%)</td>
<td>227 (86%)</td>
</tr>
<tr>
<td>Procedures and investigations (GP needs to see results and action)</td>
<td>342 (68%)</td>
<td>179 (68%)</td>
</tr>
<tr>
<td>Management plan (Other GP actions required) and intended outcomes</td>
<td>468 (93%)</td>
<td>257 (98%)</td>
</tr>
<tr>
<td>Review of case, current diagnoses/problem list</td>
<td>504 (100%)</td>
<td>263 (100%)</td>
</tr>
<tr>
<td>Answers to specific questions</td>
<td>450 (89%)</td>
<td>251 (95%)</td>
</tr>
<tr>
<td>Functional state (intermediate or permanent change of housing)</td>
<td>0 (0%)</td>
<td>16 (6%)</td>
</tr>
<tr>
<td>Information given to patient</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>504 (100%)</td>
<td>263 (100%)</td>
</tr>
</tbody>
</table>
no GP diagnosis for the admission was given for comparison on other discharge summaries (13%). GP questions were answered in 92.4% of discharge summaries.

Only four summaries were complete. The remainder lacked at least one of the categories suggested, none of the paper discharge summaries included social status (98.3% of all discharge summaries omitted social history). Few of the paper discharge summaries included outstanding investigations where the GP needed to see and act on results ($\chi^2=4, \text{ d.f.} = 1, p=0.04$). A summary of the data is shown in Table 3.

There was not a single incidence of a complete thread of communication between the GP to the hospital and back again. (The letter being complete on referral and the discharge letter being complete on discharge as defined by the recommendations of the RCP and SIGN.)

d. **GP priorities for discharge summaries**

GPs ranked changes to medicines, reasons for medicine change and procedures and investigations as their top three requirements from discharge summaries (Table 4). GPs made comment that it was important to have the reason for changes to medication and this was therefore recorded as a separate data point. Similarly, comment was made that review of case, current diagnoses, and problem list represented the same data set and so were counted together.

<table>
<thead>
<tr>
<th>Item in rank order</th>
<th>Items omitted N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes to current medicines</td>
<td>36 (5%)</td>
</tr>
<tr>
<td>Reasons for changes or stopped/new medicines</td>
<td>150 (20%)</td>
</tr>
<tr>
<td>Procedures and investigations (GP needs to see results and action)</td>
<td>246 (32%)</td>
</tr>
<tr>
<td>Management plan (Other GP actions required) and intended outcomes</td>
<td>42 (5%)</td>
</tr>
<tr>
<td>Review of case, current diagnoses/problem list</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Answers to specific questions</td>
<td>66 (9%)</td>
</tr>
<tr>
<td>Functional state (intermediate or permanent change of housing)</td>
<td>751 (98%)</td>
</tr>
</tbody>
</table>
Medicines’ information was highlighted as being the most important information for GPs on a discharge summary. Comparing paper to electronic discharges the reasons for changing medication narrowly missed significance ($X^2 = 3$, d.f. = 1, p=0.08).

**DISCUSSION**

To the best of our knowledge this is the only study to examine communication from GP to hospital care in acute admissions and the reciprocal communication from hospital to GP on discharge. Our findings suggest that communication across the divide of General Practice and hospital medicine is still in a poor state here and does not currently meet the needs of “Good Medical Practice”. The information needs of hospital doctors differs from those of GPs and this must be addressed if a unified system is to be instigated to improve communication between primary and secondary care.

It has been suggested that an electronic transfer of information such as the new NHS-wide software introduction scheduled for August 2008 will solve some of these issues. This study highlights the benefits of using an electronic template in terms of legibility of information compared to handwritten letters. Typed GP referral letters tend to contain past medical history, medicines, allergies, investigation and examination findings compared to handwritten letters. Electronic discharge summaries were more likely to include reasons for changes to medicines and outstanding investigations that the GP needed to chase up, view and act on. Generally, handwritten discharge summaries contained less information pertinent to the patients’ GP than the electronic summary. Overall, handwritten letters run the risk of being illegible and so of no help to the communications process.

However, the current computerised templates do not fulfil the needs of either the GP or the hospital doctor, to continue patient care. Our findings indicate that computerised templates only seem to marginally improve the information enclosed. Most letters were still incomplete, especially where medicines information, procedures and investigations were concerned.

Some of the items specified by the RCP and by SIGN seem to be more important than others. Good communication may be possible in an individual case if some less relevant items are omitted.

This study was confined to a single site, which means that it is difficult to conclude if our results are a local one or whether the data can be extrapolated nationally. A lack of time and resources limited the amount of information we could collect for this study and so the study is confined to the busy winter period and it is therefore not possible to state if the results are due to time pressures or reflect the normal working of the area. We have attempted to minimise this by extending the timeframe to April to incorporate the less busy
periods for the A&E department. We have also been unable to contact more
than a few of the GPs in this study to see if the ranking of information is
representative across the area but hope that the selection of practices of
different sizes will reflect this.

In order to achieve a better level of communication between GP and
hospital, it is important that referral letters include information such as past
medical history, medicines and allergies to help with the admissions process
and to aid continuity of information. At the same time, in order to continue the
best care for the patient it is important that discharge summaries include
information about changes made to medicines; the rationale for the changes;
any important investigation findings or outstanding investigations that will
require GPs to look at and action results. It is vital that the doctors involved be
consulted during the development of new standardised electronic forms to
ensure that they contain the information needed to improve good medical
practice and so the quality of on-going patient care in the years to come.

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