Survey of infection in patients receiving antibody replacement treatment for immune deficiency

S J Pettit, H Bourne, G P Spickett

Background: Primary antibody deficiency disorders are a heterogeneous group of disorders, which are treated by regular infusions of immunoglobulin. Despite replacement treatment, patients remain susceptible to infection. Effective management of infections is necessary to prevent the complications of chronic infection.

Aims: This retrospective survey of clinical practice examined the management of infections in patients who receive immunoglobulin replacement for immune deficiency.

Methods: Patients who received immunoglobulin replacement treatment in Newcastle during the year 2000 were identified. Medical records were reviewed. Basic clinical information and details of immunoglobulin replacement treatment were recorded. Episodes of infection were defined by documented symptoms, signs, or investigation results, and by the prescription of an antibiotic course. Details of episodes of infection and antimicrobial treatment were recorded.

Results: Thirty seven patients received immunoglobulin replacement during 2000. There were 101 episodes of infection. There was no correlation between the frequency of infection and the IgG trough value. Respiratory tract infections were most common (71 of 101). Where documented, 80% of infections were associated with clinical signs, 21% with pyrexia, and 64% with a raised C reactive protein value. Microbiological culture was performed in 30% of infections. Antimicrobial treatment was instituted along “best guess” lines in 99 of 101 episodes of infection.

Conclusions: Management of respiratory tract infections represents the largest problem in antibody deficient patients. Greater use of microbiological culture might allow more effective prescription of antimicrobial treatment. The generation of treatment guidelines and improved communication with general practitioners could improve the management of all episodes of infection.
male patients. Diagnoses were common variable immune deficiency (CVID; 27), X-linked agammaglobulinaemia (XLA; four), IgA deficiency (one), specific antibody deficiency (one), hyper-IgM syndrome (one), hyper-IgE syndrome (one), chronic lymphocytic leukaemia (one), and antiphospholipid syndrome with specific antibody deficiency (one).

### Immunoglobulin replacement treatment
Preparations used for immunoglobulin replacement treatment include Sandoglobulin, Octagam, Vigam Liquid, Alphaglobin, Flebogamma, Scottish National Blood Transfusion Service immunoglobulin, and Gammabulin. Immunoglobulin treatment was administered by the intravenous route in 36 of 37 patients and the subcutaneous route in one of 36 patients. Infusions of immunoglobulin took place in the hospital outpatient department in 16 of 37 patients and at home in 21 of 37 patients.

The mean trough IgG value for all patients was 9.15 g/litre (range, 5.67–12.5). Infusions were missed by three of 16 patients who attend the hospital outpatient department. One patient missed a single infusion. One patient missed nine successive infusions; no IgG trough values are available for this period. One patient attended intermittently and missed seven infusions; this was the single patient with IgG trough values below 6 g/litre.

### Episodes of infection
In the year 2000, 101 episodes of infection were recorded among the 37 patients receiving immunoglobulin replacement treatment. Seven patients remained free of infection throughout the year. Linear regression analysis was performed to assess the relation between trough IgG values and the number of infections, and fig 1 shows the results. The correlation between trough IgG values and the frequency of infection was not significantly different from zero ($r^2 = 0.027, p = 0.35$). Infection was documented and managed by the general practitioner in 36 of the 101 episodes and by hospital medical staff in 60 of the 101 episodes. In five of the 101 episodes of infection, the patient initiated antimicrobial treatment and subsequently informed medical staff.

Figure 2 summarises the total numbers of each type of infection. The most common site of infection was the respiratory tract, accounting for 70% of all infections. Examination findings were documented in 51 of the 101 episodes of infection, and were positive in 80% of these cases. In contrast, temperature was documented in only 14 of the 101 episodes of infection. When temperature was documented, only 21% episodes of infection were associated with a temperature > 38°C. Interestingly, all patients with fever were admitted to hospital for treatment of their infection.

The CRP value was measured and documented in 39 of the 101 episodes of infection. When CRP was documented, 25 episodes of infection were associated with a raised CRP concentration. The reference range for CRP in our laboratory is 0–5 mg/litre. The mean CRP value seen in episodes of infection was 37.9 mg/litre (range, 6–194). Outside defined episodes of infection, the mean CRP value was 6.85 mg/litre (range, 0–76). Ten patients had a mean CRP value of > 10 mg/litre. In four of the 10 patients, this mean CRP was skewed by a single high measurement. In six of the 10 patients, this mean CRP value represented consistently raised CRP concentrations. Linear regression analysis was performed to assess the relation between trough IgG values and the number of infections, and fig 1 shows the results. The correlation between trough IgG values and the frequency of infection was not significantly different from zero ($r^2 = 0.027, p = 0.35$).

### Table 1: Range of clinical samples sent for microbiological culture and range of pathogens cultured from each type of sample

<table>
<thead>
<tr>
<th>Sample</th>
<th>Organism</th>
<th>Range of clinical samples sent for culture</th>
<th>Numbers in parentheses refer to either the number of samples sent or the number of occasions on which a given organism was cultured.</th>
<th>Mixed growth of organisms was observed in one sputum sample and two skin swabs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum (23)</td>
<td>Haemophilus influenzae (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midstream urine (3)</td>
<td>Escherichia coli (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin swab (2)</td>
<td>Staphylococcus aureus (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool (1)</td>
<td>Nil (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal swab (1)</td>
<td>Haemophilus influenzae (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood (1)</td>
<td>Nil (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses refer to either the number of samples sent or the number of occasions on which a given organism was cultured. Mixed growth of organisms was observed in one sputum sample and two skin swabs.
to the antibiotic being used and best guess treatment did not need to be altered.

In total, 111 courses of antimicrobial drugs were prescribed during the survey period. Twenty three different antimicrobial drugs were prescribed. Intravenous antibiotics were required in only two of the 101 episodes of infection. The duration of antibiotic treatment was documented in 56 of 111 courses. The mean duration of antibiotic treatment was 12 days (range, 3–28). Antimicrobial treatment was started without performing microbiological culture or before culture results were available in 99 of 101 episodes of infection. Where details of antibiotics were recorded, best guess treatment was generally appropriate to clinical findings in 98 of 99 of these episodes of infection. The most variable best guess treatment was for respiratory tract infections, for which azithromycin (19 courses), co-amoxiclav (16 courses), amoxicillin (12 courses), and ciprofloxacin (eight courses) were the most commonly used antibiotics.

DISCUSSION

The most common diagnosis was CVID, accounting for almost three quarters of all patients. The adequacy of immunoglobulin replacement treatment was assessed by serial measurement of IgG trough values. In our survey, all compliant patients receiving immunoglobulin replacement treatment had a preinfusion IgG > 6 g/litre.

There were 101 infective episodes. The distribution was skewed—two individuals had more than seven episodes of infection in 2000. Analysis by simple linear regression showed no correlation between the number of infective episodes and IgG trough values. The two patients with IgA deficiency and selective antibody deficiency were excluded from this analysis because they had normal IgG values before immunoglobulin replacement treatment. Most clinical immunologists aim to achieve IgG trough values within the normal range. There is evidence that a higher trough value (> 8 g/litre) results in a lower infection rate in patients with XLA. No equivalent data exist for patients with CVID. Data from this limited cohort do not suggest that IgG trough values above 6 g/litre offer additional protection from infection. However, patients who have previously suffered more infections may receive larger doses of immunoglobulin replacement treatment.

Respiratory tract infections, including sinusitis, bronchitis, and pneumonia, were the most common type of infection. These constituted 78% of all episodes of infection identified during our study. Previous studies have shown that the respiratory tract is the most common site of infection in CVID, XLA, and chronic lymphocytic leukaemia. Respiratory tract infections in antibody deficient patients are commonly caused by encapsulated bacteria such as Streptococcus pneumoniae and Haemophilus influenzae, and less commonly caused by staphylococci and Pseudomonas aeruginosa. Sputum culture during the period of study yielded a similar range of organisms from 17 of 23 samples; these included H influenzae, S pneumoniae, and P aeruginosa.

The associated features of the infections were documented to a variable extent. This largely represented a lack of communication between general practitioners and hospital clinicians when episodes of infection were managed in the community. Temperature was measured and documented in only 14% of episodes of infection. However, the two patients with a temperature > 38°C required hospital admission for intravenous antibiotic treatment. CRP concentrations were measured in 39% of episodes of infection. The mean CRP value was 37.9 mg/litre during episodes of infection, compared with 6.85 mg/litre outside episodes of infection. However, there was considerable overlap in the range of CRP concentrations that were observed in the presence or absence of infection. This overlap has important implications for the use of regular CRP values to assess chronic or recurrent infection.

There is considerable concern about chronic/recurrent respiratory tract infections and the development of bronchiectasis. A national audit, performed between 1993 and 1996, identified bronchiectasis in 20% of patients with CVID and 12% of patients with XLA. The routine use of adequate immunoglobulin replacement after diagnosis has reduced the subsequent development of bronchiectasis from 77% of patients to 42% of patients. However, bronchiectasis may progress despite adequate immunoglobulin replacement. A prospective three year study using high resolution computed tomography demonstrated silent progression of bronchiectasis in five of the 14 patients, all of whom were receiving intravenous immunoglobulin replacement treatment and had trough serum IgG concentrations of > 5 g/litre.

Chronic or recurrent infections may be monitored by means of symptom diaries and by the regular measurement of CRP concentrations. No formal symptom diaries were submitted for the period of survey. However, all patients had CRP values measured regularly. Raised CRP concentrations were seen in 10 patients outside episodes of infection. This was suggestive of unnoticed acute infection in four patients (an isolated raised CRP value on a background of normal CRP concentration), and chronic infection in six patients (continuously raised CRP values). Patients with unnoticed acute infection should be promptly assessed and antibiotic treatment instituted if required. Indicators of chronic infection allow changes to basic management, including physiotherapy, regular antibiotics, and the possibility of surgical resection of badly affected areas of the bronchial tree.

Only five courses of antibiotic treatment were initiated by patients themselves. Little information is available about these episodes of infection. Because our survey depends on clinical records, it probably underestimated the number of patient managed episodes of infection. General practitioners and hospital clinicians differed in their management of infections. Lack of documented examination findings, temperature measurements, CRP values, and culture results may result largely from poor communication between these two groups. The consensus document suggested that patient held records would aid this communication. No such patient held records were available from the period of survey. Syndromes of antibody deficiency are very rare and unlikely to be encountered by most general practitioners. Protocols for the management of common infections might be helpful for these general practitioners.

This survey of clinical practice allows local targets to be set for management of episodes of infection in antibody deficiency.

Take home messages

- Respiratory tract infections are the largest problem in antibody deficient patients
- There was no correlation between the frequency of infection and the IgG trough value
- Greater use of microbiological culture might allow more effective prescription of antimicrobial treatment
- The generation of treatment guidelines and improved communication with general practitioners might improve the management of all episodes of infection

“... This survey of clinical practice allows local targets to be set for management of episodes of infection in antibody deficiency.”
guidelines for the treatment of common infections should be agreed and circulated to general practitioners. Patients should be encouraged to record details of prescriptions from general practitioners. Additional therapeutic interventions should be sought in patients who suffered chronic/recurrent infections in 2000. The final target should be to reduce the number of infections for each patient in subsequent years.

Authors’ affiliations
S J Pettit, H Bourne, G P Spickett, Department of Immunology, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne NE1 4LP, UK

REFERENCES

New JCP online submission and review system

We are pleased to inform authors and reviewers of the new online submission and review system at JCP. Developed by High-Wire Press (CA, USA), Bench Press is a fully integrated electronic system that utilises the web to allow rapid and efficient submission of manuscripts. It also allows the peer review process to be conducted entirely online. We are one of the first journals in the BMJ Special Journals group to go online in this way. The aim, apart from saving trees, is to speed up the often frustratingly slow process (for both authors and editors) from submission to publication. Many reviewers might appreciate this too. Authors may submit their manuscript in any standard word processing software. Acceptable standard graphic formats include: jpeg, tiff, gif, and eps. The text and graphic files are automatically converted to PDF for ease of distribution and reviewing purposes. Authors are asked to approve their submission before it formally enters the reviewing process. On approval by the authors, the submission is passed to the editor and/or reviewers via the web. All transactions are secure.

To access the system click on “SUBMIT YOUR MANUSCRIPT HERE” on the JCP homepage: HYPERLINK http://www.jclinpath.com, or you can access Bench Press directly at HYPERLINK http://submit-jcp.bmjjournals.com. We are very excited with this new development and would encourage authors and reviewers to use the online system whenever possible. As editors, we will use it all the time, the up side being lack of need to travel to the editorial office to deal with papers, the down side being no more excuses to postpone decisions on papers because we are “at a meeting”!

The system is very easy to use and should be a big improvement on the current peer review process. Full instructions can be found on Bench Press http://submit-jcp.bmjjournals.com and JCP online at http://www.jclinpath.com. Please contact Natalie Davies, Project Manager, HYPERLINK mailto:ndavies@bmjgroup.com for any further information.

H Holzel, P van Diest
Survey of infection in patients receiving antibody replacement treatment for immune deficiency
S J Pettit, H Bourne and G P Spickett

doi: 10.1136/jcp.55.8.577

Updated information and services can be found at:
http://jcp.bmj.com/content/55/8/577

These include:

**References**
This article cites 9 articles, 2 of which you can access for free at:
http://jcp.bmj.com/content/55/8/577#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**
Articles on similar topics can be found in the following collections

- Immunology (including allergy) (1664)
- TB and other respiratory infections (74)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/