Adequate adherence to benzathine penicillin secondary prophylaxis following the diagnosis of rheumatic heart disease by echocardiographic screening


ABSTRACT

AIMS: The primary aim of this study was to determine adherence to benzathine penicillin (BPG) for individuals diagnosed with rheumatic heart disease (RHD) by echocardiographic screening between 2007–2012.

METHODS: BPG records were obtained for 57 patients, median age 12 at time of diagnosis. A ‘days at risk’ analysis was undertaken. Annual adherence was calculated for each individual. A comparison with the Wellington region’s Rheumatic Fever 2013 adherence data was undertaken.

RESULTS: Adherence to BPG was good with a median follow-up time of 5.8 years. Days at risk analysis: median 0% at year one and 2.7% at year five. The median adherence for the entire cohort over the entire follow-up period was 92%, range 0–100%. There was no difference of proportions of late doses compared to the Wellington region. Median adherence was higher for register based (94%, n=48) compared to primary health care penicillin delivery (37%, n=7), p<0.005. During follow-up, 30% of the cohort moved between regions or overseas.

CONCLUSIONS: Good adherence rates are achievable for secondary prophylaxis when RHD is diagnosed by echocardiographic screening. This likely reflects the benefit of rheumatic fever registers and community nursing services rather than the pathway of the diagnosis for RHD.

Secondary prevention with intramuscular benzathine penicillin (BPG) has been known for many years to be effective to prevent recurrences of acute rheumatic fever (ARF) and prevent progression of chronic rheumatic heart disease (RHD). Regular BPG is evidence-based treatment, reducing the risk of recurrent ARF by 87–96%. Prophylaxis has usually been instigated after an acute episode of ARF, and in the New Zealand setting this has been very successful in reducing ARF recurrences in recent decades. In the past decade a growing number of studies have utilised echocardiography to detect latent or subclinical RHD, both internationally and in New Zealand. Health system capacity to deliver effective treatment is a core requirement for population health screening programmes. In the RHD context, initiation of BPG and long-term adherence are key measures.

School-based echocardiographic screening for RHD was performed in five known high prevalence ARF regions of New Zealand between 2007 and 2012, specifically South Auckland, Gisborne and Ruatoria, Kaitaia,
Bay of Plenty and Porirua, predominantly in 10–13 year-old children. Across these regions, 3,600 students were screened and 150 had abnormal cardiac findings. Secondary prophylaxis with BPG every 28 days was recommended empirically for individuals diagnosed with probable or definite RHD,6–8 and for some with borderline or possible RHD who, after consultation with a paediatrician, had a previous history suggestive of an ARF episode or a strong family history of ARF/RHD. Individuals were also commenced on BPG if they were found on follow up to have progressive disease.

Following episodes of ARF, high secondary prevention adherence rates were reported in patients receiving BPG through the Auckland Regional Rheumatic Fever Register in the 1990s.4

The primary aim of this study was to determine adherence to BPG secondary prophylaxis for patients diagnosed with RHD by echocardiographic screening. We hypothesised that adherence after echocardiographic case detection may not be as good as that following an episode of symptomatic ARF,9 as the latter involves hospitalisation and intensive family education.1

**Methods**

BPG administration records were sought and obtained from local providers in Counties Manukau, Tairawhiti, Bay of Plenty, Northland and Capital Coast District Health Boards. In New Zealand, BPG delivery is provided by a variety of community nursing providers according to region (district nurses, paediatric community outreach nurses and primary health care nurses) facilitated by regional RF registers10 as per the New Zealand Heart Foundation guidelines.1 The start date of penicillin injections was determined from the records of the initial clinical assessment and first injection. If patients moved between regions, injection dates were sought from the new provider in that region. Similarly, data was sought from other regions if patients were temporarily out of town on the due date of an injection.

**Adherence definitions**

The recommended RF/RHD secondary prophylaxis regimen in New Zealand is 28 days IM BPG.1,2 An injection was defined as given on time, if given less than or equal to five days after the due date of injection.3 An injection was defined as late if the injection was given greater than five but less than 28 days after the due date, and defined as missed if late by greater than or equal to 28 days.1,4

Annual adherence was calculated for each patient, based on the number of injections given on time compared to the number of injections due for the year, taking account of whether the patient should have received 12 or 13 injections in a year.4 Adherence for the entire cohort was calculated for each year since commencement of BPG on an intention to treat basis, ie, patients who became non-adherent were included in this analysis. Overall adequate adherence was defined for each patient as receiving >80% of injections on time per year.1,11

In addition, as the percentage of injections given on time may not best reflect the time a patient is at risk of a potential ARF recurrence, an additional ‘days at risk’ analysis was performed for each year per patient.12 Days at risk was defined as the number of late (>5) days plus missed days (>28 days) expressed as a percentage of days per year. Note that those patients who had discontinued adherence were also included as missed days for the year in this analysis, as they clearly remain at risk of ARF recurrence and RHD progression.

A comparison with the Wellington region (Capital Coast, Hutt Valley and Wairarapa DHBs) adherence data for patients following episodes of RF for the year 2013 was undertaken.13

**Statistics**

The annual adherence and days at risk analysis was expressed as mean and median. Group data was compared with a two sample Z-test or Wilcoxon Rank-Sum test.

**Ethics**

Ethics approval was obtained HDEC NTY/06/12/139/AM06 as an extension of “A prospective school-based study of the prevalence of rheumatic heart disease in children from a high-risk New Zealand population”.

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**ARTICLE**

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Results

Secondary antibiotic prophylaxis was recommended for 62 individuals. Two individuals were commenced on oral prophylaxis and were excluded from further analysis; one refused IM injections and one started on erythromycin for penicillin allergy. Two cases moved overseas shortly after diagnosis and one individual’s records were not available. The remaining 57 cases formed the cohort for analysis of BPG adherence.

Forty-six of the 57 individuals commenced BPG after their initial echocardiogram and consultation, and 11 commenced prophylaxis after RHD disease progression at follow-up. Due to the staggered echocardiographic screening in the different regions over time, the maximum duration of follow-up for each region varied: South Auckland (maximum eight years), Tairawhiti (seven years), Bay of Plenty and Kaitaia (six years) and Porirua (three years). The median follow-up period was 5.8 years (range 16–95 months, interquartile range (IQR) 57–81 months).

The median age range of the cohort at commencement of BPG was 12 years, range 10–17 years. Twenty-seven of 57 (47%) were female. 39% of the cohort were Māori, 59% Pacific.

Seventeen of 57 individuals, ie, 30% of the cohort moved to another region in New Zealand (n=11) or overseas (n=6) during the follow-up period. Adherence data was not obtained for the time-period any individuals were overseas. Six individuals (11% of the cohort) became non-adherent during follow-up. Of these six, one had an episode of ARF 11 months after discontinuing BPG. Eleven patients were medically discharged from BPG after median duration 5.7 years (range 23–85 months, IQR 61.5–76 months). Nine of these were discharged because they had reached 18 years of age and completed over five years of BPG and had no progression of RHD on follow-up echocardiography. One patient was discharged after

Figure 1: Mean and median days at risk of a recurrence of ARF expressed as a percentage of days in the year.

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>57</td>
<td>6.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Year 2</td>
<td>57</td>
<td>8.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Year 3</td>
<td>53</td>
<td>11.1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Year 4</td>
<td>46</td>
<td>12.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Year 5</td>
<td>45</td>
<td>17.9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Year 6</td>
<td>38</td>
<td>25.9%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Year 7</td>
<td>23</td>
<td>15.9%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Year 8</td>
<td>12</td>
<td>20.7%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>
five years as follow-up echocardiography suggested a congenital rather than rheumatic mitral valve lesion and one individual with borderline RHD was treated for two years only, after a suggestive history of ARF, which was later refuted.

Days at risk analysis (risk of recurrence of ARF or RHD progression)

Figure 1 shows a low percentage time at risk for the cohort, rising slowly over time. The median days at risk was 0% at year one (n=57), 1.5% by year four (n=46) and 2.7% in year eight (n=12). Note that this median analysis of 0–2.7% days at risk is equivalent to 0–10 days at risk per year only, representing a very low proportion of time without penicillin cover. The mean days at risk (Figure 1) rises largely due to the non-adherent patients.

Adherence rates

The mean adherence for the entire cohort over the entire follow-up period was 81%, median 92%, range 0–100%. By individual years, the mean and median adherence rate were 90% and 100% at year one (n=57), falling to 78% and 85% by year four (n=46) and 66% and 88% in year eight (n=12) (Figure 2).

The decline in adherence over time was largely due to six patients (11% of the cohort) who became non-adherent at 0, 0.3, 0.6, 2.7, 4.6 and 5.5 years. The reasons for non-adherence were not consistently identifiable. One of these six patients had an episode of ARF 11 months after discontinuing BPG.

Table 1 shows the distribution of overall adherence during the study period for the whole cohort. Sixty-eight percent of the cohort received adequate adherence (greater than 80% of injections on time) over the follow-up period to a maximum of eight years. Note that this analysis includes those that became fully non-adherent (n=6).

Table 2 shows the results of the 2013 Wellington region (Capital Coast, Hutt Valley and Wairarapa DHBs) data compared to the current study 2013 data. There is no significant difference between the proportions of late doses for the two age brackets.

Figure 2: Adherence to BPG by year since commencement.

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
<th>Year 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>57</td>
<td>57</td>
<td>53</td>
<td>46</td>
<td>45</td>
<td>38</td>
<td>23</td>
</tr>
<tr>
<td>Mean</td>
<td>90.4%</td>
<td>85.5%</td>
<td>82.6%</td>
<td>77.6%</td>
<td>75.7%</td>
<td>66.6%</td>
<td>74.7%</td>
</tr>
<tr>
<td>Median</td>
<td>100.0%</td>
<td>100.0%</td>
<td>92.3%</td>
<td>84.6%</td>
<td>91.7%</td>
<td>84.0%</td>
<td>87.5%</td>
</tr>
</tbody>
</table>
There was a higher percentage of missed doses in the echocardiographic detected cohort.

Adherence for those receiving register compared to primary health care-based secondary prophylaxis is shown in Table 3. Forty-eight of 57 patients had ‘register-based’ penicillin delivery by community nursing services, and seven received BPG injections at their primary health care clinic. Two cases who had part register-based and part primary health BPG delivery were excluded from this analysis. Adherence was higher for register-based penicillin delivery compared to primary health care penicillin delivery despite the numbers of patients in the primary health care group being fewer. This likely reflects that there are fewer patients being managed in the primary care setting, and systems for recall are less well-developed.

Discussion

This study provides important contemporary data concerning adherence to secondary prevention for individuals with echocardiographically detected RHD in New Zealand. Although the cohort is relatively small, this has allowed a detailed analysis of every intended injection of penicillin in the follow-up period, due to the high-quality records kept by nursing staff responsible for the penicillin delivery. Thirty percent of the cohort moved region within New Zealand or overseas during the eight years of follow-up, which has important implications for organisation of secondary prevention services, including support for a national register.

The study shows that BPG adherence can be adequate for disease control following a diagnosis of RHD detected by echocardiography, especially over the first five years.

Table 1: Distribution of adherence for the cohort over entire follow-up period.

<table>
<thead>
<tr>
<th>Overall adherence (% of injections on time)</th>
<th>Percentage of cohort (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80%</td>
<td>68.4% (n=39)</td>
</tr>
<tr>
<td>70–79%</td>
<td>12.3% (n=7)</td>
</tr>
<tr>
<td>60–69%</td>
<td>3.5% (n=2)</td>
</tr>
<tr>
<td>50–59%</td>
<td>5.3% (n=3)</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>10.5% (n=6)</td>
</tr>
</tbody>
</table>

Table 2: Comparison of 2013 percentage of late or missed doses.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Percentages of doses late</th>
<th>Wellington</th>
<th>Echo detected RHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td></td>
<td>3.6% (n=58)</td>
<td>4.8% (n=13)</td>
<td>0.4692</td>
</tr>
<tr>
<td>16–21</td>
<td></td>
<td>11.4% (n=58)</td>
<td>8.4% (n=39)</td>
<td>0.1051</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group</th>
<th>Percentages of doses missed</th>
<th>Wellington</th>
<th>Echo detected RHD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16</td>
<td>0.5%</td>
<td>9.6%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>16–21</td>
<td>14.4%</td>
<td>21.7%</td>
<td>0.0017</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Register versus non-register BPG adherence comparison.

<table>
<thead>
<tr>
<th></th>
<th>Overall median adherence</th>
<th>IQR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Register (n=48)</td>
<td>93.8%</td>
<td>82.2–97.6%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Non-register (n=7)</td>
<td>37.2%</td>
<td>4.3%–61.3%</td>
<td></td>
</tr>
</tbody>
</table>
years when patients with RHD are most at risk of a recurrence of ARF or progression of RHD. This is of significance for RHD screening programmes internationally. The data suggests that the infrastructure for BPG delivery is more important than whether individuals were started on penicillin following an episode of ARF or following case detection of RHD by echocardiography. Qualitative research methodology could better elucidate this question.

Engelmann et al 2016, recently reported the first international analysis of secondary prophylaxis following echocardiographic screening in Fiji. Only 6% of individuals received adequate adherence with median follow-up of three years. Without a comparison group from that country it was not possible to determine whether it was the infrastructure for secondary prophylaxis or the pathway of diagnosis that was the dominant reason for the low adherence. An extensive programme is currently being undertaken to strengthen the infrastructure for secondary prevention by the Fiji RHD control programme.

Following an episode of ARF, it is well established that there is a high recurrence rate of ARF and often progression of RHD and thus secondary prophylaxis is strongly recommended. However, rates of progression of RHD and risk of ARF following echocardiographic detection are less certain and are still being studied internationally. It is also not known whether the duration of prophylaxis should be as long as that recommended following an episode of ARF. Over the study period, the New Zealand community paediatricians in conjunction with cardiology advice have empirically recommended a minimum duration of BPG of at least five years or to age 18. This is a shorter period than that following ARF in the New Zealand setting.

Part of the rationale is that the onset of the previous ARF episode may have been some years earlier in those with RHD detected by echocardiography. The analysis of days at risk provides a more detailed assessment of adherence than the 80% threshold, for which there is no biological basis, but enables comparison with previous New Zealand and international data. Like Edwards, we believe days at risk is more valid biologically. For example, a patient who has three injections late in a year would be classified as 75% adherence for the year, but if the three late injections were each given seven days late, that patient would only have six days at risk (2% of the year). The five days grace post-28 day regimen is justified by previous New Zealand data: a 28 day BPG regimen resulted in a very low ARF recurrence rate of 0.07 per 100 patient years. The median days at risk (Figure 1) reveal that BPG adherence was very good. The WHF and RhEACH handbook recommend that adherence be expressed as median percentage of doses delivered rather than the mean percentage.

It is pertinent that 11% of the cohort became non-adherent, and this group influenced the overall adherence rates. The results of the current study suggest that adherence is lower than 1–2 decades ago in the Auckland region where very high rates of adherence (mostly over 90%) were reported following clinically diagnosed ARF. However, direct comparison with that data is not valid, as patients who had opted out of secondary prevention or moved region were not included, and a number of patients with ‘poor or incomplete’ nursing office forms were not included.

It is important that analysis of adherence includes these patients who no longer engage health services as Engelman and colleagues have done, otherwise a falsely high adherence rate can be reported.

The only New Zealand contemporary published data of adherence following clinical diagnosis of ARF/RHD is from the Wellington region for 2013. Their data showed decreasing compliance with increasing age and time from commencement of BPG. This Wellington cohort showed a similar proportion of late doses compared to the current study. The higher proportion of missed injections in the current study likely reflects the intention to treat analysis, but it is possible that some patients opted out as they did not accept the need for secondary prophylaxis following echocardiographic detection of RHD.

Unpublished contemporary New Zealand adherence data collected by the Ministry of Health as part of the Primary Prevention Programme, indicated the proportion of late doses in one Auckland DHB over a three-month period in 2016 were 5–7% (Ministry of Health personal communication 2016). Complete data sets were available for 91–92% of the patients in that DHB, suggesting that some patients had moved region or have opted out of care. Another Auckland DHB recorded 1% late injections in the under-15 year age group rising to 13% for those greater than 15 years for two months in 2016 (Dr Tim Jelleyman, personal communication, 2016). Again, that DHB does
not collect data for secondary prevention undertaken by primary care.

Taken together, it can be concluded that in New Zealand overall there are very high rates of BPD adherence, particularly for those receiving BPD via a register and for those attending school. Adherence levels fall for those over 15 years of age, but it is well established that the risk of recurrence diminishes with age. 

Little is known about adherence for those receiving BPG through primary health clinics in New Zealand. Our data showing low adherence, albeit for a small number of patients, supports that best practise for secondary prevention of ARF/RHD is referral to a register. The findings of low adherence for primary health care delivery of secondary prevention and the high mobility of RHD patients in New Zealand found in our study both give support for the establishment of a national rheumatic fever register in New Zealand.

Conclusions

We conclude that adherence rates for echocardiographically detected RHD are similar to adherence rates following ARF or clinically detected RHD for at least the first five years after diagnosis. Enrolment in a rheumatic fever register is likely to have greater influence on penicillin adherence than the pathway to the diagnosis of RHD. The study results give support to the formation of a national rheumatic fever register in New Zealand.

Limitations

The overall cohort is small, but this is offset by the meticulous record keeping by nursing staff. The comparison with the Wellington regional data are not strictly comparable as the time on prophylaxis was not stated in the Wellington analysis nor was it stated that non-compliant patients were included in their analysis.

Competing interests:
Nil.

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