LONG-TERM SUPPRESSION OF ADULT BLADDER MORBIDITY AND SEvere HYDRONEPHROSIS FOLLOWING SELECTIVE POPULATION CHEMOTHERAPY FOR SCHISTOSOMA HAEMATOBIUM

ARUNA K. SUBRAMANIAN, PETER MUNGAI, JOHN H. OUMA, PHILLIP MAGAK, CHARLES H. KING, ADEL A. F. MAHMOUD, AND CHRISTOPHER L. KING

Division of Geographic Medicine, Department of Medicine, University Hospitals of Cleveland and Case Western Reserve University, Cleveland, Ohio; Division of Vector Borne Diseases and Radiological Services, Ministry of Health, Nairobi, Kenya

Abstract. Repeated selective population chemotherapy of school age children reduces infection and morbidity associated with Schistosoma haematobium infection. To examine the long-term effect of this treatment on susceptibility to re-infection and late disease, a cohort of Kenyans (n = 194) were re-examined for infection and urinary tract morbidity 7–13 years after they underwent annual ultrasonography and treatment for an average of 5 years beginning in 1984 as children. Controls were previously untreated age-matched individuals residing in the same or adjacent villages. The overall prevalence and intensity of infection were equivalent between the 2 groups. In contrast, the prevalence of bladder wall pathology was 11-fold lower in previously treated (1.5%) versus untreated subjects (17%). Severe hydronephrosis was completely reversed. These data demonstrate that treatment significantly reduced urinary tract morbidity despite re-infection, and suggest that the important risk factors for urinary tract morbidity in adulthood are cumulative intensity and duration of infection during early adolescence.

Schistosoma haematobium infection affects more than 90 million people worldwide, representing a major health problem in central and southern Africa and the eastern Mediterranean. In urinary schistosomiasis, adult female worms deposit their eggs into the lower urinary tract from the pelvic venous plexus and mesenteric veins. The pathology of urinary schistosomiasis results from host granulomatous inflammatory response to eggs trapped in the bladder, ureters, and other pelvic structures. Consequent urinary tract injury manifests as hematuria, proteinuria, bladder wall thickening, and bladder irregularities (e.g., polyps, calcifications), and a predisposition to squamous cells carcinoma of the bladder. A concern regarding this strategy has been that repeated therapy might alter acquired down-modulation of the granulomatous inflammation and thereby enhance an individual’s risk for morbidity upon re-infection. Studies of treatment of S. japonicum infection have demonstrated significantly worsened hepatic pathology with re-infection after repeated therapy. The short-term impact of re-infection with S. haematobium on urinary tract morbidity treatment has recently been reported. Levels of infection and urinary tract morbidity were re-established within 2 years after a single treatment, but overall, treatment did not appear to worsen subsequent urinary tract disease. The impact of repeated treatment on subsequent infection and disease has not been previously studied.

To investigate the long-term morbidity associated with re-infection after repeated therapy, the present study performed a 13-year follow-up of a cohort of school children from Msambweni, Coast Province, Kenya. From 1984 to 1989, more than 7,000 school children (5–21 years old) participated in a population-based targeted chemotherapy program using either praziquantel or metrifonate for suppression of S. haematobium infection-related morbidity. As part of this study in 1984, a stratified random sample of 517 individuals was selected to undergo annual ultrasound examinations to follow urinary tract morbidity. Repeated selective population chemotherapy reduced the overall prevalence, intensity of infection, and severe bladder and kidney pathology. To assess the long-term consequences of this treatment strategy, the present study examined the frequency of re-infection and its impact on morbidity in the same cohort of children after a hiatus of 6–8 years without intervention.

METHODS

Study population. The original 1984 cohort of 517 individuals was from 9 neighborhood villages, collectively referred to as the Msambweni region, Kwale District, in Coast Province, Kenya. These individuals were traced 13 years later, in 1997, based on previously collected demographic information and current house-to-house surveys of the study area and nearby villages. Previously assigned household and project numbers were used for identification. Demographic follow-up revealed that 239 individuals of the original 517 subjects remained in the Msambweni study area. Another 200 had moved to other areas on the south coast of Kenya, and 8 had passed away from causes unrelated to schistosomiasis or its therapy. The remaining individuals had moved out of the south coast area altogether. Of the 239 individuals who remained in or near the study area, 194 (81%) participated in the follow-up study by submitting two urine specimens and undergoing ultrasound examination.

The 194 individuals studied were representative of the original cohort with respect age, sex distribution, initial prevalence and intensity of infection, and their pre-treatment prevalence of urinary tract morbidity (Table 1).

All study subjects (or their parents in the 1980s) gave verbal consent for the ultrasound and urinalysis. The risks
(negligible for pelvic ultrasound and urinalysis) and benefits were explained to village leaders and elders with the village present. The risks and benefits were re-explained to each study subject prior to the procedure in the local language. The study protocol was approved by the Kenyan Medical Research Institute and Case Western Reserve University Institutional Review Boards.

### Control populations

Two groups were selected that represented infection and morbidity control groups (Table 2). The historical infection control group comprised 250 adults from Bomani, one of the 9 villages in the Msambweni study area, who were examined in 1985 for the presence of schistosomiasis and associated morbidity (infection control group, Table 2). They had never been previously treated for schistosomiasis. The prevalence and intensity of infection in 1985 was similar to the current cohort (now adults of similar age residing in the same area) surveyed in 1997 ($n = 194$, Table 2). The only difference observed was that none of the current study cohort subjects had heavy infection ($> 400$ ova/10 ml of urine). The morbidity control group was composed of 77 adults from the area who received ultrasound examinations. Thirty-six individuals were randomly sampled from the 250 adults from Bomani (described above) in 1985. The remaining 41 individuals were age-matched adults from a nearby village (Mbuwani) adjacent to the original study villages that had not received prior selective population-based chemotherapy. Residents of Mbuwani, selected as controls, represented a stratified random sample of 209 adults (age range = 18–37 years) that fulfilled the criteria of having an ultrasound examination and who were long-term residents of village (> 10 years, or had attended Mbuwani primary school as children). Mbuwani village had similar level of endemicity (prevalence of 68% and a geometric mean egg count of 19 ova/10 ml of urine based on a survey performed on school age children 5–18 years of age, $n = 729$ in 1994) to that of the original study villages examined in 1984 prior to treatment (Table 1). As shown in Table 2, the morbidity control group had a similar age, sex, and prevalence and intensity of infection to the current study cohort.

### Parasitologic examination and treatment

All participants submitted two urine samples at least 24 hr apart, which were collected between 10:00 AM and 2:00 PM. The presence of *S. haematobium* eggs was measured by Nuclepore (Pleasanton, CA) (polycarbonate) filtration as previously described. The average egg count of the two specimens from each individual was recorded. Any participant with evidence of *S. haematobium* infection was offered therapy with praziquantel (40 mg/kg as a single dose). Pregnant subjects were excluded from the treatment phase of the study.

### Urinary tract imaging

To assess structural urinary tract abnormalities associated with *S. haematobium* infection, a portable ultrasound examination was performed on all participants. Images were recorded on a thermal printer and scored for renal size, hydronephrosis, hydroureter, bladder thickening, and bladder irregularities. Severity of bladder pathology was classified as previously described as either mild, which represented bladder wall thickening of 8–10 mm (normal $< 6$ mm) with one area of involvement; moderate, which represented 8–10 mm of thickening that involved multiple areas; or severe disease, which consisted of bladder wall thickness $> 10$ mm of thickening or 8–10 mm of thickening with the presence of polyps within the bladder lumen. Hydronephrosis was based upon the degree of dilation of the renal calyces as shown in Figure 1. Mild hydronephrosis was scored only if the dilation persisted after the subject emptied their bladder. Pregnant women with mild hydronephrosis were excluded due to potential nonspecific dilation of the renal calyces during pregnancy. Ultrasound readings were independently confirmed by another radiologist. Both readers were blinded to the participant’s current and previous infection status.

### Data analysis

The chi-square test (with Yates’ correction as appropriate) or Fisher’s exact test was used to assess differences between subgroups within the cohort and between the study group and controls; $P$ values are two-tailed.

### RESULTS

### Effect of repeated treatment on infection levels and morbidity

Prior to treatment in 1984, 71% of the current

### Table 1

Entry characteristics of 1997 follow-up group in comparison with the original cohort

<table>
<thead>
<tr>
<th></th>
<th>Original cohort</th>
<th>1994 follow-up group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>517</td>
<td>194</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>53%:47%</td>
<td>50%:50%</td>
</tr>
<tr>
<td>Median age in 1984</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Prevalence in 1984</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>% Hydronephrosis</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>% Bladder wall morbidity</td>
<td>42%</td>
<td>43%</td>
</tr>
</tbody>
</table>

### Table 2

Population characteristics of study cohort and controls

<table>
<thead>
<tr>
<th></th>
<th>1997 study cohort</th>
<th>Infection controls*</th>
<th>Morbidity controls†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>194</td>
<td>250</td>
<td>77</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>50%:50%</td>
<td>27%:73%</td>
<td>39%:61%</td>
</tr>
<tr>
<td>Age range</td>
<td>16–35</td>
<td>16–39</td>
<td>16–38</td>
</tr>
<tr>
<td>Median age</td>
<td>24</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Prevalence</td>
<td>40 (21%)</td>
<td>54 (22%)</td>
<td>19 (25%)</td>
</tr>
<tr>
<td>0–99 ova/10 ml</td>
<td>35 (18%)</td>
<td>44 (18%)</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>100–399 ova/10 ml</td>
<td>5 (3%)</td>
<td>3 (1%)</td>
<td>2 (2.6%)</td>
</tr>
<tr>
<td>&gt;400 ova/ml</td>
<td>0</td>
<td>7 (3%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Geometric mean egg count (range)</td>
<td>2 (0–323)</td>
<td>2 (0–1,000)</td>
<td>2 (0–550)</td>
</tr>
</tbody>
</table>

* These represent data collected in 1985 from previously untreated adults residing in one of the Msambweni area study villages, Bomani.† 36 adults from Bomani village and 41 age-matched adults from a nearby village (Mbuwani) that had not received prior chemotherapy (ultrasound examination performed in 1985 and 1994 by the same investigators).
LONG-TERM MORBIDITY IN TREATED URINARY SCHISTOSOMIASIS

Figure 1. Ultrasonographic views of the renal calyces associated with different grades of hydronephrosis in Kenyan patients with *Schistosoma haematobium* infection. The arrows indicate the renal calyces in each image. No area of decreased echogenicity is observed in normal kidneys (upper left panel). Mild (grade I) dilation referred to any detectable echogenicity in the renal calyx (upper right panel). Moderate (grade II) hydronephrosis shows a significant echogenicity within the calyx that is approximately ¼ to ⅓ in width relative to its length (lower left panel). Severe (grade III) hydronephrosis shows marked dilation of the calyx to form an almost circular pattern (lower right panel).

Study cohort (n = 194) were infected, with a geometric mean egg count of 25 per 10 ml of urine. Nine percent of the cohort had mild, moderate, or severe hydronephrosis and 43% had bladder lesions before treatment (Table 3). One year after therapy the overall prevalence of infection had decreased to 25% and the intensity of infection had decreased by 90% (Table 3). Subsequent annual treatment further reduced the prevalence, such that in 1989, only 18% of the cohort were infected. After the first year of treatment, the geometric mean intensity of infection remained stable at 2 eggs/10 ml of urine.

Bladder morbidity rapidly improved with treatment. By 1989, none of the study children had ultrasonographically detectable bladder morbidity (Table 3). The proportion of individuals with hydronephrosis increased from 8% to 31% after the first year of therapy (Table 3) and moderate to severe hydronephrosis increased from 3% to 11%. Five years after annual treatment, however, none of the children had moderate to severe hydronephrosis. Mild hydronephrosis persisted in 17% of the children in 1989.

Impact of repeated treatment on subsequent infection levels and morbidity. The proportion of subjects with bladder wall pathology (Figure 2, upper panel) and hydronephrosis (Figure 2, lower panel) was compared between the study cohort and morbidity controls shown in Table 2. Prior treatment markedly reduced the proportion of young adults who had bladder wall pathology even after subsequent reinfection, compared with previously untreated adult control subjects. Individuals with prior treatment had a lower frequency of moderate to severe hydronephrosis to 1 (0.5%) of 194 subjects compared with 1 (1.3%) of 77 in the previously untreated control population, although this difference was not significant because of low prevalence of severe hydronephrosis observed in the populations. Prior therapy did not

| Table 3 |
| Effect of repeated treatment in the study cohort on infection and morbidity from 1984 to 1989 (n = 1994) |

<table>
<thead>
<tr>
<th>Prevalence of infection</th>
<th>Geometric mean egg count</th>
<th>% mild hydronephrosis</th>
<th>% moderate/severe hydronephrosis</th>
<th>% bladder morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>71%</td>
<td>25</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>1985</td>
<td>25%</td>
<td>2</td>
<td>20%</td>
<td>11%</td>
</tr>
<tr>
<td>1988/1989</td>
<td>18%</td>
<td>2</td>
<td>17%</td>
<td>0%</td>
</tr>
</tbody>
</table>
significantly reduce (or increase) the risk of mild hydronephrosis (Figure 2).

**Impact of intensity of infection on morbidity.** Table 4 shows the relationship between infection intensity and urinary tract morbidity among the study cohort in 1984 (prior to therapy) and in 1997. With respect to bladder pathology in 1984, children with severe infections (egg counts > 399 per 10 ml of urine) had a significantly greater frequency of infection intensity-matched control adults from the same area. However, individuals who had not received prior treatment. These findings suggest that repeated chemotherapy for 5 years is beneficial in reducing the long-term burden of disease in a community attributable to *S. haematobium*.

Treatment of school age children can significantly reduce the cumulative projected lifetime egg burden because the intensity of infection is greatest during early teenage years. The effect of therapy is more pronounced when younger children are treated, as shown in Figure 3. Repeated treatment is necessary to induce a significant reduction in older children. We estimate that the Msambweni program produced a 60% reduction in the projected cumulative egg burden among young adults 21 years old by 1997 (Figure 3). Therefore, in endemic communities, repeated treatment is likely to be necessary to achieve the protection against morbidity we have demonstrated for young adults.

Ultrasound detectable bladder pathology represents granulomatous response to eggs trapped in the bladder wall. Both acute and chronic inflammation produces a mixed cell infiltrate that contains macrophages, eosinophils, lymphocytes, and neutrophils and a component of fibrosis. The observation that bladder lesions resolve with treatment indicates that a cellular infiltrate around viable ova in the bladder is what is primarily detected by ultrasound. Several factors
possibly contribute to the whether bladder lesions of sufficient size will develop and be detected by ultrasound. Heavier infections that release many eggs will produce a more marked granulomatous response. This has been supported by autopsy and cystoscopy studies that show a direct relationship between the intensity of *S. haematobium* infection and the severity of bladder wall lesions.21,22 However, many children and adults with heavy infections do not show ultrasound detectable bladder wall pathology, which indicate that other factors contribute to the increased risk of gross bladder morbidity. This is supported by other studies that have failed to show a consistent correlation with bladder wall pathology with intensity of infection.2,15–20 The duration of infection may also contribute significantly to the severity of bladder wall pathology. The cumulative frequency of urinary tract pathology increases with age, up to a point.2 The reduced morbidity observed with a history of repeated treatment over 4–5 years, as reported in the present study, implicates the importance of development of bladder pathology. Finally, the degree of down-modulation of the granulomatous response may also contribute to the extent of pathology. It has been observed that diminished egg antigen-driven tumor necrosis factor-α and/or enhanced interleukin-10 production may contribute to diminished inflammatory responses to schistosome ova in humans.21,22 The repeated antigenic boosting by continuously released ova is reduced with treatment and may also contribute to diminished egg-antigen induced granulomatous responses rather than its enhancement.

Moderate to severe hydronephrosis were uncommon in adults compared with untreated children. Longstanding hydronephrosis of this severity impairs renal function in other causes of obstructive uropathy (e.g., prostate cancer and urologic tumors).23,24 Presumably similar grades of hydronephrosis due to urinary schistosomiasis can also cause renal dysfunction, but this has not been as well studied. Treatment of children with schistosomiasis transiently increased the frequency of moderate to severe hydronephrosis; however, this finding totally resolved over the course of 2–3 years of therapy. More importantly, the presence of moderate to severe hydronephrosis and treatment in childhood did not increase the risk of developing similar grades of hydronephrosis with re-infection as adults. Indeed, the prevalence of moderate to severe hydronephrosis tended to decrease in treated individuals (0.5%) compared with untreated control subjects (1.3%).

The presence of mild hydronephrosis behaved differently from the other measures of urinary tract morbidity. It did not completely resolve with repeated chemotherapy in childhood, its presence in childhood resulted in an increased risk of developing hydronephrosis as an adult, and it reoccurred with a similar frequency in adults that had been treated as children compared with untreated control subjects. However, mild hydronephrosis could be transient, and may not represent significant urinary tract or kidney morbidity in some individuals. It is also possible that mild hydronephrosis may result from causes other than schistosomiasis, such as recurrent bacterial urinary tract infections.

Overall, these data indicate that although repeated selective population chemotherapy programs may not eradicate schistosome transmission, the burden of disease is significantly reduced even after re-infection occurs. The risk of redeveloping hydronephrosis in some children suggests that intervention should be made as early as possible. Selective population chemotherapy programs targeted at children have provided the important benefit of reducing the burden of urinary tract disease to this widespread and chronic infection.

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Authors’ addresses: Aruna K. Subramanian, Division of Infectious Diseases, Johns Hopkins University, Baltimore, MD 21205. Charles H. King and Christopher L. King, Division of Geographic Medicine, Case Western Reserve University, 2109 Adelbert Road, Room W137, Cleveland, OH 44106-4983. Peter Mungai, John H. Ouma, and Philip Magak, Division of Vector Borne Diseases, Kenyan Ministry of Health, PO Box 20750, Nairobi, Kenya. Adel A. F. Mahmoud, Merck & Co., Inc., One Merck Drive, SW 3A-07, White House Station, NJ 08889.

Reprint requests: Christopher L. King, Division of Geographic Medicine, Case Western Reserve University, 2109 Adelbert Road, Room W137, Cleveland, OH 44106-4983.

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