Global Health Critically Appraised Topic: Treatment of Stroke in CT-Poor Settings

Tim Anderson, PGY2

October 8th, 2013

Stroke remains on top 5 causes of mortality in the world with a higher incidence and higher mortality in developing countries. Standard stroke care in the US and Europe consists of fast presentation to healthcare & frequently specialty stroke centers, diagnosis using neuroimaging and clinical scales, and acute treatment based on stroke sub-type with anti-platelets, thrombolytics, antihypertensives and anti-coagulants followed by long-term treatment with rehabilitation and risk factor management. The hallmarks of stroke management consist of expensive diagnostic imaging; expensive acute interventions and expensive specialty care (both neurology and rehabilitation) making stroke hospitalizations amongst the most expensive in the US, averaging $9,500 (AHRQ 2005). Developing countries face substantial cost barriers at all management levels to improve stroke outcomes and practicing evidence-based medicine in this setting is particularly difficult given that the majority of “standard-of-care” interventions are not feasible in many developing country hospitals.

This appraisal focuses on two topics in stroke management: diagnosis of ischemic vs hemorrhagic stroke and acute treatment of stroke with aspirin. The first step in US stroke guidelines is clinical diagnosis of stroke severity and suspected stroke subtype (hemorrhagic vs. ischemic) followed by confirmatory neuroimaging. In much of the developing world neuroimaging is not available thus despite WHO guidelines treatment recommending neuroimaging, clinicians must adopt to classifying strokes into suspected ischemic or suspected hemorrhagic categories with the knowledge that clinical signs are only moderately sensitive at best. The Siriraj stroke scale from Thailand provides an algorithm based on clinical features and past medical history though subsequent studies assessing accuracy have ranged from 50-80%.

Regardless of scoring system used, an attempt to assess severity and subtype of stroke as well as assessing risk factors and co-morbidities may assist with prognosis and concurrent treatment (Grade 2C).

Using aspirin in the acute management of ischemic stroke is well validated (Grade 1A evidence) and endorsed by the American College of Chest Physicians and American Stroke Association. However, this recommendation is based on the assumption that ischemic stroke has been confirmed by neuroimaging as aspirin is contra-indicated in hemorrhagic stroke. These recommendations are based on a pair of randomized controlled trials the International Stroke Trial and Chinese Acute Stroke Trial which together enrolled ~40,000 patients. Further reviews of these trials note that ~22% of patients were randomized to aspirin vs no-aspirin without neuroimaging with a similar net risk and net benefit of aspirin. Furthermore, 800 patients in the trials whose presenting event was subsequently discovered to have been a hemorrhagic stroke has no difference in outcomes between aspirin and control group, though these patients regardless of intervention fared poorly compared to ischemic stroke patients. The authors conclude that their studies “give no good reason to withhold early aspirin treatment when ischemic stroke is suspected and rapid CT scanning is not conveniently available.” though this has not been endorsed by any guidelines or professional medical societies (Grade 2B). tPA is neither available or affordable for much of the developing world thus the remainder of treatment should focus on controlling associated risks from which data in developed countries may be applied to the developing country setting. This includes optimizing head position for intracranial pressure (Grade 1C) treating hyperglycemia (Grade 2C) and fevers (Grade 2C), and blood pressure management based on suspected sub-type of stroke.
References

3. Indications for Early Aspirin Use in Acute Ischemic Stroke: A Combined Analysis of 40,000 Randomized Patients - Chen et al, Stroke 2000
5. Stroke in Rural Areas and Small Communities - Stroke, 2008, Joubert et al
6. Stroke Presentation and Outcome in Developing Countries: A Prospective Study in The Gambia Garbusinski et al. Stroke, 2005
Global Health CAT Project: What are the causes of ESRD in Nigeria compared to the US and what is the mortality rate of patients on hemodialysis?

Chronic kidney disease is a growing problem not just in the developed countries but also in the developing world. In Nigeria, end-stage renal disease, which is defined as GFR <15 ml/min, is seen as a terminal condition according to the NKF-KDQOI (National kidney foundation-Kidney disease quality outcomes initiative) [1]. In Nigeria, CKD represents about 8–10% of hospital admission [2, 3]. In South eastern Nigeria, death from renal causes constituted 22.03% of medical deaths [4]. This has been thought to be a gross underrepresentation of the true situation because it is well known that CKD is under recognized and under diagnosed, patients tend to present late with end-stage renal failure (ESRD) or not at all to health facilities due to prohibitive costs. Interestingly, there are a number of hemodialysis centers that are privately funded in Nigeria that serve patients with ESRD, but the actual prevalence of ESRD is unknown due to paucity of data and variation among in documented cases in different regions [40].

The situation in Nigeria led to the clinical question to determine the most common causes of ESRD in Nigeria and the long-term survival of the patients receiving hemodialysis treatments. Using the PICO format, the question is formatted below:

**Problem/Patient:** End-stage renal disease (and causes)
**Intervention:** Hemodialysis
**Comparison:** United States
**Outcome:** Mortality rate

Using the key words ESRD, hemodialysis, mortality, and Nigeria 16 articles were found. Most of the articles were retrospective case-control studies by individual hospitals or dialysis centers; thus level 3B. One was a systematic review of a number of case control studies; thus, a level 3A. Only one of the studies directly compared their outcomes to the United States or other countries. Data on mortality in the United States and developed countries was obtained for a recent systematic review of cohort studies, which is a level 2a study.

Overall, compared to the United states where the top causes of ESRD are hypertension and diabetes, in Nigeria the most common causes of ESRD are chronic glomerulonephritis (31%), hypertension (42%), and chronic pyelonephritis (10%) based on a systematic review of 6 retrospective studies [5]. However, there is a large degree of variation as one studies from university teaching hospital in Lagos reported that as high as 62% of their cases of ESRD were of unknown etiology [6]. Furthermore, a 7-year study of a single-center dialysis facility demonstrated that diabetic nephropathy made up 17% of the patient population on hemodialysis [7].

The prognosis of ESRD is poor in both developed and developing countries. In a recent systematic review of prospective cohort studies in ten developed countries, the average mortality rate was 26.7, 16.9 and 13.7 within the first
120 days, 1 year, and after 1 year, respectively. Interestingly, the United States had the highest mortality among the developed countries that were compared with 33, 21.8, 18.1 within the first 120 days, 1 year, and after 1 year, respectively [10]. However, the prognosis of ESRD in Nigeria is abysmal due high dropout rate and loss to follow-up attributed to the prohibitive costs of dialysis. One study demonstrated as a mortality rate as high as 54% in ESRD patient with diabetic nephropathy [8]. A different study demonstrate mortality rate as high as at least 41 % in first 12 weeks [7]. This particular study further investigated dropout rates in their maintenance hemodialysis program and found that the mean duration before drop-out was 5.7 weeks and the range was 1 to 37 weeks [7]. The study found that 98% of the patients could not sustain dialysis for more than 12 weeks and by this time 41% of the patients were confirmed dead and another 41.8% had absconded and were presumed dead [7]. Eight percent of the patients were able to raise funds to be referred out of the country for continued therapy and the remaining who were confirmed alive after 6 months were those who were able to obtain renal transplant [7]. Analysis of funding for the service demonstrated that 82% of the funding came from the individual or extended family, 7.5% was from employer support and 10% from philanthropic support [7]. Another retrospective study demonstrated that due to the financial burden of repeated hemodialysis sessions, majority of the patients were under dialyzed such that only 3.3% of the patients had thrice weekly dialysis, 21.7% dialyzed twice weekly, 23.3% once weekly, 16.7% once in two weeks, 2.5% once in three weeks and 11.7% once monthly [9]. Over a 21-month period, 8.3% of the patients were confirmed dead while 38.3% were lost to follow-up and could have been presumed dead [9].

It is clear that very that much has to be done to improve the current situation in ESRD treatment. First, is a functional organizational structure for the reporting of CKD and ESRD incidence and outcomes must be developed (i.e. Nigerian Renal Registry) to accurately assess the gravity of the problem. Additional important steps that must be taken are to develop prevention programs and increased funding to ensure increased availability of RRT. In most developed countries, the government finances hemodialysis to make it affordable and accessible. The same rule should apply to the Nigerian government, who should take the primary responsibility of financing hemodialysis facilities such that affected patients can obtain adequate treatment as well as improving educational training of the health professionals who take care of these patient.

References:


**Question:** What is the evidence for adjunctive corticosteroid therapy in TB pericarditis?

**Search strategies:**

<table>
<thead>
<tr>
<th>Cochrane Database</th>
<th>Search: “adjunctive corticosteroid therapy in tuberculous pericarditis”</th>
<th>1 review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pub Med</td>
<td>MeSH: “Pericarditis, Tuberculous” and “Steroids”</td>
<td>12 articles total, 2 clinical trials, 6 reviews</td>
</tr>
<tr>
<td>Ovid Medline</td>
<td>Search terms: “steroids” and “pericarditis, tuberculous” [Drug Therapy, Therapy] Limit: Core clinical journals</td>
<td>9 articles total, 3 RCTs (1 incomplete), 5 case reports and 1 editorial</td>
</tr>
</tbody>
</table>

**Articles Level 1b = individual RCTs:**


This double blind, randomized placebo controlled trial was designed to determine the effect of adjunctive prednisolone on morbidity, pericardial fluid resolution, and mortality in HIV seropositive patients with effusive tuberculous pericarditis. Two medical school affiliated referral hospitals in Harare, Zimbabwe, enrolled 58 HIV seropositive patients aged 18–55 years with tuberculous pericarditis. Patients were admitted into the study on the basis of an echocardiographic demonstration of a large fibrinous pericardial effusion and a clinical diagnosis of tuberculous pericarditis, supported by a high lymphocyte count and a high protein content in the pericardial aspirate. All patients received standard short course antituberculous chemotherapy and were randomly assigned to receive prednisolone or placebo for six weeks, at a dose of 60 mg/day for the first week, and tapering by 10 mg every week until the sixth week. Randomization was achieved using a computer-generated randomization list with an equal number assigned to receive prednisolone and placebo. Outcome measures included death, corticosteroid-related side effects as well as resolution of pericardial effusion, pre-treatment signs/symptoms and ECG changes. 29 patients were assigned to prednisolone and 29 to placebo. After 18 months of follow up, there were five deaths in the prednisolone treated group and 10 deaths in the placebo group. The study claimed mortality was significantly lower in the prednisolone group (log rank +2 = 8.19, df = 1, p = 0.004), but further analysis by two systematic reviews determined that this was not statistically significant (RR 0.50; 95% CI 0.19 to 1.28, p = 0.15). Resolution of raised jugular venous pressure (p = 0.017), hepatomegaly (p = 0.007), and ascites (p = 0.015), and improvement in physical activity (p = 0.02), were significantly more rapid in the prednisolone treated patients. However, there was no difference in the rate of radiologic and echocardiographic resolution of pericardial effusion, the risk of constrictive pericarditis ((RR 1.00; 95% CI 0.15 to 6.63, p =1) or the frequency of steroid-related complications. The authors concluded that high dose prednisolone in addition to antituberculous drugs resulted in reduced mortality and quicker improvement of clinical features. They suggested that, in the absence of any specific contraindication, HIV seropositive individuals with effusive tuberculous pericarditis should receive adjunctive prednisolone.

This double blind, randomized placebo controlled study in Umtata, South Africa, recruited 143 participants with suspected tuberculous constrictive pericarditis without significant pericardial effusion aged 5 years and older. All of them received the same daily 6-month antituberculosis regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide for 14 weeks followed by isoniazid and rifampicin. They were randomly allocated to receive in addition either prednisolone or placebo for the first 11 weeks. Adult dose entailed 60 mg/day for first 4 weeks, 30 mg/day for weeks 5 to 8, 15 mg/day for weeks 9 to 10 and 5 mg/day for week 11. Randomization was conducted using a register drawn up centrally in the UK. 29 individuals were excluded from analysis due to failure to comply with the study protocol. Outcome measures included death from pericarditis, favorable clinical status at 24 months, and pericardiectomy for constriction. In the 114 patients assessable up to 24 months, improvement was significantly more rapid in the prednisolone group, as shown by the rate of fall in the mean pulse rate and the rate at which jugular venous pressure and level of physical activity became normal. During follow-up, 2 (4%) of the 53 prednisolone and 7 (11%) of the 61 placebo patients died from pericarditis, and 11 (21%) and 18 (30%), respectively, required pericardiectomy. These trends of decreased mortality and lower need for pericardiectomy were not statistically significant, RR 0.65, 95% CI 0.36-1.16, p=0.14 and RR 0.85, 95% CI 0.51-1.42, p = 0.5, respectively. By 24 months 50 (94%) prednisolone and 52 (85%) placebo patients had a favorable clinical status. The authors recommended that, in the absence of a specific contraindication, antituberculosis chemotherapy should be initially supplemented by steroids.

Articles Level 1a = systematic review of RCTs:


Critical Appraisal:

<table>
<thead>
<tr>
<th>Validity</th>
<th>Hakim – Yes, randomized.</th>
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</thead>
<tbody>
<tr>
<td>Was it randomized?</td>
<td>Hakim – Yes, randomized.</td>
</tr>
<tr>
<td></td>
<td>Strang – Yes, randomized</td>
</tr>
<tr>
<td>Was randomization concealed?</td>
<td>Hakim – Yes, computer generated randomization. A randomization code list was kept sealed and was released at the end of the study.</td>
</tr>
<tr>
<td></td>
<td>Strang – Yes, randomization was conducted using a register drawn up centrally in the UK.</td>
</tr>
<tr>
<td>Was the follow up sufficiently long and complete?</td>
<td>Hakim – Yes, 18 months from the entry into the study.</td>
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<td></td>
<td>Strang – Yes, 2 years.</td>
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<tr>
<td>Was the data analyzed on an intention to treat basis?</td>
<td>Hakim – Yes, all analyses were performed on an intention-to-treat basis with two sided p-values.</td>
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<td></td>
<td>Strang – No, the study did not use an intention-to-treat analysis, resulting in the exclusion of participants from analysis due to failure to comply with the study protocol. In the published data, 29/143 participants (20%) were excluded from analysis.</td>
</tr>
</tbody>
</table>
| Was there adequate blinding of subjects and researchers? | Hakim – Yes, clinicians and patients were blinded to the identity of the tablets.  
Strang – Yes, the investigators in South Africa entered participants into the trial consecutively according to the register, without prior knowledge of who was receiving active or placebo treatment. |
| Were there similar baseline characteristics in each group? | Hakim – Yes, no significant difference between the two treatment groups with regard to demographic information, clinical variables and baseline laboratory features was noted.  
Strang – Yes, the participants in the treatment and control groups were well matched in terms of clinical characteristics and completion of antituberculous chemotherapy. |
| Groups treated equally other than intervention? | Hakim – Yes, both groups underwent same assessments at regular intervals.  
Strang – Yes |

| Applicability | Hakim - No, these results would be applicable to HIV seropositive patients living in low-resources settings. However, the diagnosis of tuberculosis was confirmed in 22/58 (38%) participants, 12 [41%] and 10 [35%] in the treatment and control groups, respectively.  
Strang – No. However, a definite diagnosis of tuberculosis was made in only 10% (14/143) of the participants. |
<p>| Is treatment feasible? | Hakim and Strang – Yes, except for cost, depending on the clinical setting |
| Benefits vs harms | Hakim and Strang – Unproven, suggestive of beneficial effects in terms of morbidity and mortality. |</p>
<table>
<thead>
<tr>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>• Search for studies confirmed the paucity of rigorous evidence on this topic.</td>
</tr>
<tr>
<td>• Investigations suggested potentially large beneficial effects in terms of morbidity and mortality (about 50% reduction in case fatality rate), but trials and the meta-analysis did not reach statistical significance.</td>
</tr>
<tr>
<td>• There was no sufficient data to explore whether any effect of steroids was in all patients, or confined to particular subgroups, such as patients with effusive or constrictive disease.</td>
</tr>
<tr>
<td>• Trials were small, and thus results were more susceptible to be due to chance.</td>
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<tr>
<td>• None of the studies were adequately powered to assess the effect of steroids on mortality.</td>
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<tr>
<td>• Loss of follow-up was as high as 20%.</td>
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<tr>
<td>• Bacteriological characterization of cases was limited, as many lacked definitive diagnosis of tuberculosis.</td>
</tr>
<tr>
<td>• Rifampin induces the hepatic metabolism of steroids, so it is possible that the steroid dose used in the trials to date was too low, 120 mg of prednisolone rather than 60 mg may be more appropriate.</td>
</tr>
</tbody>
</table>
Clinical Bottom Line: In regions with high prevalence of zinc deficiency or malnutrition, zinc supplementation during acute episode of diarrhea in children aged six months or older may be beneficial.

Citation: Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. The Cochrane database of systematic reviews 2013;1:CD005436.

Question: What is the evidence for zinc therapy in the management of diarrhea?

Search Strategy: zinc + diarrhea
Limits: English, human, meta-analysis

The study: Some studies have shown that zinc supplementation during an acute episode of diarrhea reduces overall duration and hospitalization. Thus, the purpose of this study was to perform a meta-analysis of randomized controlled trials comparing oral zinc supplementation with placebo in children with diarrhea. A total of twenty-four randomized control trials, enrolling 9128 children, were identified and used in the study. The primary outcome of the study was the duration of diarrhea while the secondary outcome was adverse events of zinc supplementation.

The evidence: In children greater than six months of age, the mean duration of diarrhea ranged from 41 to 170 hours. Zinc may reduce the mean duration by about 10 hours (mean difference of -10.44 hours, 95% CI -21.13 to 0.25; 2175 children). The results were not statistically significant and moderate heterogeneity was noted. However, in children with signs of moderate malnutrition, zinc supplementation reduced the duration of diarrhea by about 27 hours (mean difference of -26.98 hours, 95% CI -14.62 to -39.34; 336 children). The mean duration of diarrhea in children with signs of moderate malnutrition without zinc supplementation ranges from 103 to 147 hours. While no trials reported serious adverse events, it was found that zinc supplementation during acute episode of diarrhea causes vomiting (RR 1.59, 95% 1.27 to 1.99; 5189 children).

Comments: While the use of oral rehydration solution has been shown to decrease mortality, it has not been shown to effect the duration of diarrhea. Thus, the use of zinc supplementation in hope of decreasing the duration of illness has been analyzed. Based on the meta-analysis, the use of zinc supplementation in children with moderate signs of malnutrition to reduce duration of diarrhea is level 1a evidence (Grade A recommendation) based on oxford center for evidence-based medicine levels of evidence. Thus, in the areas where the prevalence of zinc deficiency or malnutrition is high, zinc supplemtations maybe reduce duration of diarrhea in children aged six months or older. However, it is important to note that the studies have some limitations including the fact that not all studies were double blinded and the dosage frequency of zinc was not standardized. In addition, the majority of studies used in the analysis were from Asia, which has a high risk of zinc deficiency. Only two of the 24 studies used were conducted in Africa. Thus, based on the findings and since no significant adverse events were noted, if my patient population has high risk of zinc deficiency, I will use zinc supplementation in children six months of age or greater in hope of reducing the duration of their acute episode of diarrhea.
Clinically Relevant Question: What is the cost-effectiveness of rapid diagnostic test (RDT) versus microscopy in the evaluation of acute febrile illness in sub-Saharan Africa?

Malaria is the single most common diagnosis made in most African countries but the accuracy of clinical diagnosis is limited by the low specificity of both the signs and symptoms of the disease and by the availability of confirmatory diagnostic testing for malaria. Presumptive antimalarial treatment for any febrile illness is as common practice in endemic areas which leads to significant overuse of antimalarial drugs throughout Africa. The overuse of antimalarial drugs then leads to the growth of resistance to older drugs requiring the use of newer, more expensive drugs which are less available in resource limited settings. Reduction of malaria morbidity and mortality in addition to drug resistance intensity are two of the most important factors driving the need for evidence based guidelines for the diagnosis and treatment of malaria.

Microscopy remains the gold standard for the diagnosis of malaria but its accuracy under operational conditions in resource limited environments is often low. Microscopy has the advantage of being inexpensive, readily available, and allows the ability for species identification. However poor microscopic practices has long been recognized due to multiple factors including: training and skills of lab technicians, slide preparation techniques, heavy workload and quality of essential laboratory supplies. Variability in lab performance and results combined with the risk of untreated malaria leads clinicians to treat febrile patients without regard to microscopy results.

Several commercially available rapid diagnostic tests (RDT) are sensitive, specific and stable under many operational conditions. The RDT is a device that detects malaria antigen in a small amount of blood by immunochromatographic assay with monoclonal antibodies directed against the target parasite antigen. The result is obtained in 5-20 minutes. The RDTs require no capital investment or electricity and are both simple to perform and easy to interpret. Some RDTs can also distinguish between P. falciparum from the three non-falciparum species. RDTs have achieved 95% sensitivity for P. falciparum but not for non-falciparum species (closer to 85%). Other factors including environmental conditions including humidity and temperature can affect RDT performance. Successful implementation of RDT’s requires complex planning. Implementation will be a challenge as self-diagnosis and self-treatment in the informal health sector is rampant. The current cost of RDTs is $0.60 per test while microscopy is as low as $0.32 per test.

In the face of rising costs of effective antimalarial therapy, over-diagnosis (presumptive and otherwise) can quickly become expensive for both local health infrastructure and individual patients. Multiple studies show that RDT cost effectiveness varies with malaria prevalence; particularly, lower prevalence of malaria increases the sensitivity of RDT. In higher prevalence of malaria, presumptive treatment and microscopy remains a more attractive option unless the cost of RDT’s goes down. An additional factor is the price of antimalarials: if the more expensive Coartem is used for treatment in a specified area, then testing should be relied upon more heavily. A mathematical model that assists in decision making of RDT introduction in areas of high-level malaria transmission is available online by the WHO. In summary, RDT’s should be considered as tools for the composite management of febrile illnesses in sub-Saharan Africa. Cost effectiveness of RDT’s relies heavily upon the prevalence of malaria in a given area, price of antimalarials, cost of treatment of other febrile illnesses when malaria is ruled out, and quality of lab technician skills to perform both microscopy and RDT’s.
Bronchodilators Administered Via Nebulization Versus Metered-dose Inhaler with Homemade Spacer for Acute Asthma Exacerbations in Children

Clinically Appraised Topic

Marisa Sochacki, PharmD

Clinical scenario: At the Clinica Medica in San Jose, Honduras, asthma is a common condition treated. Frequently, children present during an acute exacerbation and the clinic is responsible for treating the acute attack. Although the facility has electricity, it is not guaranteed to be available. Moreover, bronchodilators in either nebulized or metered-dose inhaler dosage forms are not always stocked. Commonly, only one of the two dosage forms will be available. Cost-effectiveness is a very important factor when choosing treatment at the low-resource facility and, consequently, commercial, valved spacers are not routinely stocked.

Request: How effective are metered dose inhalers used with a homemade nonvalved spacer when compared to nebulized bronchodilators for the treatment of acute asthma exacerbations in children?

Search strategy:

1. GINA Guidelines
2. PubMed: Inhalation spacer (MESH) AND (child [MESH] OR child, pediatric [mesh])
3. PubMed: Homemade spacer
4. PubMed: Home-made spacer
5. PubMed: Bottle spacer
6. PubMed: Holding chamber
7. PubMed: Home-made spacer nebuli*
8. PubMed: Homemade spacer nebuli*
9. Where there is no doctor
10. Cochrane Collaboration: Homemade spacer
11. Cochrane Collaboration: Home-made spacer
12. Cochrane Collaboration: Bottle spacer

Background:

Guidelines

- During an exacerbation, a metered-dose inhaler should always be used with a spacer. This produces at least an equivalent response as nebulization and is more cost effective.
  - Commercially produced spacers with well characterized drug output characteristics are the preferable spacers.

Spacers

- Spacers increase efficacy and decrease side effects from inhaled medications.
- Unreliable availability and cost have limited use in developing countries.

Homemade spacers
• Directions on how to make a spacer
  - Tape two thin plastic cups together at their wide ends. Cut a small hole for the inhaler on one end, and a larger hole for your mouth on the other.\(^2\)
  - Cut a hole large enough for your mouth in the bottom of a plastic soda bottle. Put the inhaler in the other end of the bottle.\(^2\)
  - Plastic bottle spacers (250 mL, 500 mL, 700 mL) are made by forming a hole in the bottom of a cold drink plastic bottle where the inhaler is inserted.\(^3,4,5\) For improved fit a heated mold has been used to melt a hole in the bottle that is the exact shape of the inhaler mouthpiece. Glue or epoxy resin can be used to seal the opening.\(^6\) The neck of the bottle is used as a mouthpiece for the child, or it can be connected to a mask for use in younger children.\(^7,8\)

Evidence:

Reducing electrostatic charge:

- Water does not significantly reduce electrostatic charge.\(^9\)
- Rinsing with detergent eliminates charge for 24 hours. Charge at one week remains lower than the charge of a new spacer.\(^9\)
- Studies have primed the spacer with 15 puffs of medication in order to reduce electrostatic charge.\(^10\)

Homemade spacers compared with commercial spacers:

- A meta-analysis failed to show a difference in efficacy between homemade spacers (plastic bottles, cardboard cones, and polystyrene cups) when compared to commercially available spacers.\(^4\)
- Studies have shown that sealing the homemade spacer with glue increases efficacy.\(^10\)
- Polystyrene cups have been shown to be less effective than plastic bottles.\(^10\)
- Lung deposition was significantly increased when a 500 mL homemade spacer was compared to a 350 mL commercially available spacer.\(^11\)

Homemade spacers compared with nebulization:

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duarte M and Camargos P. 2002(^12)</td>
<td>500 ML plastic bottle coated with detergent (5 100 mcg puffs per cycle; breathed for 20 seconds between puffs); nostrils occluded with nasal clip Nebulized salbutamol (0.15mg/kg/dose)</td>
<td>Children 4-15 years with mild or moderate asthma attacks (50-80% predicted)</td>
<td>1. PEFR, heart rate, respiratory rate, SaO2 2. Side effects</td>
<td>1. PEFR, SaO2, respiratory rate were not significantly different after first, second, or third cycle; an increase in heart rate was seen with nebulized treatment 2. More side effects were seen with nebulized treatment 3. Comparable number of doses and cycles needed</td>
<td>Home-made nonvalved spacers should be considered for patients with acute asthma who need low-cost treatment</td>
</tr>
<tr>
<td>Vilarinho LCS et al. 2003(^3)</td>
<td>Saline bottle (250 mL was used for children under 3 and 500 mL for children 3-12), unsealed. Nose was held closed by the provider. Salbutamol (100 mcg per 3kg) one puff every 20 seconds Nebulized salbutamol (250 mcg per 3 kg)</td>
<td>Children up to 12 years of age with wheezing crisis (initial global score of 13)</td>
<td>1. Clinical signs and symptoms 2. Costs, time spent</td>
<td>1. No statistically significant differences in clinical signs and symptoms 2. Cost for MDI was 22% of the cost of nebulizer. Time spent on the inhaler group was 28.3% of that spent on the nebulizer group</td>
<td>Results support the recommendation for preferential use of inhaler with a hand-made spacer instead of nebulizer in moderate asthmatic crisis</td>
</tr>
</tbody>
</table>
Response:

Metered-dose inhalation of albuterol inhaled through homemade spacers appear to be as effective as nebulized albuterol for treatment of children with mild to moderate asthma exacerbations. Costs and time for preparation are decreased with use of metered-dose inhalers. Adverse events, such as tachycardia, may be decreased with metered-dose inhalation, but studies have not convincingly proven this.

It appears that the most effective homemade spacers are made with sealed, 500 mL plastic drink bottles that have been rinsed with detergent and allowed to air dry.

The most studied dose of albuterol is 4 100 mcg puffs every 20 seconds with repeating cycles if necessary. Only one puff should be sprayed into the spacer at a time.

References:


Theodore Belsches, PGY1

Question: How should developing countries prevent the spread of tuberculosis within hospitals?

Clinical Bottom Lines:
1. It is most important to limit potential exposure with early diagnosis, early treatment, and early discharge.
2. Use open-air or natural ventilation wherever possible.
3. Have patients with TB wear surgical masks (be aware of potential stigma) and reserve personal respirators for particularly high risk locations such as MDR-TB wards, sputum collection/bronchoscopy rooms, surgical/autopsy suites.

Guidelines:
A. Administration controls- limit exposure
   - have open waiting areas and prioritize evaluation of patients with potential TB
   - expedite laboratory diagnosis, collecting sputum preferably outside
   - educate patients about cough etiquette and provide tissues/clothes to cover their mouths
   - separate TB and non-TB patients, particularly immunosuppressed and HIV patients, as much as possible
   - treat TB outpatient whenever possible
   - remove from isolation when received 2 weeks of treatment and clinically improved. Require negative sputum smear for MDR-TB
   - monitor compliance and infection rates

B. Environmental controls- decrease infectious droplets
   - have openings at opposite ends of rooms to allow for air exchange with TB patients placed downwind
   - potentially use window fans to direct air flow and create a negative pressure room
   - high risk rooms which have little ventilation can be equipped with ultraviolet germicidal irradiation (UVGI, beware of potential cutaneous and ocular damage) or HEPA filters

C. Personal Respiratory Protection
   - surgical masks should only be used by patients with TB. Be aware of a potential stigma
   - respirators require proper fitting and should be reserved for health care workers in MDR-TB wards, sputum collection procedures, bronchoscopy, autopsy

Sources

Clinical Question

For pregnant women living in regions with endemic soil transmitted helminth (STH) infection, is the mass administration of anthelminthic medication indicated to improve maternal and neonatal outcomes despite the risk of teratogenic effects?

Evidence

In 1994, the Report of the WHO Informal Consultation on Hookworm Infection and Anemia in Girls and Women recommended single-dose, oral anthelminthic treatment in STH endemic regions for all pregnant women after the first trimester. This guideline was largely based on experiences in Sri Lanka, where high rates of anemia (56-78%) and hookworm infection (6-89%) were found among pregnant women. Mass anthelminthic administration was initiated for this population, which included a single course of mebendazole given after the first trimester, in addition to iron-folate supplements. The implementation of this regimen for Sri Lankan pregnant women produced an increase in hemoglobin concentration and iron status. Although the WHO acknowledged existing evidence of teratogenic effects from albendazole and mebendazole in certain lab animals, these effects were not found in all species. The WHO asserted that anthelmintics likely exhibit distinct pharmacokinetics for different species. Overall, it was concluded that the potential benefit of improving maternal anemia outweighed the risk of teratogenicity for pregnant women in STH-endemic regions.

Since the 1994 report, four observational studies and four randomized controlled trials (RCTs) have assessed the efficacy of following WHO guidelines in improving maternal and neonatal outcomes. These data are summarized in a 2012 meta-analysis in *Pediatric and Perinatal Epidemiology*. Among the four observational studies, three showed that treatment improved maternal iron status, two suggested beneficial effects on birthweight, and two found an improvement in infant survival. In all four randomized controlled trials, anthelminthics in pregnancy significantly decreased the prevalence of STH infection. For the two trials that assessed birthweight, the risk of very low birthweight was decreased in the anthelminthic group. Despite these suggested benefits, meta-analysis of the four randomized studies suggested no significant effect of anthelminthics during pregnancy on maternal anemia, low birthweight, or infant survival.

Strength of the Evidence

Anthelminthic treatment during pregnancy is associated with:

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of STH infection</th>
<th>Rate of Maternal Anemia</th>
<th>Infant Survival</th>
<th>Infant Birth Weight</th>
<th>Infant Eczema</th>
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<tbody>
<tr>
<td><strong>Level 1a</strong></td>
<td>Decreased (meta-analysis)</td>
<td>No difference (meta-analysis)</td>
<td>No difference (meta-analysis)</td>
<td>No difference (meta-analysis)</td>
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<tr>
<td><strong>Level 1b</strong></td>
<td></td>
<td></td>
<td>Improved (2 RCTs)</td>
<td>Improved (2 RCTs)</td>
<td>Increased (1 RCT)</td>
</tr>
<tr>
<td><strong>Level 2a</strong></td>
<td>Decreased (3 observational studies)</td>
<td></td>
<td>Improved (2 observational studies)</td>
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- Decreased prevalence of STH infection: Supported by meta-analysis of four RCTs (Level 1a).
- Decreased rates of maternal anemia: Supported by three observational studies (Level 2a), but not supported by meta-analysis of four RCTs (Level 1a).
- Improved birthweight: Supported by two observational studies (Level 2a) and two RCTs (Level 1b), but not by meta-analysis (Level 1a).
- Improved infant survival: Supported by two observational studies (Level 2a), but not by meta-analysis (Level 1a).
- Increased risk of infant eczema: Supported by one RCT (Level 1b).

**Recommendations**

Foremost it is clear that further RCTs are warranted to evaluate the suggested beneficial effects of anthelminthics on maternal and infant outcomes. Meta-analysis showed no impact on maternal anemia, infant birth weight, or infant survival. Research in humans is also needed to describe the safety of deworming medications during pregnancy.

When considering indications for deworming pregnant women, it is first important to target the appropriate population: specifically, pregnant women after their first trimester who are living in STH-endemic regions. The most robust level 1a evidence-based outcome is that treatment decreases the prevalence of STH infection, so this therapy must be targeted toward women who are likely to be infected. RCTs were conducted in regions with STH prevalence of 56-82%.

To further guide treatment in endemic regions, it is appropriate to clinically assess women for signs and symptoms of STH infection. If available, obtaining stool studies and hemoglobin levels would contribute to informed decision making. Although no RCTs have specifically evaluated the benefit of targeting deworming for pregnant women who are infected or anemic, most likely the benefit would be more apparent in these women and potentially outweigh the risk of teratogenicity.

For pregnant patients without demonstrated infection or anemia, further Level 1a evidence is needed to recommend anthelminthic treatment. In the regions that do treat pregnant women, it is recommended to track maternal and neonatal outcomes including benefits as well as pharmacovigilance data about teratogenic or toxic consequences. Pregnant mothers should be informed that there is a lack of human data, but the WHO suggests teratogenicity is unlikely. Patients should also be aware of the potential risk of infant eczema. Further studies are needed to assess the risk for eczema and related consequences such as atopy or allergy later in life.

As healthcare practitioners in the developing world, it is important to share with patients what is known: that hookworms cause anemia and malnutrition and that anthelminthics are shown to treat infection. It is also important to discuss what is not known regarding the effects of deworming medications on fetal outcomes in humans. Further research is needed to support the beneficial effects of deworming on maternal and perinatal health in addition to assessing the risk of teratogenicity. Healthcare providers should prioritize targeting treatment appropriately while collecting necessary data.
Resources


<table>
<thead>
<tr>
<th>Year</th>
<th>Location, Author</th>
<th>Study Design</th>
<th>Study Description</th>
<th>Predictive factors identified</th>
<th>Strengths/Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987* abstr. only</td>
<td>Malaysia, Ross IN</td>
<td>Retrospect review</td>
<td>110 +EF 150 –EF 19 clinical/lab features thought to be helpful Unclear – not all had +BC</td>
<td>(1) +Widal at 1:40 (5) WBC&lt; 9 (2) Temp &gt;39 C (6) PMN &lt;3.5 (3) Fever &gt; 7days (7) Splenomegaly (4) Previous tx fever (8)Hepatomegaly <strong>Clinical prediction rule:</strong> Presence of 6+ features has Spec 0.80, Sens 0.92</td>
<td>-old : prior to HIV epidemic -unclear how “enteric fever” defined as some has +Cx and others not</td>
</tr>
<tr>
<td>1997* abstr. only</td>
<td>Bangladesh, Haq SA</td>
<td>Retrospect review</td>
<td>106 +BCx 170 other fever</td>
<td><strong>With specificities:</strong> (1)stepladder rise in temp- 100% (2)loose BM- 94.7% (3)relative bradycardia-94.7 (4)coated tongue-94.1%</td>
<td>-hard to believe high specificities -no PPV/NPV given -matching of cases and controls?</td>
</tr>
<tr>
<td>2009</td>
<td>Turkey, Kuvandik C</td>
<td>Retrospect case-control</td>
<td>Pts admitted with fever &gt;4 days and presumptive EF stratified by bcx results: 60 +bcx, 53 -bcx</td>
<td>Significant signs (OR) (1) splenomegaly - 8.16 (2) relative brady- 17.2 (3) rose spots- 4.94 (4) TCP – 7.92 (5) elevated AST – 5.4 SM + RS: sens 78.3%, spec 48.3%</td>
<td>-clear method of case identification -shady stats? (sens vs. specificity) -no guidance as to how should use data</td>
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<td>2010</td>
<td>Pakistan, Khan</td>
<td>Retrospect review</td>
<td>421 ED pts at 3⁰ care hospital adm. for suspected EF from 2000 – 2005. Compared clinical and lab signs of pts with +bcx (53) and –bcx (296) (48% left hospital with dx of EF)</td>
<td>No single clinical sign/sx or lab test had significant PPV or NPV or likelihood ratio</td>
<td>-clear methodology with broad inclusion -bcx have low sensitivity: may have skewed data</td>
</tr>
<tr>
<td>2012</td>
<td>Tanzania, Thriemer K</td>
<td>Prospective observational</td>
<td>2209 febrile patients presenting to clinics, compared WHO case definitions to Widal and Bcx results (46 +bcx) -WHO “suspected” EF: fever&gt; 3 days -WHO “probabal” EF: fever + Widal (+)</td>
<td>Only sig different sign=fever length—longer in EF, OR 1.07 -WHO suspected: sens 82.6%, spec 41.3% -WHO probable: sens 36.3%, spec 99.7% -Widal at 1:80: sens 47.3%, spec 99.4%</td>
<td>- well-designed, inclusive study -starts with “fever” pt - surprisingly low rate of bcx +</td>
</tr>
<tr>
<td>2006</td>
<td>Nepal, Neopane A</td>
<td>Prospective observational</td>
<td>All pts admitted to Kathmandu Teaching Hosp with provisional</td>
<td><strong>Major Criteria identified (dx accuracy):</strong></td>
<td>-prospective -blood and bone marrow cx = improved accuracy</td>
</tr>
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The problem: Enteric fever, caused by S. typhi and S. paratyphi, continues to be a major public health concern in developing countries where sanitation is lacking. Estimates show 16 million cases and 600,000 deaths in 2012. This number is likely an underestimate, given the difficulty of definitive diagnosis. Culture of salmonella from blood is the “gold standard,” but only 60-80% sensitive due in part to small blood volume collection from children and prior antibiotic use. Culture from bone marrow is more accurate: 80-95% sensitivity. However, many areas lack capabilities to perform culture and results can take up to 7 days. A simple, rapid, inexpensive method of diagnosis is needed. The Widal test, which measures antibody agglutinins to H and O, has been used for over 100 years but suffers from unacceptable levels of false positives (cross-reactivity with other enterics, vaccination) and false negatives (late in disease). Newer lab tests include ELISA for S. typhi antibodies, which neglects the substantial disease caused by S. paratyphi, and PCR, which is more sensitive than blood culture, but not readily available. Furthermore, the rising resistance of S. typhi and S. paratyphi to available antibiotics makes correct diagnosis even more important.

The question: In a setting where blood culture is not readily available, can clinical features be used to predict likelihood of enteric fever in the patient presenting with fever?

Search: PubMed “enteric fever” or “typhoid fever” + “diagnosis” + “clinical” in title/abstract, 6 relevant studies + 1 validation study identified.

Grade of Evidence: mostly retrospective case-controls or cohorts (Level 2-3), few prospective cohorts (Level 2). However, evidence between studies is not consistent and methods varied greatly, therefore: GRADE C

Conclusion: Studies have not consistently shown clinical features to be useful in predicting enteric fever. However, these studies have been limited by poor sensitivity of “gold standard” blood cultures, low pt numbers, poor methodology in some cases. Most convincing evidence is clinical prediction rule from Nepal, which performed well in validation study. However, unclear how applicable this would be to other regions, particularly the malaria-belt in Africa where typhoid is less endemic and there may be significant overlap of symptoms with malaria.
A 32 year old man in Sub-Saharan Africa presents with chronic splenomegaly and hematuria. He lives near a lake and everyone in his village seems to develop the same problem by adulthood. He is diagnosed with Schistosomiasis. What is the role of preventive praziquantel therapy in controlling Schistosomiasis in this village?

Schistosomiasis affects approximately 243 million people in 78 countries, and has been designated a Neglected Tropical Disease (NTD). The World Health Organization recommendations regular preventive pharmacotherapy of schoolchildren – often several times during childhood – as a strategy for controlling Schistosomiasis in whole communities. A literature review revealed a review of RCT’s for preventive therapy targeted to multiple neglected tropical diseases (LOE=1a). This review featured two RCT’s of pharmacotherapy for Schistosomiasis simultaneously with at least one other NTD; the most recent study is reviewed in depth, with a brief description of the other study.

**Treatment for Schistosomiasis, Hookworm, Roundworm, and Whipworm**

**Patients:** schoolchildren, age 4-19yrs, in Kenya, China, Philippines (n=380 per treatment group)

**Intervention:** Albendazole x1, Praziquantel x1 or x2

**Comparison:** placebo controlled, factorial (albendazole alone vs. praziquantel alone vs. both)

**Outcome:**
- 45 day follow-up: Reduced prevalence of eggs in stool, p< .0001 for all groups
  - S. mansoni 43.6% vs. 78.3% in placebo
  - S. japonicum 6.7% vs. 39.3% in placebo
  - S. haematobium 38.5% vs. 79.8% in placebo
  - Placebo prevalence not statistically different from pretreatment
- Extended follow-up: Prevalence significantly reduced vs. placebo at 90 and 180 days, p<.00001. Positive cases retreated at 6 months. At 1 year, there was no significant difference in prevalence between children treated once in the year and those retreated at 6 month interval.
  - Reduced Liver span
    - Liver span below mid-sternum (xiphoid process) reduced to 6.71% of subjects vs. 21.52% pretreatment
    - Using child as own control, there was a significant reduction in liver span below mid-sternum (p<.05), from mean 0.787 ± 1.677 cm to mean of 0.295 ± 1.217 cm at 1 year.

**Earlier Study**

Stephenson et al 1989: schoolchildren, grade 1-7, in Kenya (n=103 per treatment group); treated with praziquantel x1 vs. metrifonate x1 vs. placebo. Pretest egg prevalence was 100%. At 32 weeks, the praziquantel group had 62% egg prevalence vs. 100% in the placebo group.

**Conclusion**

These studies provide a theoretical foundation for praziquantel-based therapy to control Schistosomiasis in communities. However, stronger evidence would demonstrate sustained decreases in stool egg prevalence among all community members, and decreased incidence of Schistosoma-related diagnoses over months and years.

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Stephenson LS, Kinoti SN, Latham MC et al. Single dose metrifonate or praziquantel treatment in Kenyan children, I: effects on Schistosoma haematobium, hookworm, hemoglobin levels, splenomegaly, and hepatomegaly.