Community-based Treatment of Serious Bacterial Infections in Newborns and Young Infants

A Randomized Controlled Trial Assessing Three Antibiotic Regimens

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Background: Sepsis in the neonatal period is a major cause of child mortality in low-income countries. Hospitalization and parenteral penicillin/ampicillin and gentamicin therapy are recommended for management. Many families, however, are unable to access hospital care, and most home-delivered newborns who develop sepsis die without receiving antibiotic therapy. Appropriate community-based therapy in such situations is undefined. We compared failure rates of 3 clinic-based antibiotic regimens in 0- to 59-day-old infants with possible serious bacterial infection whose families refused hospitalization in Karachi communities with high neonatal mortality rates >45/1000 live births.

Methods: Eligible infants were randomly assigned to 7 days of: (1) procaine penicillin [50,000 units/kg once daily (OD) by intramuscular injection (IM)] and gentamicin (5 mg/kg OD IM) reference arm, (2) ceftriaxone (50 mg/kg OD IM), or (3) oral trimethoprim-sulfamethoxazole (TMP-SMX) at 10 mg/kg/day divided twice daily and gentamicin IM OD. Primary outcome was treatment failure, defined as death, deterioration in clinical condition during therapy or no improvement after 2 days.

Results: Possible serious bacterial infection was diagnosed in 704 infants, among 5766 screened. Among 434 (61.6%) randomized to clinic-based therapy, there were 13 of 145 failures with penicillin-gentamicin, 22 of 145 with ceftriaxone and 26 of 143 with TMP-SMX-gentamicin. Treatment failure was significantly higher with TMP-SMX-gentamicin compared with penicillin-gentamicin [relative risk 2.03, 95% confidence interval: 1.09–3.79] by intention-to-treat analysis. Differences were not significant in the ceftriaxone versus gentamicin [relative risk 2.03, 95% confidence interval: 1.09–3.79] by intention-to-treat analysis. Differences were not significant in the ceftriaxone versus gentamicin [relative risk 2.03, 95% confidence interval: 1.09–3.79] by intention-to-treat analysis.

Conclusion: When hospitalization of sick infants is unfeasible, outpatient therapy with injectable antibiotics is an effective option. Procaine penicillin-gentamicin was superior to TMP-SMX-gentamicin. Ceftriaxone is a more expensive option, and may be less effective, although this requires further research.

Key Words: neonatal sepsis, newborns, neonatal mortality, bacterial infections, young infants, community-based, antibiotic therapy, developing countries, procaine penicillin, gentamicin, trimethoprim-sulfamethoxazole, cotrimoxazole

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Serious bacterial infections are a major cause of neonatal mortality in South Asia and sub-Saharan Africa. An estimated one-fifth of all child deaths in Pakistan are due to neonatal infections. Current World Health Organization recommendations for management of sepsis in young infants (<2 months old) include hospitalization and parenteral antibiotic therapy for at least 10 days with a penicillin agent (eg, benzylpenicillin or ampicillin) combined with an aminoglycoside (eg, gentamicin). These guidelines are not feasible for many low-income countries including Pakistan, where a majority of births take place at home and hospital care is inaccessible for many families.4 In low-income communities in Karachi, approximately 70% of families refuse hospital referral for a sick young infant despite provision of free transport and hospitalization. Barriers to seeking hospital care include inefficient and poor quality health systems, logistic, cultural and economic constraints.6 As a result, most newborns with sepsis in Pakistan die without receiving appropriate antimicrobial therapy.

Bang et al7,12,15 have previously demonstrated significant reductions in neonatal mortality in rural India, using a home-based case management approach to treat neonates with suspected sepsis with oral trimethoprim-sulfamethoxazole (also known as cotrimoxazole) and intramuscular (IM) gentamicin for 7 days. Evidence from other studies using different antibiotic regimens such as cephalexin and amikacin, procaine penicillin and gentamicin3,15 and ampicillin and gentamicin1 for community-based management of neonatal sepsis in countries with high rates of home births and neonatal mortality is also supportive. However, which antibiotic regimen would be most efficacious for management of sick young infants with presumed sepsis in primary care or home settings is unknown. Lack of evidence on the optimal antimicrobial regimen for management of newborn sepsis outside of hospitals has hindered programmatic implementation and scale-up of sepsis management in community-based newborn care packages in areas with high neonatal mortality rates. There is, thus, an urgent need to define which antibiotic regimens are optimal for use at home or in first-level facilities for the management of neonates and young infants with sepsis in resource-poor areas where hospital care is inaccessible.10,16,17

Considerations in the choice of an appropriate antibiotic for such settings include adequate antimicrobial coverage against...
common neonatal pathogens, long half-life permitting once-daily (OD) dosing of injectable antibiotics, an established safety record in the neonatal period and cost implications.\textsuperscript{13,15} In this study we evaluated the effectiveness of IM ceftriaxone injection, and gentamicin injection combined with twice-daily oral trimethoprim-sulfamethoxazole (TMP-SMX), to IM procaine penicillin and gentamicin injections (reference treatment) given for 7 days in primary care clinics for the management of clinically diagnosed possible serious bacterial infection (PSBI) in young infants, 0–59 days old, whose families refused referral to a hospital.

MATERIALS AND METHODS

Study Setting and Subject Recruitment

Patients were enrolled at primary health care (PHC) clinics run by Aga Khan University’s Department of Pediatrics and Child Health in 3 low-income communities in and around Karachi between November 2003 and December 2005, where a household-based pregnancy and newborn surveillance network and PHC centers had been established. In these communities, >70% of births took place at home by unskilled birth attendants, neonatal mortality rates exceeded 45 per 1000 live births and there were no health facilities in which overnight inpatient care was available. The nearest hospital with neonatal services was located within 45–60 minutes driving distance. In contrast, the PHC clinics were located within a half-hour walk from the farthest households.

Trained community health workers (CHWs) visited newborns at home at regular intervals and referred any baby whose caretakers reported illness or who appeared sick to the local clinic for evaluation by a physician. Families residing in the area also sought care directly at these clinics for their sick infants because PHC is provided without charge. Eligible patients for the antibiotic treatment trial were infants 0–59 days of age who were evaluated at the PHC clinics and met the case definition of PSBI adapted from the Young Infants Clinical Signs Study as diagnosed by a physician\textsuperscript{20} (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B175), and whose family refused hospital referral despite counseling, provision of transport with a facilitator and free therapy at the hospital. Reasons for hospital refusal are documented elsewhere.\textsuperscript{4} Written/thumb imprint documentation of refusal of referral care and written informed consent to participate in the clinic-based trial were obtained from the family. Infants were excluded from the trial if the family refused injectable therapy, if signs of severe jaundice or clinically obvious meningitis were present, or if the patient had been previously enrolled in the same trial. Blood cultures were obtained from all infants whose family consented to have blood obtained. However, refusal for blood culture was not an exclusion criterion from the trial. One to three milliliters of blood was incubated in Peds Plus Bactec bottles in the Bactec 9240 system for 7 days. Bottles flagging positive for microbial growth were processed for evaluation by a physician. Families residing in the area also sought care directly at these clinics for their sick infants because PHC is provided without charge. Eligible patients for the antibiotic treatment trial were infants 0–59 days of age who were evaluated at the PHC clinics and met the case definition of PSBI adapted from the Young Infants Clinical Signs Study as diagnosed by a physician\textsuperscript{20} (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B175), and whose family refused hospital referral despite counseling, provision of transport with a facilitator and free therapy at the hospital. Reasons for hospital refusal are documented elsewhere.\textsuperscript{4} Written/thumb imprint documentation of refusal of referral care and written informed consent to participate in the clinic-based trial were obtained from the family. Infants were excluded from the trial if the family refused injectable therapy, if signs of severe jaundice or clinically obvious meningitis were present, or if the patient had been previously enrolled in the same trial. Blood cultures were obtained from all infants whose family consented to have blood obtained. However, refusal for blood culture was not an exclusion criterion from the trial. One to three milliliters of blood was incubated in Peds Plus Bactec bottles in the Bactec 9240 system for 7 days. Bottles flagging positive for microbial growth were processed per standard microbiologic practice.\textsuperscript{21}

Management Protocol

Infants who met the eligibility criteria were randomly assigned to receive 1 of 3 treatment regimens at the clinics: procaine penicillin 50,000 units/kg/day OD and gentamicin 5 mg/kg day OD, both by IM injections for 7 days; ceftriaxone 50 mg/kg/day OD by IM injection for 7 days; or oral TMP-SMX 10 mg/kg divided in twice-daily doses and gentamicin 5 mg/kg day OD IM injection for 7 days (Fig. 1). Block randomization in varying multiples of 3 stratified by site was done with a computer-generated list, and treatment group assignment was placed in opaque sealed envelopes that were opened sequentially by study physicians. The injectable antibiotics were administered at the clinics by study physicians according to infant’s group assignment. Oral TMP-SMX was given by the mother at home. Compliance was encouraged by daily community health worker visits to the house. If an infant was not brought for a scheduled follow-up visit, a community health worker visited the house within 2 hours of scheduled visit to bring the baby to the clinic. If the family refused to comply with a clinic visit, the study physician visited the baby at home to assess the baby and offer treatment at home. Blinding of treatment allocation was not possible in this study because of the varying number of injections. Acceptability of treatment regimens was an important secondary outcome of interest. Baseline characteristics were recorded at initial presentation (Table 1). On follow-up, clinical signs of illness and health status were recorded daily for 7 days, and also on day 14, on structured assessment forms to observe treatment success or failure.

The study was approved by Aga Khan University’s Ethical Review Committee, and an independent Data Safety Monitoring Board monitored the trial.

Study Outcomes

Treatment failure was the primary study outcome, defined as: (1) death at any time during the 7-day treatment period, (2) deterioration in clinical condition at any time after the start of therapy, or (3) no improvement after 2 days of therapy, necessitating antibiotic change. Deterioration was defined as development of ≥1 new clinical sign not present on initial presentation. Improvement was defined as resolution of at least 1 clinical sign documented on initial presentation. Clinical success of treatment was defined as patient cured (well) or improved with the regimen assigned on assessment at day 7 of therapy. Secondary outcomes included case fatality rates at 7 and 14 days after enrollment, relapse, withdrawal, therapy completion rates and adverse events. Relapse was defined as deterioration in clinical condition during the 7 days following end of therapy in a baby who was well or improved on day 7 of therapy. However, development of an illness unrelated to the presenting illness was not defined as a relapse. Withdrawal was defined as refusal of therapy after receipt of ≤ 2 days of assigned therapy or acceptance of hospitalization within 2 days of randomization. The cutoff of 2 days of therapy was arbitrarily chosen as the number of days and doses of antibiotic necessary before significant clinical improvement in the condition of the baby could reasonably be observed. Completion of therapy was defined as completing an entire 7-day course of therapy. Both withdrawal and completion reflected treatment acceptability by families. Adverse events were defined as the occurrence of bleeding or infection at an injection site, worsening of jaundice, development of rash or any other sign not associated with the natural history of disease during the course of therapy.

Statistical Analysis

Sample size was calculated for an equivalence study with procaine penicillin and gentamicin as the reference arm. Treatment success with procaine penicillin and gentamicin was expected to be 90% based on our observational experience in the field sites before the trial started, and equivalency was defined a priori as a difference of ≤ 10% in treatment failures at the end of 7 days of therapy compared with the penicillin and gentamicin group.\textsuperscript{22} An equivalence margin of 5% between experimental and reference therapy would have been more desirable but as this was conceived as a pilot study to inform a larger trial, an equivalence margin of 10% was deemed acceptable for this study. A sample size of 142 in each arm was needed to reject the null hypothesis of nonequivalence of ceftriaxone compared with procaine penicillin and gentamicin, and
of TMP-SMX and gentamicin compared with procaine penicillin and gentamicin, with a 2-sided \( \alpha \) error of 0.05 and 80% power. A sample size of 145 in each arm was planned to account for the small loss to follow-up expected by 7 days.

Differences between baseline characteristics of patients enrolled in the 3 arms were assessed using \( t \) tests or \( \chi^2 \) tests as appropriate using SPSS 16.0 (SPSS, Chicago, IL) software package. Outcomes were analyzed according to intention-to-treat (ITT) principles (all eligible patients assigned to treatment arms) as well as modified per-protocol principles (accounting for treatment withdrawal and protocol violations). Modified per-protocol was defined to include all infants who had received at least 2 full days of assigned therapy as this was considered to provide a substantial chance of treatment success, and we anticipated high dropouts in infants who were looking well by the third day of therapy. We calculated relative risk (RR) and 95% confidence intervals (CI) for treatment failure and case fatality rates. To determine factors associated with treatment failure at the end of 7 days, a multiple logistic regression analysis was undertaken for all baseline characteristics. Data were analyzed with Stata (version 9.2; StataCorp, College Station, TX). The study was registered with ClinicalTrials.gov, number 00189384.

**Role of Funding Source**

The sponsor provided technical input in study design and trial monitoring. However, the sponsor was not involved in subject recruitment, data collection and interpretation, or in data analysis or preparation of this manuscript.

**RESULTS**

**Patient Enrollment and Baseline Characteristics**

Among 5766 young infants 0–59 days old who were screened for eligibility (Fig. 1), PSBI was diagnosed in 704 (12.2%) infants. Of these, 155 (22%) accepted hospital referral, 98 (13.9%) refused trial participation, 17 (2.4%) were excluded for other reasons (eg, presence of suspected meningitis or severe jaundice) and 434 (61.6%) underwent randomization. Forty-six percent of infants were 0–6 days old, 26% were 7–28 days old and 28% were 29–59 days old. Infants randomized to the 3 arms were similar in baseline characteristics.
There was 1 protocol violation in the trial in which a baby assigned to receive TMP-SMX plus gentamicin actually received ceftriaxone and died during therapy without ever receiving TMP-SMX and gentamicin. In a modified per-protocol analysis, excluding all withdrawals and the infant with protocol violation, the TMP-SMX plus gentamicin group still had a higher treatment failure rate than the penicillin plus gentamicin group after 7 days of therapy (RR 1.84, 95% CI: 0.98–3.44), but did not reach statistical significance. However, at 14 days, the relative risk of death in infants treated with TMP-SMX and gentamicin was significantly higher (RR 4.78, 95% CI: 1.07–21.41) than those treated with procaine penicillin and gentamicin in the modified per-protocol analysis (Table 2).

### Other Secondary Outcomes

There were significantly more withdrawals [14 (9.7%)] in the penicillin plus gentamicin group compared with the ceftriaxone group [5 (3.4%)] (RR 2.80, 95% CI: 1.04–7.57) and the TMP-SMX plus gentamicin group [5 (3.5%)] (RR 2.76, 95% CI: 1.02–7.47). Excluding deaths, overall, only 59% of babies completed the full 7-day regimens. However, 75% completed at least 5 days of therapy. There was no significant difference among 7-day therapy completion rates in the 3 groups, with 84 of 143 (59%) completing 7 days of penicillin and gentamicin, 80 of 142 (56%) completing 7 days of ceftriaxone and 83 of 137 (61%) completing 7 days of TMP-SMX and gentamicin. There were no major adverse events noted in any of the groups. Two infants in the TMP-SMX plus gentamicin group exhibited worsening of jaundice but it was unclear whether this was related to therapy. No relapses were noted in the trial.

### Bacteriology

Blood for culture was obtained from 218 of 434 (50%) babies randomized, whose parents consented to venupuncture. Excluding contaminants, 11 of 218 (5%) blood cultures yielded a pathogen (Table 3). Eight isolates were gram-negative bacilli; the most common pathogen was *Pseudomonas aeruginosa* (4/11, 36%).

### Predictors of Treatment Failure

In univariate analysis using Mantel-Henzel odds ratios (OR), assessing the baseline variables (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B176), as well as whether an infant had a positive blood culture, only presence of prolonged capillary refill was a significant predictor of treatment failure (OR = 2.44, 95% CI: 1.33–4.48). The presence of lethargy on initial examination was marginally significant (OR = 2.99, 95% CI: 0.93–9.55; \(P = 0.05\)). In the multivariate analysis, the only clinical sign associated with treatment failure was a weak or absent cry (OR = 3.05, 95% CI: 1.36–6.87). The presence of local infections (skin or umbilical infection) on initial examination was associated with

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**TABLE 1.** Primary and Secondary Treatment Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Procaine Penicillin and Gentamicin, n (%)</th>
<th>Ceftriaxone, n (%)</th>
<th>TMP-SMX and Gentamicin, n (%)</th>
<th>Overall, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td>145</td>
<td>145</td>
<td>143*</td>
<td>433</td>
</tr>
<tr>
<td>Treatment failure at 1 week</td>
<td>13 (9)</td>
<td>22 (15.2)</td>
<td>26 (18.2)</td>
<td>61 (14.1)</td>
</tr>
<tr>
<td>Deaths at 1 week</td>
<td>2 (1.4)</td>
<td>3 (2.1)</td>
<td>7 (4.9)</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>Deaths at 2 weeks</td>
<td>2 (1.4)</td>
<td>3 (2.1)</td>
<td>11 (7.7)</td>
<td>16 (3.7)</td>
</tr>
<tr>
<td><strong>Modified per-protocol analysis</strong></td>
<td>131</td>
<td>140</td>
<td>137</td>
<td>408</td>
</tr>
<tr>
<td>Treatment failure at 1 week</td>
<td>13 (9.9)</td>
<td>22 (15.7)</td>
<td>25 (18.2)</td>
<td>80 (14.7)</td>
</tr>
<tr>
<td>Deaths at 1 week</td>
<td>2 (1.5)</td>
<td>3 (2.1)</td>
<td>6 (4.4)</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>Deaths at 2 weeks</td>
<td>2 (1.5)</td>
<td>3 (2.1)</td>
<td>10 (7.3)</td>
<td>15 (3.7)</td>
</tr>
</tbody>
</table>

*One infant was lost to follow-up and excluded from the analysis.

**TABLE 2.** Risk of Treatment Failure and Death on Ceftriaxone, and TMP-SMX Plus Gentamicin Regimens Compared With Procaine Penicillin and Gentamicin

<table>
<thead>
<tr>
<th></th>
<th>Ceftriaxone vs. Procaine Penicillin and Gentamicin</th>
<th>TMP-SMX and Gentamicin vs. Procaine Penicillin and Gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (95% confidence interval)</td>
<td>RR (95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td>Treatment failures 1.69 (0.89–3.23) 2.03 (1.09–3.79)</td>
<td>Treatment failures 1.58 (0.83–3.01) 1.84 (0.98–3.44)</td>
</tr>
<tr>
<td>at 1 week</td>
<td>Deaths at 1 week 1.50 (0.25–8.84) 3.55 (0.75–16.79)</td>
<td>Deaths at 1 week 1.40 (0.24–8.27) 2.87 (0.59–13.96)</td>
</tr>
<tr>
<td>Deaths at 2 weeks</td>
<td>1.50 (0.25–8.84)</td>
<td>5.58 (1.26–24.72)</td>
</tr>
</tbody>
</table>

**Modified per-protocol analysis**

|                      | Treatment failures 1.58 (0.83–3.01) 1.84 (0.98–3.44) | Treatment failures 1.40 (0.24–8.27) 2.87 (0.59–13.96) |
| at 1 week | Deaths at 2 weeks | 1.40 (0.24–8.27) | 4.78 (1.07–21.41) |

**RR** indicates relative risk; TMP-SMX, trimethoprim-sulfamethoxazole.

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**Characteristics** (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B176).

### Primary Outcomes

Therapy was successful at 7 days in 132 of 145 (91%) babies in the penicillin plus gentamicin group, 123 of 145 (85%) in the ceftriaxone group and 117 of 143 (82%) in the TMP-SMX plus gentamicin group (Table 1). Treatment failure was significantly higher in the TMP-SMX plus gentamicin group versus the penicillin plus gentamicin group (RR 2.03, 95% CI: 1.09–3.79) in the ITT analysis (Table 2). Differences were not significant in the penicillin plus gentamicin versus ceftriaxone comparison (RR 1.69, 95% CI: 0.89–3.23). There were 2 (1.4%) deaths in the penicillin plus gentamicin group, 3 (2.1%) in the ceftriaxone group and 7 (4.9%) in the TMP-SMX plus gentamicin group (all comparisons statistically nonsignificant).

On 14 days after enrollment, there were no additional deaths between 7 and 14 days of treatment in the penicillin plus gentamicin group or the ceftriaxone group; however, there were 4 additional deaths among babies who had failed therapy in the TMP-SMX plus gentamicin group, totaling 11 (7.7%) in this group (Table 1). The RR of death at 14 days after enrollment (ITT analysis) in the ceftriaxone group compared with the penicillin plus gentamicin group was 1.50 (95% CI: 0.25–8.84); the RR of death in the TMP-SMX plus gentamicin group at 14 days after enrollment compared with the penicillin plus gentamicin group was statistically significant at 5.58 (95% CI: 1.26–24.72) (Table 2).
higher odds of treatment failure (OR = 2.06, 95% CI: 0.94-4.49), but did not reach statistical significance.

**Mortality Outcome in Young Infants Where Families Refused Hospital Referral, Trial Participation and Injectable Antibiotic Therapy**

A case fatality rate of 11.2% (11 deaths) was observed 2 weeks after initial presentation among the 98 infants whose families refused clinic-based injectable therapy as well as hospitalization; among these, 64 (65%) accepted oral antibiotics and the remaining refused all care. The baseline characteristics of this group were similar to those who underwent randomization (data not shown). The RR of death after 14 days of diagnosis of possible sepsis among infants who did not receive any injectable therapy compared with babies who underwent randomization was 3.04 (95% CI: 1.46-6.34). Seven of the 11 deaths were among 34 infants whose families refused all antibiotics (oral as well as injectable antibiotic therapy) and opted for traditional faith-healer care.

**DISCUSSION**

Our results show that in primary care clinic-based treatment of PSBI in young infants, higher treatment failure rates were observed in infants who received TMP-SMX plus gentamicin therapy compared with procaine penicillin plus gentamicin therapy. Treatment outcomes were similar with ceftriaxone compared with procaine penicillin plus gentamicin, although a trend toward higher failure rates with ceftriaxone was noted. Although it is customary to report per-protocol analyses for equivalence trials, we have reported both ITT and per-protocol analyses as we did not find equivalence in the study arms, and the ITT analyses provide additional comparative information. The higher case fatality rate observed in the TMP-SMX plus gentamicin group has important implications for programmatic scale-up of community-based intervention packages for perinatal care. Based on our study results, TMP-SMX and gentamicin should be discouraged as a treatment regimen for suspected neonatal sepsis in community-based settings.

The most likely explanation for the higher treatment failure rates observed with TMP-SMX plus gentamicin is inadequate antimicrobial activity against gram-positive organisms causing neonatal sepsis such as streptococci, pneumococci and enterococci, which penicillin provides effective therapy against.

Our data also suggest that ceftriaxone may be less effective than combination treatment with penicillin and gentamicin. There are also legitimate concerns about indiscriminate use of ceftriaxone promoting antimicrobial resistance, especially extended-spectrum β-lactamase-producing gram-negative pathogens. Relative expense is another consideration. A 7-day course of injectable therapy with ceftriaxone costs $6.30 compared with $1.17 for procaine penicillin and gentamicin, a significant financial barrier to public health programs considering scale-up to national levels.

The major impediment to programmatic scale-up of IM procaine penicillin and gentamicin for management of sepsis in young infants is the difficulty of giving 2 injections daily to very small babies for 7 days. Among all babies randomized to this regimen, 10% withdrew from therapy after the first day. Study physicians also reported difficulties in injection preparation and delivery with procaine penicillin because the medication is viscous and difficult to dissolve.

Our study also demonstrates the high success rate that can be achieved with primary care clinic-based therapy of babies with suspected sepsis. A success rate of 91% was observed with procaine penicillin plus gentamicin, the best performing arm. It is possible that many babies enrolled in the trial had a self-resolving illness, and not bacterial sepsis, because the diagnosis was made on the basis of clinical signs. Blood cultures were positive for a pathogen in only 5% of young infants who had a blood culture. However, this isolation rate is consistent with that observed from blood cultures of newborns with suspected sepsis in industrialized countries as well as in other developing country studies. Moreover, only 704 of 5766 (12%) babies presenting with a complaint who were screened were given a diagnosis of possible serious bacterial infection.

Our study had several limitations. Blinding of therapy was not possible because of the observable differences in delivery of the 3 regimens. Also, assessment of treatment failure was subjective based on the presence or absence of clinical signs. The treating physician was also the assessor of treatment failure outcomes because we thought that he/she was the best judge of whether the baby had improved with therapy. However, the difference in death rates observed, a nonsubjective outcome, provides strength to our findings. Another limitation is that use of TMP-SMX was ascertained by mother/family member report when the baby was brought to the clinic, not directly observed.

Generalizability of our findings of high success rates with primary care clinic-based therapy for suspected sepsis in young infants may be affected by several factors. First, these results were obtained in a research setting with trained physicians using appropriate medication doses with a maximum effort to ensure compliance with therapy. In programmatic settings, actual compliance may be much lower. We also by design excluded infants with a clinical suspicion of meningitis, because it would have been unethical to randomize these babies to regimens with poor cerebrospinal fluid penetration. In addition, the infant group excluded from the trial whose families accepted hospital referral included a larger proportion of premature newborns with suspected sepsis in industrialized countries as well as in other developing country studies.

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**TABLE 3. Blood Culture Results Among Enrolled Infants**

<table>
<thead>
<tr>
<th>Pathogen name</th>
<th>Number with blood culture obtained</th>
<th>Ceftriaxone Group (n = 145)</th>
<th>Cotrimoxazole and Gentamicin Group (n = 144)</th>
<th>Total (n = 434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus pneumoniae</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus Group D</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>1</td>
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</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>2</td>
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<td>4</td>
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</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1</td>
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</tr>
<tr>
<td>Pseudomonas diminuta</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Acinetobacter baumanii</td>
<td>1</td>
<td>1</td>
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<td>1</td>
</tr>
</tbody>
</table>

*Contaminants have been excluded*
and low birth weight infants with multiple clinical signs of sepsis than those enrolled in the trial. Success rates with all 3 regimens may have been lower if all these babies were also included in the trial. Finally, generalizability of our findings to other settings could also be affected by local antimicrobial resistance patterns.

In the context of available evidence2,11,14,15,17,27 and the findings of this trial, OD injections of IM procaine penicillin and IM gentamicin for 7 days are the most effective regimen for management of suspected sepsis in young infants in settings with high neonatal mortality rates and poor access to hospital-based care. The role of oral antibiotics and shorter duration of parenteral therapy needs to be defined. Research to identify a simpler regimen is underway in multicenter studies in South Asia and sub-Saharan Africa.

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