Feasibility and efficacy of gentamicin for treating neonatal sepsis in community-based settings: a systematic review

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Meta-analysis

Background: **Neonatal sepsis is a leading cause of neonatal deaths in developing countries. The current recommended in-hospital treatment is parenteral ampicillin (or penicillin) and gentamicin in young infants for 10-14 days; however, very few could access and afford. The current review is to evaluate the feasibility of gentamicin in community based settings.**

Methods: **Both observational and randomized controlled trials were included. Medline, Embase, Cochrane Central Register of Controlled Trials and Central Trial Register of India were searched until September 2013. We assessed the risk of bias by Cochrane Collaboration's "risk of bias" tool.**

Results: **Two observational studies indicated feasibility ensuring coverage of population, decrease in case fatality rate in the group treated by community health workers. In an RCT, no significant difference was observed in the treatment failure rates [odds ratio (OR)=0.88], and the mortality in the first and second week (OR=1.53; OR=2.24) between gentamicin and ceftriaxone groups. Within the gentamicin group, the combination of penicillin and gentamicin showed a lower rate of treatment failure (OR=0.44) and mortality at second week of life (OR=0.17) as compared to the combination of gentamicin and oral cotrimoxazole.**

Conclusions: **Gentamicin for the treatment of neonatal sepsis is both feasible and effective in community-based settings and can be used as an alternative to the hospital-based care in resource compromised settings. But there was less evidence in the management of neonatal sepsis in hospitals as was seen in this review in which we included only one RCT and three observational studies.**

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Key words: **gentamicin;**
neonatal sepsis;
neonates

Introduction

Neonatal deaths (i.e. deaths within first 28 days of life) claim about 4 million lives each year globally. They account for about 41% of all deaths in children under the age of 5 years.[1,2] Almost all (99%) deaths occur in the developing countries with more than half in just five countries including India, Pakistan, China, Nigeria and the Democratic Republic of Congo.[3] Neonatal mortality rate in India (32 per 1000 live births in the year 2010) is among the highest in the world, contributing to one-fourth of the global burden.[4]

Neonatal sepsis is a clinical syndrome of bacteremia (probable or proven) characterized by systemic manifestations of infection in the first month of life. Neonatal sepsis encompasses systemic infections of the newborn including septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection of the newborn.[5] Treatment must be effective against the causative pathogen and safe for the newborn. World Health Organization's pocket book of Hospital Care for Children, currently recommends treatment with parenteral ampicillin (or penicillin) and gentamicin in young infants for 10-14 days.[6] These antibiotics are safe and retain efficacy when administered at extended intervals (e.g., twice daily or daily dosing)[7-9] The combination of aminoglycoside and penicillin has remained the treatment of choice for neonatal sepsis in many nurseries world-wide[10,11] and this combination has synergistic mechanism of action. It is hypothesized that management of neonatal sepsis at a community

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level by trained health workers would be important in reducing mortality and morbidity as it will be available at primary health centers (PHCs) and would prevent delays in institution of treatment just because of lack of access to hospital based care. So far, the use of gentamicin in community settings has not been commented upon and thus it becomes essential to do this review to figure out the feasibility of such an approach.

There are many potential concerns when we think of giving gentamicin in community settings. Firstly, gentamicin needs to be administered parenterally and thus it would require trained healthcare workers for administration. Secondly, gentamicin is a drug with low therapeutic index hence monitoring is essential after administration for any signs of toxicity. Further, gentamicin has to be given in combination with beta-lactams or cotrimoxazole. Thus, this review attempts to address all these questions and find answers to the queries by policy makers to make a rationale evidence-based policy decision. The primary objectives of the study are to assess the feasibility of community-based intervention program and to determine the effect of gentamicin on neonatal mortality caused by sepsis in community-based settings.

Methods

Search strategy

Two authors individually searched the literature, including both the electronic searches of Cochrane Central Register of Controlled Trials, Medline, Embase and cross references of retrieved relevant studies or reviews. We used the following MeSH terms or text words: gentamicin or gentamicins; sepsis, septicemia or septicemia; neonate, premature* or newborn; clinical trials, randomized controlled trials or observational studies.

The searches were current as of May, 2014. We also searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov and www.ctri.nic.in). Authors were contacted if it was felt that data additional to the published may be useful.

Study selection

Three authors independently reviewed the full text of articles or abstracts identified from the search to select trials, which fulfilled the inclusion criteria. They recorded reasons for excluding trials. They resolved any differences in the extracted data by consulting the other review authors. The authors settled any disagreement on article selection by consensus.

Inclusion criteria

We included observational studies and randomized or quasi-randomized or cluster-randomized controlled trials (RCT) published or unpublished (if data was provided by authors). Both blinded and unblinded studies were included. For the studies in abstract form or unpublished studies the authors made sincere attempts to obtain full details. Criteria for the participant selection were newborn babies from birth to 59 days of age with diagnosis of sepsis and/or severe bacterial infection requiring treatment in hospital or community regardless of the gestational age. The type of intervention included was parenteral gentamicin given along with other antibiotic (oral or parenteral) in a hospital or home based care for the treatment of neonatal sepsis.

Study outcomes

Primary outcomes

1) Percentage of coverage of target population;
2) Mortality in the first month of life;
3) Mortality at one and two weeks of life.

Secondary outcomes

1) Need for referral to higher center;
2) Treatment failure defined as the need to change empirical antibiotic therapy;
3) Superinfection (clinical signs of sepsis with isolation of a new pathogen or the same pathogen with different susceptibility);
4) Colonization with resistant bacteria;
5) Adverse events;
6) Cost of treatment;
7) Safety of the intervention.

Data extraction

Pilot tested data extraction forms were used to obtain the following information: study design, number and characteristics of participants, interventions, and outcomes. Three authors independently recorded the quality characteristics of each included study. Differences were removed by consensus. The details of the included studies are given in Supplementary Table 1.

Assessment of risk of bias in included studies

We assessed risk of bias in the study done by Zaidi et al,[12] using the Cochrane Collaboration's "risk of bias" tool on the basis of parameters like random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome, incomplete outcome data and selective outcome reporting. For each of these parameters, levels of risk were assessed as low, high and unclear.

For the observational studies we used the following parameters for assessment of risk of bias: Participants, missing data, incomplete outcome, selective reporting and methodology.

Measures of treatment effect

For the dichotomous outcomes, *n* (%) was used to calculate the odds ratio (OR) and 95% confidence intervals (CIs). For continuous outcomes, we recorded mean post-intervention values and standard deviation or standard error for each group. We planned to pool the data only if there were more than two studies for either randomized controlled trial or observational studies and the data were in a format which permitted pooling.

Dealing with missing data

In order to allow an intention-to-treat analysis, the authors sought data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Assessment of heterogeneity

It was planned to test heterogeneity using I^2 statistics. However, since only one RCT was found eligible, this could not be applied.

Results

We identified 49 studies through electronic and manual searching, out of which 8 studies were considered as potentially eligible. Only 3 studies were finally included for the review. One randomized controlled trial[12] qualified for inclusion in the review (Fig. 1). Three observational studies[13-15] were included for assessing feasibility. The RCT done by Zaidi et al[12] was a three arm study for our analysis. We pooled in the results of the two arms with gentamicin and compared it with group where ceftriaxone was given. Characteristics of the included and excluded studies are detailed in Supplementary Tables 1 and 2.

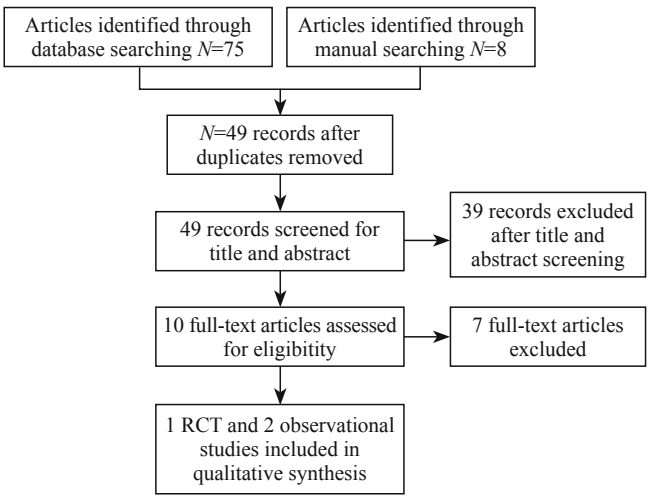

Fig. 1. Study flow diagram. RCT: randomized controlled trial.

The included RCT was identified as having a low risk of bias for the following parameters: randomization, allocation concealment, completeness of outcome data and selective reporting and high risk of bias for parameters of detection and performance bias (Supplementary Table 3, Figs. 1 and 2).

Out of three observational studies, two studies of Bang et al[15,16] were evaluated for the risk of bias and were identified as a low risk of bias (Supplementary Tables 4 and 5). Another study, Banqui et al assessed as one arm of the cluster randomized controlled trial, was used as a before and after design.

Two protocol designs of new RCT by Baqui et all[17] and Zaidi et al[18] were reviewed. It will be carried out in neonates and young infants with serious infections (0-59 days). Zaidi et al[18] will perform a trial in first-level facilities in Karachi, Pakistan while Baqui et al[17] has included both urban hospitals and rural settings.

Study outcomes

Primary outcomes

Percentage of coverage of target population

Percentage coverage of a target population was obtained from two field trials included in the study[13,14] Bang et al[16] studied the impact of gentamicin + cotrimoxazole among home based neonates in 39 villages for the period of 7 years (1993-2003) by voluntary health workers (VHWs) and it was found that out of 5919 neonates presented, 5510 were visited by VHWs, giving a coverage of 93.1%. But another observational study[14] had not described the percentage coverage of target population.

Mortality in the first month of life

Three observational studies[13,15,16] included in the review described mortality at first month of life. Bang et al[16] observed the case fatality rate (CFR) in untreated and treated neonates by village health workers by estimated gestational age, birth weight and age of diagnosis. The CFR was decreased in both term (62.1% reduction) and preterm infants (67.2% reduction) and a 71.9% reduction was noted in those who were under 2500 weight. For the age of diagnosis, they had observed the neonates for 4 weeks and an estimated 81% reduction in case fatality for both of the groups. Bang et al[16] in another field trial found that the CFR decreased from 16.6% to 2.8% after interventions by village health workers.

Baqui et al[13] observed CFR among the three groups divided on the basis of signs and symptoms observed by community health workers (CHWs) and estimated that the CHW treatment was associated with the lowest case

fatality rate (4.4%) as compared with other treatment types. It was also observed that no complications were reported with the CHW treatment and it had lowest hazard ratio (HR) for death in both adjusted (HR=0.13, 95% CI=0.06-0.26) and unadjusted analyses (HR=0.22, 95% CI=-0.07-0.71).

Mortality in the first and second week of life

Mortality in the first and second week of life was reported in a RCT and one observational study.[16] In the RCT, the percentage of patients dying in the first week was similar in the group receiving gentamicin as compared with the group receiving ceftriaxone (OR=1.53, 95% CI=0.41-5.73) (Fig. 2). Deaths at 2 weeks of treatment were also similar in the group which did not receive gentamicin (OR=2.24, 95% CI=0.63-7.98) (Fig. 3). The group received gentamicin in combination with two different antibiotics, i.e. procaine penicillin and trimethoprim-sulphamethoxazole. The two subgroups showed that the group receiving gentamicin in combination with procaine penicillin had 5 lesser deaths than those receiving gentamicin with trimethoprim -sulphamethoxazole after one week of treatment (Fig. 4). After 2 weeks of follow-up, there were significantly less number of deaths in those receiving a combination of gentamicin with procaine penicillin (Fig. 5). Whereas in the observational study, Bang et al[16] observed that after day of diagnosis till the first week, there was a 53.8% reduction in the CFR in neonates treated by VHWs.

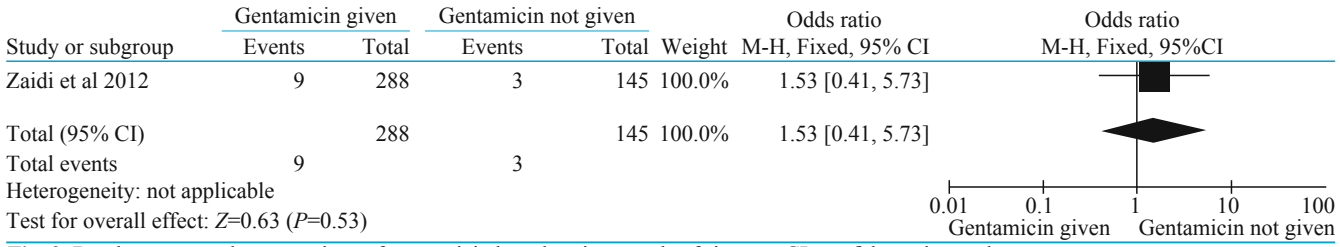

Fig. 2. Death at one week: comparison of gentamicin based regimen and ceftriaxone. CI: confidence interval.

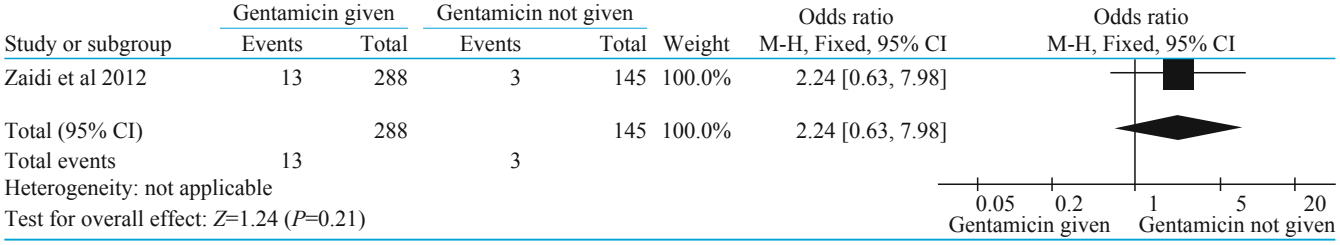

Fig. 3. Death at 2 week: comparison of gentamicin based regimen and ceftriaxone. CI: confidence interval.

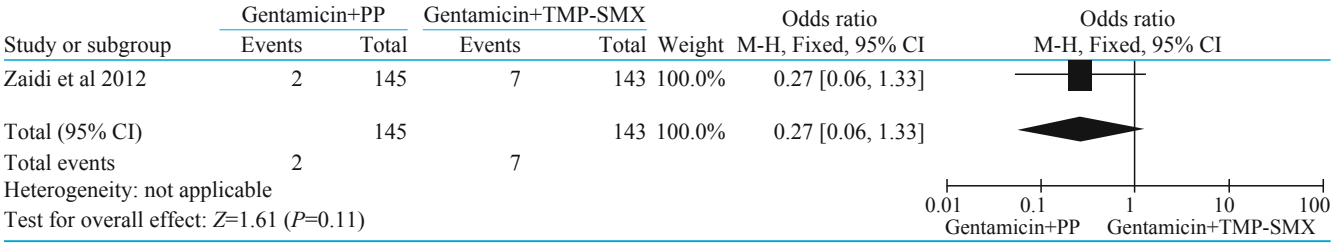

Fig. 4. Death at one week: comparison of gentamicin+PP and gentamicin+TMP-SMX. PP: procaine penicillin; TMP-SMX: trimethoprim-sulphamethoxazole; CI: confidence interval.

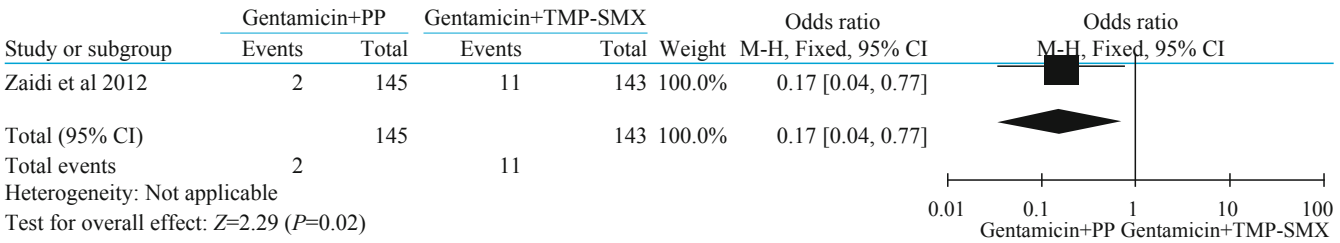

Fig. 5. Death at 2 week: comparison of gentamicin+PP and gentamicin+TMP-SMX. PP: procaine penicillin; TMP-SMX: trimethoprim-sulphamethoxazole; CI: confidence interval.

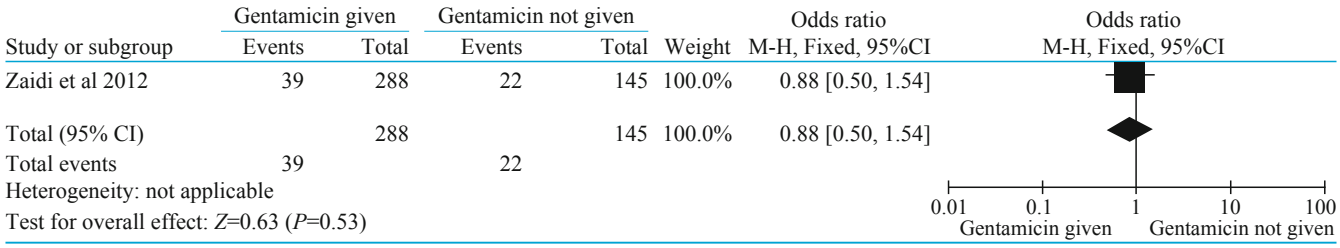

Fig. 6. Treatment failure rate: comparison of gentamicin based regimen and ceftriaxone. CI: confidence interval

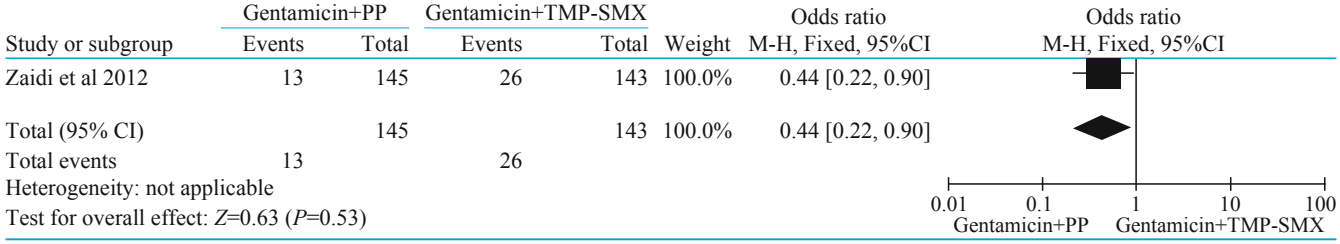

Fig. 7. Treatment failure rate: comparison of gentamicin+PP and gentamicin+TMP-SMX. PP: procaine penicillin; TMP-SMX: trimethoprim-sulphamethoxazole; CI: confidence interval.

Secondary outcomes

Need for referral to a higher center

One study reported such outcomes and it was an observational study.[13] It was reported that the rate for referral to the qualified medical providers was 34% for very severe disease, 25% for possible very severe disease with multiple signs, and 10% for possible very severe disease with single sign based on the signs observed and symptoms reported by caregivers.[13]

Treatment failure

Zaidi et al[12] reported that treatment failure rate in the group in which gentamicin was administered was not statistically significantly different from that in the group in which ceftriaxone was given (OR=0.88, 95% CI=0.5-1.5) (Fig. 6). Within gentamicin groups, treatment failure rates were significantly lower when it was given in combination with procaine penicillin than when given in combination with trimethoprim-sulphamethoxazole (OR=0.44, 95% CI=0.22-0.90) (Fig. 7).

No major adverse events were noted in any of the groups in the randomized controlled trial. Bang et al in their observational study[16] also did not find any neonates with injection related complications including infection at the injection site, hemorrhage, nerve injury or allergic rash. Cost evaluation was not done in the study.

Discussion

Neonatal sepsis can be treated effectively with gentamicin and penicillin in hospitals.[14] However the majority of neonates in the developing countries like India do not receive hospital care probably because they are not accessible to health services. Thus community based setting becomes particularly important but it should be evidence based. The lack of evidence was evident from our systematic review in which we could include only one RCT and three observational studies.

Three field trials were included for addressing the feasibility and effectiveness of such programs. These trials revealed that with the help of trained village health workers it was possible to cover more than 90% of the target population and correctly diagnose and treat around 89% of neonates with sepsis, thereby decreasing the fatality rate to 6.9% in contrast to 22% in the untreated neonates ($P<0.0001$).[14,15] Since both trials were conducted in community settings in the developing countries (Bangladesh, India) which are representative of real world situation compared to controlled conditions under which clinical trials are carried out. The inclusion of observational studies for evaluating such a program stands justified. Another important aspect shown in these studies is the acceptability of the medical community in the community up to 91%. Also there were no problems encountered by village health workers in giving the injectable treatment[13] and neither there was any increase in the injection related complications (such as injection site abscess, hematoma formation and nerve injury etc.) in neonates who received home-based care. Another point in favour of successful administration of injectable treatment by trained healthcare workers can be seen in immunization clinics at PHCs which have been widely accepted in our setup today. However, these studies have emphasized the need for developing

adequate training programs both for field workers and their supervisors for achieving optimal results.

Regarding the role of gentamicin in the treatment of neonatal sepsis, it was found that the treatment with gentamicin+oral cotrimoxazole/procaine penicillin was as effective as ceftriaxone in reducing neonatal deaths.[12] These findings can be extrapolated to our healthcare setup as the randomized controlled community-based trial was done in a developing country like ours. The maternal mortality rate was 260 deaths/100 000 live births and 200 deaths/100 000 in Pakistan and India respectively, and the infant mortality rate was 59.35 deaths/1000 live births and 44.6 deaths/1000 live births in Pakistan and India respectively.[19]

An important outcome that was evaluated was the need for referrals to the hospital. Since the study excluded those neonates who were in need of immediate hospitalization, management of such individuals cannot be commented upon in the present study.

Data from a limited amount of available evidence do suggest the promising role of gentamicin in treating neonatal sepsis and reducing the neonatal mortality rate. However, this agent is not given alone. Hence, an important issue is to make a choice of regimen. Both penicillin and co-trimoxazole have been used in combination with gentamicin. The regimens of co-trimoxazole could be argued for use in community-based settings for ease of administering it orally. Over a decade, however, resistance patterns have changed and this regimen may be not as effective as others. The option is that ceftriaxone alone can be used as another regimen. This agent again is injectable and should be given as an infusion. The cost of administration of gentamicin and penicillin versus ceftriaxone would be an important consideration. A further issue in consideration would be inconsistent availability of penicillin. The ongoing studies[18,19] will add more evidence to the community based management of neonatal sepsis.

It is evident from above discussion that gentamicin treatment for neonatal sepsis is both feasible and effective in community-based settings and can be used as an alternative to the hospital-based care in resource compromized settings with poorly functioning healthcare systems. However, there are a number of issues that need to be addressed before implementing such a program. First, it is necessary to find out cost and logistics involved in the training of healthcare workers and whether such training programs would prove to be cost effective in the long-term period or not. An approximation for the same can be obtained from an observational field study[15] which estimated that home-based care for each neonate with sepsis would cost around 5.3 US dollars (Rs 300). Secondly, it is imperative to identify what kind of health care workers (e.g., ASHA workers, village health workers) can be reliably trained and will be able to diagnose and manage neonatal sepsis in community settings. Thirdly, a rational choice of antibiotic regimen has to be made, and it needs to be validated in community settings so that we may not end up in increasing the problem of antimicrobial resistance.

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(Supplementary information is linked to the online version of the paper)