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Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-59 months in low resource settings: multicentre randomised controlled trial (SPEAR study)

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ABSTRACT

Objective To evaluate whether five days' treatment with injectable ampicillin plus gentamicin compared with chloramphenicol reduces treatment failure in children aged 2-59 months with community acquired very severe pneumonia in low resource settings.

Design Open label randomised controlled trial.

Setting Inpatient wards within tertiary care hospitals in Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen, and Zambia.

Participants Children aged 2-59 months with WHO defined very severe pneumonia.

Intervention Chloramphenicol versus a combination of ampicillin plus gentamicin.

Main outcome measures Primary outcome measure was treatment failure at five days. Secondary outcomes were treatment failure defined similarly among all participants evaluated at 48 hours and at 10 and 21 days.

Results More children failed treatment with chloramphenicol at day 5 (16% v 11%; relative risk 1.43, 95% confidence interval 1.03 to 1.97) and also by days 10 and 21. Overall, 112 bacterial isolates were obtained from blood and lung aspirates in 110 children (11.5%), with the most common organisms being *Staphylococcus aureus* (n=47) and *Streptococcus pneumoniae* (n=22). In subgroup analysis, bacteraemia with any organism increased the risk of treatment failure at 21 days in the chloramphenicol group (2.09, 1.41 to 3.10) but not in the ampicillin plus gentamicin group (1.12, 0.59 to 2.13). Similarly, isolation of *S pneumoniae* increased the risk of treatment failure at day 21 (4.06, 2.73 to 6.03) and death (5.80, 2.62 to 12.85) in the chloramphenicol group but not in the ampicillin plus gentamicin group. No difference was found in treatment failure for children with *S aureus* bacteraemia in the two groups, but the power to detect a

difference in this subgroup analysis was low. Independent predictors of treatment failure by multivariate analysis were hypoxaemia (oxygen saturation <90%), receiving chloramphenicol, being female, and poor immunisation status.

Conclusion Injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for the treatment of community acquired very severe pneumonia in children aged 2-59 months in low resource settings.

Trial registration Current Controlled Trials [ISRCTN39543942](http://www.ccrtrials.com).

INTRODUCTION

Pneumonia is a leading cause of death in under 5s in low resource settings.¹⁻³ Very severe pneumonia carries the highest mortality.⁴ First line treatment recommended by WHO is injectable chloramphenicol followed by oral chloramphenicol⁵ against the common bacterial pathogens: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and Gram negative bacteria such as *Escherichia coli*.^{6,7}

The increasing resistance of bacteria, particularly *H influenzae* and *S aureus*, to chloramphenicol adds to the concerns that it is bacteriostatic and associated with bone marrow toxicity, particularly in malnourished children.⁸⁻¹³ An alternative regimen being used in some areas, ampicillin plus gentamicin, is bactericidal and provides good coverage against *H influenzae*, *S pneumoniae*, *E coli*, and *Proteus mirabilis*.

Given the lack of evidence on regimens other than chloramphenicol, we carried out a multicentre study to determine if injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for the treatment of very severe pneumonia in children aged 2-59 months in seven developing countries.

METHODS

The primary outcome was treatment failure at five days. Secondary outcomes were treatment failure defined similarly among all participants evaluated at 48 hours and at 10 and 21 days. This randomised, non-blinded efficacy study was carried out at eight sites in seven countries: Bangladesh, Ecuador, India, Mexico, Pakistan (two sites), Yemen, and Zambia (see bmj.com).

Children were eligible for the study if they were aged 2-59 months, had a history of cough or difficulty breathing, had WHO defined very severe pneumonia,¹⁴ and had central cyanosis or were unable to drink. See bmj.com for exclusion criteria.

WHO prepared randomisation lists for each site by nutrition status (severely malnourished (see bmj.com) versus not severely malnourished), and each assignment was placed in an opaque sealed envelope. After each patient was selected, the next envelope in number order was opened: thus the investigator could not know the order of randomisation or predict the next assignment (see bmj.com for allocation concealment).

On admission to hospital the children underwent a physical examination, laboratory evaluations, and chest radiography, and a history was taken. Blood was obtained for complete blood count, blood glucose levels, and bacterial culture. Lumbar puncture was done on children with suspected bacterial meningitis, and we examined cerebrospinal fluid for total leucocyte count, differential leucocyte count, biochemistry, and bacterial culture by Gram stain.

Children received the first dose of antibiotics within two hours of enrolment. Children in the ampicillin plus gentamicin arm received ampicillin 200 mg/kg/d in four doses six hourly and gentamicin 7.5 mg/kg/d as one dose. Children in the chloramphenicol arm received 75 mg/kg/d in three doses eight hourly. Oxygen was provided for hypoxaemia ($\leq 90\%$, or $\leq 88\%$ in Yemen and Mexico, high altitude sites) for a minimum of three hours. Study doctors assessed the children every six hours. Each case of treatment failure and change in management was reviewed with the site clinical investigator.

Once children had completed five days of inpatient care and were improved enough for discharge they received ampicillin plus gentamicin as an outpatient. The parenteral gentamicin was given at the outpatient clinic or other venues. Follow-up was at 10-12 days and 21-30 days after discharge.

The primary outcome was treatment failure at five days. Secondary outcomes were treatment failure defined similarly among all participants at 48 hours and at 10 and 21 days. Any change in treatment after randomisation was classified as treatment failure.

Statistical analysis

We analysed the data using SAS software. PROC FREQ was used to calculate relative risks and 95% confidence intervals. To identify risk factors

predictive of treatment failure by day 5 and death by day 30, we calculated relative risks for a selected group of factors: immunisation status, sex, hypoxaemia (oxygen saturation $\leq 90\%$, or $\leq 88\%$ in the two high altitude sites in Mexico and Yemen), blood glucose, central cyanosis, age, weight for age z score, and breastfeeding status. We then included all variables with statistically significant relative risks in a multivariate logistic regression model built using a backward elimination procedure with PROC LOGISTIC. Treatment group and study site were forced into the model and we retained all variables with a Wald P value of 0.20 or less. We used the GLIMMIX macro to calculate the final multivariate models, in which study site was included as a random effect. Because diagnostics are not available for the random effects model we report model diagnostics (area under the receiver operating curve characteristic and Hosmer and Lemeshow goodness of fit test) for a fixed effects model.

RESULTS

Enrolment of children occurred between August 2000 and April 2004. Overall, 958 children aged 2-59 months with very severe pneumonia were randomised: 479 to ampicillin plus gentamicin and 479 to chloramphenicol (see bmj.com). The groups were similar at baseline. All randomised children were included in the intention to treat analysis for treatment failure at five days. Overall compliance with treatment was 95%.

Primary outcome

Of the 131 (13.6%) children who failed treatment by day 5, the cumulative rate was higher among those in the chloramphenicol group (relative risk 1.43, 95% confidence interval 1.03 to 1.97; table). Treatment failure most commonly resulted from a change in antibiotic ($n=71$), for several reasons (see bmj.com). Persistence or worsening of the pneumonia ($n=31$) was the second most common cause of failure. With the exception of persistence of very severe pneumonia, these outcomes occurred more commonly in the chloramphenicol group but only change in antibiotic treatment approached statistical significance.

Several factors were associated with treatment failure on univariate analysis: poor immunisation status, being female, hypoxaemia, and receiving chloramphenicol (see bmj.com). By multivariate analysis predictors of treatment failure were hypoxaemia, poor immunisation status, and being female (see bmj.com).

Secondary outcomes

Overall, 87 (9.1%) children had failed treatment at 48 hours (48% of cumulative number of treatment failures). An excess of children failed treatment in the chloramphenicol group compared with the ampicillin plus gentamicin group (54 *v* 33; relative risk 1.6, 95% confidence interval 1.1 to 2.5). With the exception of persistence of very severe pneumonia, the cumulative

number of children who failed treatment through days 10 and 21 remained higher in the chloramphenicol group, and the reasons remained similar to those observed at day 5 (table).

Deaths

Of the 65 deaths, 24 occurred in children after treatment failure had been declared for other reasons. In 46 cases (74%) the child died within 48 hours of enrolment. By univariate analysis poor immunisation status, being female, and hypoxaemia were associated with mortality, and by multivariate analysis these factors independently predicted mortality (see bmj.com).

Microbiology

Baseline bacteriological investigations were done on 471 children in the chloramphenicol group and 474 in the ampicillin plus gentamicin group. Of the 987 cultures undertaken at enrolment, 112 (two children had two organisms isolated) gave positive results for pathogenic organisms in all but one aspirate, from the

blood (see bmj.com). The two most common organisms were *Staphylococcus aureus* (n=47) and *Streptococcus pneumoniae* (n=22).

On sensitivity testing most of the *S pneumoniae* organisms were susceptible to chloramphenicol (13/14) or ampicillin (15/16), and all were susceptible to third generation cephalosporins. Only half (19/37) of the *S aureus* isolates exhibited in vitro susceptibility to chloramphenicol and 42% (16/38) to ampicillin.

Treatment failure in the presence of bacteraemia

Treatment failure at 21 days was significantly more likely if any bacteraemia was present at enrolment (see bmj.com). The size of the effect and the degree of statistical significance for treatment failure at 21 days and death increased in the presence of *S pneumoniae* bacteraemia, however, but was not associated with bacteraemia due to *S aureus*, irrespective of treatment.

In a subgroup analysis of children with bacteraemia stratified by treatment (see bmj.com), chloramphenicol

Cumulative treatment failures by specific causes at 5, 10, and 21 days and treatment arms for children aged 2-59 months with very severe pneumonia. Values are numbers (percentages) of children unless stated otherwise

Outcome	Cumulative treatment failure at 5 days			Cumulative treatment failure at 10 days			Cumulative treatment failure at 21 days		
	Chloramphenicol arm (n=479)	Ampicillin plus gentamicin arm (n=479)	Relative risk (95% CI)	Chloramphenicol arm (n=479)	Ampicillin plus gentamicin arm (n=479)	Relative risk (95% CI)	Chloramphenicol arm (n=479)	Ampicillin plus gentamicin arm (n=479)	Relative risk (95% CI)
Total	77 (16)	54 (11)	1.43 (1.03 to 1.97)	92 (19)	67 (14)	1.37 (1.03 to 1.83)	103 (22)	77 (16)	1.34 (1.02 to 1.75)
Persistence or worsening of very severe pneumonia	14 (3)	17 (4)	0.82 (0.41 to 1.65)	15 (3)	19 (4)	0.79 (0.41 to 1.54)	17 (4)	20 (4)	0.85 (0.45 to 1.60)
Death	15 (3)	9 (2)	1.67 (0.74 to 3.77)	15 (3)	9 (2)	1.67 (0.74 to 3.77)	15 (3)	9 (2)	1.67 (0.74 to 3.77)
Voluntary withdrawal	3 (1)	2 (0)	1.50 (0.25 to 8.94)	5 (1)	4 (1)	1.25 (0.34 to 4.63)	7 (1)	7 (1)	1.00 (0.35 to 2.83)
Antibiotic changed	45 (9)	26 (5)	1.73 (1.09 to 2.76)	57 (12)	35 (7)	1.63 (1.09 to 2.43)	64 (13)	41 (9)	1.56 (1.08 to 2.26)
Reason for changing antibiotic:*									
Persistence of one danger sign	18 (4)	9 (2)	2.00 (0.91 to 4.41)	18 (4)	9 (2)	2.00 (0.91 to 4.41)	18 (4)	9 (2)	2.00 (0.91 to 4.41)
Bacterial meningitis	3 (1)	2 (0)	1.50 (0.25 to 8.94)	3 (1)	2 (0)	1.50 (0.25 to 8.94)	3 (1)	3 (1)	1.00 (0.20 to 4.93)
Empyema	3 (1)	2 (0)	1.50 (0.25 to 8.94)	4 (1)	3 (1)	1.33 (0.30 to 5.93)	4 (1)	3 (1)	1.33 (0.30 to 5.93)
Septic shock	14 (3)	9 (2)	1.56 (0.68 to 3.56)	14 (3)	9 (2)	1.56 (0.68 to 3.56)	15 (3)	10 (2)	1.50 (0.68 to 3.31)
Renal failure	3 (1)	0 (0)	—	3 (1)	0 (0)	—	3 (1)	0 (0)	—
Serious adverse drug reaction	1 (0)	0 (0)	—	1 (0)	0 (0)	—	1 (0)	0 (0)	—
New comorbid condition	8 (2)	5 (1)	1.60 (0.53 to 4.86)	8 (2)	7 (1)	1.14 (0.42 to 3.13)	11 (2)	7 (1)	1.57 (0.61 to 4.02)
Oxygen saturation <90% on room air	n/a	n/a	n/a	7 (1)	5 (1)	1.40 (0.45 to 4.38)	13 (3)	9 (2)	1.44 (0.62 to 3.35)
Doctor's decision	6 (1)	5 (1)	1.20 (0.37 to 3.91)	14 (3)	10 (2)	1.40 (0.63 to 3.12)	14 (3)	10 (2)	1.40 (0.63 to 3.12)

*Participants could have only one reason for failure (persistence or worsening of severe pneumonia, voluntary withdrawal, death, or change of antibiotic). Participants could have more than one reason for change of antibiotic.

was associated with a higher risk of treatment failure at 5, 10, and 21 days. No increased risk of treatment failure was, however, found among children with bacteraemia in the ampicillin plus gentamicin group. The excess risk in the chloramphenicol group occurred in children with *S pneumoniae* bacteraemia, when treatment failure was three to four times more likely at any of the end points, and death was nearly six times more likely. Bacteraemia due to *S aureus* or *S pneumoniae* was not, however, associated with higher treatment failure or death in the ampicillin plus gentamicin group.

DISCUSSION

Children aged 2-59 months with very severe pneumonia were more likely to fail treatment with injectable chloramphenicol than with injectable ampicillin plus gentamicin. A trend to higher treatment failure in the chloramphenicol group was evident after 24 hours of treatment. Of particular concern are the adverse outcomes of treatment failure and death when children develop bacteraemia due to *S pneumoniae*. Although the most common isolate from sterile sites was *S aureus* we found that very severe pneumonia due to this organism may be adequately treated with chloramphenicol or ampicillin plus gentamicin. The high rate of *S aureus* in blood might have been a contaminant in some cases although we provided training in an aseptic technique, which was regularly monitored.

The clear benefit we observed among children receiving ampicillin plus gentamicin in the presence of *S pneumoniae* bacteraemia occurred despite a high degree of in vitro antimicrobial susceptibility to chloramphenicol and ampicillin. Only half of the *S pneumoniae* isolates were tested for antimicrobial sensitivity to the study drug, however, and it is possible that a high degree of resistance to chloramphenicol among the untested isolates accounts for our findings. Alternatively, in vitro antimicrobial susceptibility testing may not correlate closely with clinical outcome of bacterial pneumonia.¹⁵⁻¹⁸

S pneumoniae is one of the more common causes of meningitis—often occurring with pneumonia.¹⁹⁻²¹ It is possible that some participants who presented with very severe pneumonia due to *S pneumoniae* also had meningitis. Although no child with suspected meningitis was admitted to this study, in a previous trial of very severe pneumonia, 13% of a similar group of children had meningitis during the course of illness.²² In our study the bacteriostatic properties of chloramphenicol might have been insufficient to kill *S pneumoniae* organisms in the central nervous system, accounting for the higher failure and death rate in this group.²¹ Likewise, the bacteriostatic properties of chloramphenicol might have been insufficient to eradicate advanced infection of the lungs with *S pneumoniae* in children with very severe pneumonia.

Our rate of adverse treatment outcome is consistent with findings in a trial of benzylpenicillin plus gentamicin.²² The relative risk for an adverse outcome in that study was 1.14 (95% confidence interval 0.97 to 1.47), which falls within the 95% confidence limits of our results; however, we show a larger and statistically significant effect size, with a 43% relative improvement in treatment failure at five days and a greater than twofold better outcome among children with confirmed bacteraemia due to *S pneumoniae*. Moreover, the bacteriological data reported in the benzylpenicillin plus gentamicin trial were obtained once children failed initial treatment, whereas our samples were obtained before treatment.

Several baseline factors predicted treatment failure on multivariate analysis: poor immunisation status, being female, hypoxaemia, and receiving chloramphenicol. It is possible that poor immunisation status was a proxy for poor health seeking behaviour, which might have contributed to delay in seeking care, as evidenced by many deaths occurring within 48 hours of the children's presentation to hospital. Being female was independently associated with higher treatment failure and death, which is similar to other studies.²³⁻²⁵ Hypoxaemia at presentation was strongly associated with failure, as observed in other settings.^{22 26-29}

The strengths of this study are its randomised controlled design using one protocol across different paediatric populations in seven low income countries. The microbiological data also increase our understanding of the bacteria associated with WHO defined very severe pneumonia in these settings and permit us to determine the treatment failure and death rates by organism. Also, the low losses to follow-up in both groups (<1%) strengthen confidence in the outcomes and minimise classification error associated with an intention to treat analysis.

Limitations of the study are its non-blinded design, which may have introduced bias by doctors' determination of treatment failure, particularly for change in antibiotic. It was considered unethical to give placebo injections to tackle differences in inpatient antibiotic schedules, however, and it was not possible to adequately blind extra doctors to treatment assignment because of differences in outpatient antibiotic schedules. We therefore developed rigorous criteria for treatment failure, and monitored treatment failures to ensure that the study was being done according to protocol. Misclassification of pneumonia due to a bacterial cause may have also occurred owing to the non-specific nature of the definition of very severe pneumonia. Although this would tend to minimise our power to detect a difference in treatment groups, we did detect a statistically significant difference between chloramphenicol and ampicillin plus gentamicin. These findings have limited applicability in areas of high HIV prevalence, where the causes for pneumonia are different and include *Pneumocystis jiroveci*,^{30,31} an organism not covered by either study drug.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Community acquired very severe pneumonia has high mortality and is caused by a variety of bacterial organisms
Parenteral chloramphenicol is the standard treatment but has not been rigorously tested

WHAT THIS STUDY ADDS

Streptococcus pneumoniae and *Staphylococcus aureus* are the most common causes of very severe pneumonia
Ampicillin plus gentamicin is superior to chloramphenicol, especially against *S pneumoniae*

We believe that our study shows clinical superiority of injectable ampicillin plus gentamicin in the treatment of very severe pneumonia in children aged 2-59 months in an urban referral hospital setting, where patients with very severe pneumonia are expected to be treated. These findings have important implications for updating WHO's global guidelines for the case management of pneumonia, which until now have recommended chloramphenicol as the first line treatment for very severe pneumonia.

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Competing interests: None declared.

Ethical approval: This study was approved by the institutional ethical review committees at all study institutions, plus Boston University School of Public Health, Johns Hopkins University Bloomberg School of Public Health, and WHO. A data safety monitoring board reviewed cumulative data once a year. O'Brien Fleming stopping rules were used twice to determine the safety and utility of continuing the study.

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