Research

Failure of standard antimicrobial therapy in children aged 3–59 months with mild or asymptomatic HIV infection and severe pneumonia

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Objective To determine whether children aged 3–59 months with mild or non-symptomatic human immunodeficiency virus (HIV) infection and WHO-defined severe pneumonia have a higher failure rate than do HIV-uninfected children when treated with the standard WHO treatment of parenteral penicillin or oral amoxicillin.

Methods This study was a planned sub-analysis of a randomized trial of 3–59-month-old children presenting with WHO-defined severe pneumonia (the APPIS study). We included two sites with high HIV prevalence in Durban, South Africa and Ndola, Zambia. Primary outcome measures were clinical treatment failure at day 2 and day 14.

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Findings Of the 523 children enrolled, HIV status was known for 464 participants; 106 (23%) of these were infected with HIV. By day 2, 57 (12.3%) children had failed treatment and 110 (23.7%) failed by day 14. Twenty (18.9%) HIV-infected children failed by day 2 compared with 37 (10.3%) uninfected children (adjusted odds ratio (OR) 2.07; 95% confidence interval (CI): 1.07–4.00). Thirty-four (32.1%) HIV-infected children failed treatment by day 14 compared with 76 (21.2%) uninfected children (adjusted OR 1.88; 95% CI: 1.11–3.17). Analysis stratified by age showed that the greatest differential in treatment failure at day 2 and day 14 occurred in the children aged 3–5 months.

Conclusions HIV-infected children with severe pneumonia fail WHO-standard treatment with parenteral penicillin or amoxicillin at day 2 and day 14 more often than do HIV-uninfected children, especially young infants. Standard case management of acute respiratory infection (ARI) using WHO treatment guidelines is inadequate in areas of high HIV prevalence and reappraisal of empiric antimicrobial therapy is urgently needed for severe pneumonia associated with HIV-1.

Keywords Pneumonia/drug therapy; HIV infections; Infant; Child; Penicillins; Amoxicillin; South Africa; Zambia (*source: MeSH, NLM*).

Mots clés Pneumonie/chimiothérapie; Infection à VIH; Nourrisson; Enfant; Pénicillines; Amoxicilline; Afrique du Sud; Zambie (*source: MeSH, INSERM*).

Palabras clave Neumonía/quimioterapia; Infecciones por VIH; Lactante; Niño; Penicilinas; Amoxicilina; Sudáfrica; Zambia (*fuente: DeCS, BIREME*).

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Voir page 274 le résumé en français. En la página 274 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية في صفحة 275.

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Introduction

Acute respiratory infection (ARI) is the most common cause of hospitalization and death in children living in developing countries.[1,2] Nearly all of these ARI deaths are caused by pneumonia with case-fatality rates tenfold higher than those in developed countries.[3] However, in areas where WHO standard ARI case management has been implemented, mortality in infants and children under 5 years old has been greatly reduced.[4]

Before the widespread use of prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP; formerly known as *Pneumocystis carinii*) and highly active antiretroviral therapy, human immunodeficiency virus (HIV)-positive children in developed countries had a rate of ARI that was 5–10 times higher than HIV-negative children.[5] PCP has been identified in 10–49% of children with HIV-1 in Africa,[3,6–8] A recent autopsy study of Zambian children with HIV who died of a respiratory illness showed that pyogenic pneumonia was present in 39% of cases, but PCP (27%) and tuberculosis (19%) were nearly as frequent.[9] In the same study, PCP was found more commonly in infants aged 0–5 months (51%) than in those aged 6–11 months (26%).

The current WHO treatment guidelines for ARI were designed before the sharp rise in paediatric HIV infection in sub-Saharan Africa became evident, and they do not include empiric treatment for PCP. The benefits of these guidelines would be enhanced if they could also be applied (with modification) throughout areas with high rates of HIV infection and where the pneumonia burden is high, even in HIV-negative children.

We wanted to determine whether children with mild or non-asymptomatic HIV infection and WHO-defined severe pneumonia have a higher failure rate when treated with the standard WHO treatment of parenteral penicillin or an equivalent dose of oral amoxicillin compared with HIV-uninfected children.

In this trial, we analysed data from two sites in the large randomized clinical trial, the APPIS study.[10] We chose sites with high HIV prevalence and aimed to assess whether the WHO treatment guidelines could be applied to children with severe pneumonia in areas of significant HIV burden. The clinical responses of HIV-infected and HIV-uninfected children with WHO-defined severe pneumonia treated either with oral amoxicillin or parenteral penicillin are compared.

Methods

Trial design

The trial presented here is a planned subanalysis of data collected from two of the nine sites included in the APPIS study — a multicentre, open label randomized equivalency trial to compare the efficacy of oral amoxicillin with that of parenteral penicillin in children aged 3–59 months.[10,11] The two sites (Durban, South Africa and Ndola, Zambia) have high rates of HIV infection. Our goal was to assess whether HIV-infected children without overt (Class N) or mild (Class A) HIV symptoms[12] and with community-acquired severe pneumonia who are treated in accordance with standard WHO ARI case management guidelines[13] failed treatment more often than did HIV-uninfected children with severe pneumonia.

The trial design for the APPIS study has been described elsewhere.[11] In brief, between January 1999 and August 2001 children aged 3–59 months who presented with difficult breathing or cough, and lower chest wall indrawing were referred for enrolment. Researchers excluded children with very severe pneumonia (presence of danger signs), history of asthma, penicillin allergy, >48 hour antibiotic use, severe malnutrition (weight-for-age Z-score <–3), hospitalization in past 2 weeks, chronic cardiopulmonary condition, measles, or Centres for Disease Control HIV Clinical Stage B or C.[12]

Written informed consent for study enrolment was obtained from parents or guardians of all participants and ethics approval for the study was granted by the local and international sponsoring institutions. Same day testing of HIV-1 was offered to parents or guardians at the Durban, South Africa site if the study team judged that it was clinically warranted. In these instances, pre-test and post-test counselling were provided and specific consent for HIV testing was obtained. Same day HIV testing was not available at the Ndola, Zambia site.

Neither primary prophylaxis of PCP for children born to HIV-infected women nor inclusion of cotrimoxazole in the initial empiric therapy of community-acquired pneumonia were the standard of care at either site at the time of this study. The standard practice was to treat community-acquired pneumonia empirically, in accordance with WHO guidelines, and to add cotrimoxazole once therapy had appeared to fail. Initially, children who presented with evidence of mild HIV infection (hepatosplenomegaly or dermatitis) were not excluded from enrolment. Baseline assessment included a clinical history, physical examination, pulse oximetry, and nasopharyngeal and blood samples. HIV-1 infection was judged to be present in children older than 15 months with two positive HIV enzyme-linked immunoabsorbent assay (ELISA) antibody results (Axym H1/2gO, Abbott, Johannesburg, South Africa) or, in children younger than 15 months, a positive HIV DNA polymerase chain reaction (PCR) result (AMPLICOR, Roche Diagnostics, Basel, Switzerland).

Participants in the APPIS study were randomly assigned either amoxicillin syrup at 45 mg/kg per day in three doses or parenteral penicillin at 200 000 IU/kg per day in four doses for 2 days. The HIV status of participants had no part in the assignment of treatment. Standardized clinical evaluation, including pulse oximetry (Nellcor N-200-E, with N-25 sensor), was performed every 6 hours. Children who showed clinical improvement (disappearance of lower chest wall indrawing) or resolved were discharged with a 5-day course of oral amoxicillin with follow-up 5 and 14 days later.

We assessed participants for treatment failure at day 2 and day 14 using the definition reported in the APPIS study. At day 2, we judged that treatment had failed if there was a presence of danger signs (inability to drink, convulsions, and the patient being abnormally sleepy or difficult to wake), persistence of lower chest wall indrawing, saturated oxygen less than 80% on room air, serious adverse drug reaction, change in antibiotic therapy, newly diagnosed co-morbid condition, withdrawal from the trial, and/or death. Evidence of treatment failure by day 14 included having previously been declared a treatment failure, the presence of danger signs, lower chest wall indrawing, saturated oxygen less than 90% on room air, serious adverse drug reaction, change in antibiotic therapy, newly diagnosed co-morbid condition, withdrawal from the trial, or death. Relapse was defined as response to treatment by day 2, but subsequent development of

danger signs or re-emergence of lower chest wall indrawing by day 14. One of the two principal investigators or one of the study physicians made the assessment of treatment failure. All the researchers were unaware of participants' HIV status at the time of assessment for treatment failure. Deaths were included as study deaths if they occurred within 28 days of enrolment.

Data safety and monitoring board

Two formal interim analyses were conducted during the APPIS trial. At the second interim analysis an early (non-significant) trend towards a higher rate of early deaths was noted at the sites with high HIV prevalence (Durban and Ndola) compared with the other trial sites. Considering that these deaths might be due to clinically unrecognized HIV infection, the Data Safety and Monitoring Board recommended expansion of the exclusion criteria to exclude all children under 1 year of age with oral thrush, hepatosplenomegaly or who had a parent known to be infected with HIV. These changes to protocol were implemented after 286 (55%) of the participants at Durban and Ndola had been enrolled.

Data management and statistical analysis

Data were collected on case report forms and double entered into EPI Info version 6 and we used SAS Statistical Software (version 8.2; Cary NC, USA) for data analysis. We compared baseline characteristics using risk differences (RD) and 95% confidence intervals (CI) for categorical data and differences in means and 95% CI for continuous data. We report mortality using Kaplan–Meier estimates. Differences in mortality between HIV-infected and uninfected children were compared using the Kaplan–Meier log-rank test for equality between strata.

We used multivariate logistic regression analysis to determine the predictors of treatment failure and adjust for confounders. Three models were fit for failure at day 2 and day 14: model 1 included only HIV status; model 2 included HIV status, study site and treatment group; model 3 included baseline characteristics outlined in Table 1. The variables eligible for inclusion in the model were age, sex, up-to-date immunization status, antibiotics in the past 24 hours, weight-for-age Z-score, and temperature (Table 2). We included variables in the model if T derived from the likelihood ratio test was < 0.05. We did not include respiratory rate or low oxygen saturation in the model because we believe that these are consequences of HIV, and therefore inappropriate to treat as confounders.

Results

Between January 1999 and August 2001, 523 children with severe pneumonia were enrolled at the two sites (425 in Durban and 98 in Ndola) and 480 (91.8%) were tested for HIV. Forty-three participants (8.2%) refused HIV testing and 16 (3.0%) samples were lost. Baseline characteristics of children not tested for HIV did not differ significantly from those in children who were tested. The analysis presented here is restricted to the 464 participants with known HIV status. Mean age was 17 months (range 3–58 months) and there were more boys than girls enrolled (Table 1). 262 participants were randomly allocated to the penicillin group and 261 to the amoxicillin group. Of the 106 children (22.8%) who were HIV-positive, 82 were enrolled at the Durban site (22.4%) and 24 at the Ndola site (24.5%). HIV-infected children and HIV-uninfected children did not differ with respect to most, but not all, covariates that were found to be predictive of treatment failure in the main analysis. For example, HIV-infected children were more likely to have a weight-for-age Z-score less than –2 than were HIV-uninfected children. Likewise, HIV-infected children aged 3–11 months presented with higher respiratory rates than did children without HIV and they were more than twice as likely as HIV-uninfected children to present with low oxygen saturation at baseline.

Treatment failure

Overall, 57 of 464 children (12.3%) failed treatment at day 2 and the rate was significantly higher in the HIV-infected children (unadjusted OR 2.02; 95% CI: 1.11–3.65). A similar pattern of treatment failure was seen on day 14 (unadjusted OR 1.75; 95% CI: 1.08–2.83). Treatment failure at both day 2 and day 14 increased with age with 25% of infants aged 3–5 months having treatment failure. Nine participants failed to return for the day 14 follow-up visit.

The results of a multivariate logistic regression analysis (Table 2) show that HIV infection and male sex were associated with a higher risk of treatment failure at day 2 and day 14. Age is also associated with treatment failure; the youngest groups of children (3–5 months and 6–11 months) were both at much higher risk of treatment failure at day 2 than were the reference group (children aged 24–59 months). The 12–17 month and 18–23 month groups also had a higher risk of treatment failure at day 2 than did the reference group. For cumulative treatment failure by day 14 a similar pattern was noted, although the point estimates of the odds ratios are smaller and only the results of the 3–5 month-olds were not significant. In our analyses, treatment failure at day 2 and day 14 was independent of the drug administered and trial site. As we have noted in Methods, respiratory rate, and low oxygen saturation were both associated with failure in HIV-positive participants and were not included in the model. When we included children with unknown HIV status into this model, the odds ratios were not appreciably different from results that did not include participants with unknown HIV status.

Relapse

HIV-infected children who initially responded to treatment were no more likely to relapse (with non-severe or severe pneumonia) within 2 weeks than were HIV-negative children. Four of the 86 HIV-infected participants (4.7%) with an initial response to therapy relapsed by day 14 compared with nine of the 321 (2.8%) HIV-uninfected children (rate ratio (RR) 1.66; 95% CI: 0.52–5.26). We did not note a difference in relapse rates by treatment group within each HIV-infection-status group. All children who relapsed after completion of the initial antimicrobial treatment were successfully treated with either a broad-spectrum penicillin or cephalosporin and cotrimoxazole.

Mortality

The overall case-fatality rate in the 464 children was 2.2% (10 deaths). Eight (Kaplan–Meier estimate 3.5%) of these occurred in the penicillin group compared with 2 (Kaplan–Meier estimate 0.8%) in the group who received amoxicillin (log-rank test $P>0.05$). Mortality

Table 1. **Comparison of baseline characteristics of HIV-infected and HIV-uninfected children aged 3–59 months with WHO-defined severe pneumonia**

Characteristic	HIV-infected[a] (*n* = 106)	HIV-uninfected[a] (*n* = 358)	Risk difference (95% CI[b])	Difference in means (95% CI)
Age 3–11 months	45/106 (42.5%)	170/358 (47.5%)	−0.05 (−0.16 to 0.06)	–
Male	59/106 (55.7%)	200/358 (55.9%)	0.00 (−0.11 to 0.11)	–
Breastfeeding[c]	52/78 (66.7%)	218/293 (74.4%)	−0.08 (−0.19 to 0.04)	–
Immunizations up to date	103/105 (98.1%)	348/354 (98.3%)	0.00 (−0.03 to 0.03)	–
Antibiotics in the past 48 hours	6/106 (5.7%)	13/356 (3.7%)	0.02 (−0.03 to 0.07)	–
Weight-for-age Z-score < −2	20/106 (18.9%)	52/357 (14.6%)	0.04 (−0.04 to 0.13)	–
Low oxygen saturation				
3–11 months	11/45 (24.4%)	20/170 (11.8%)	0.13 (−0.01 to 0.26)	–
12–59 months	2/61 (3.3%)	18/188 (9.6%)	−0.06 (−0.12 to 0.00)	–
Randomly allocated amoxicillin	44/106 (41.5%)	190/358 (53.1%)	−0.12 (−0.22 to −0.01)	–
Durban study site	82/106 (77.4)	284/358 (79.3%)	−0.02 (−0.11 to 0.07)	–
Weight-for-age Z-score	−0.8 (1.4)[d]	−0.4 (1.5)[d]	–	−0.4 (−0.7 to −0.1)
Temperature (°C)	37.9 (1.1)[d]	37.6 (0.8)[d]	–	0.2 (0.0 to 0.4)
Respiratory rate per minute				
3–11 months	70.3 (15.7)[d]	65.6 (11.7)[d]	–	4.7 (0.6 to 8.8)
12–59 months	59.5 (9.8)[d]	59.4 (12.6)[d]	–	0.1 (−3.4 to 3.5)

[a] Data are *n*/total (%) unless otherwise indicated.
[b] CI = confidence interval.
[c] Denominators for breastfeeding are the number of children younger than 24 months.
[d] Data are mean (standard deviation).

was 2.3 times higher in HIV-positive participants than in uninfected children: 3.8% (4 of 106) versus 1.7% (6 of 358), (log-rank test $P = 0.19$). All six deaths in the HIV-uninfected group were in infants. Mortality was nearly the same in HIV-infected participants in the amoxicillin treated group (1 of 2) and the penicillin treated group (3 of 8).

Discussion

We have shown that rates of treatment failure for community-acquired severe pneumonia are substantially higher in HIV-infected children who have no or limited clinical signs of HIV infection than in HIV-negative children. In this subanalysis of data collected from two sites in a large multicentre equivalence trial, we observed that empiric treatment of severe pneumonia with injectable penicillin (WHO ARI treatment guidelines) or an equivalent oral medication for severe pneumonia resulted in a twofold higher failure rate at day 2 in HIV-infected children compared with uninfected children; and a higher failure rate persisted through to day 14. Moreover, we noted that most of this effect was seen in the 3–5 month and, to a lesser extent, the 6–11 month age groups of HIV-infected children than the older children. Infancy is well known to be associated with a worse prognosis for community-acquired pneumonia in children,[14,15] and this finding seems to be repeated in children with early signs of HIV infection. There were no discernable differences in treatment failure associated with HIV status in older children.

Pneumonia is one of the most common manifestations of HIV infection in children from both developed[5,6,16] and developing areas of the world.[7,17] While PCP is notably absent as a major cause of illness in HIV-infected adults in Africa, its role in paediatric pneumonia in children with HIV in Africa is now established.[9,18,19] Nevertheless, routine bacterial agents, such as *Streptococcus pneumoniae* are a more common cause of pneumonia in HIV-infected children.[3,9] Diagnostic capabilities in most developing-world settings are limited for both HIV infection and PCP, and children with respiratory infection are usually managed on the basis of clinical algorithms; there is a limited range of antimicrobials available and treatment is initiated without confirmation of HIV status. In this study we have shown that the empiric treatment of severe pneumonia with use of the WHO clinical treatment algorithm resulted in a substantially higher failure rate in HIV-positive children, despite our attempt to exclude children with a history or evidence of moderate or severely symptomatic HIV-disease.

Our findings suggest that infants with no previous symptoms or signs of HIV or with mildly symptomatic HIV infection were twice as likely to present with low oxygen saturation than were infants without HIV. This difference suggests that many of the HIV-infected children in this study probably had PCP, with the interstitial nature of this pneumonia[20] and the associated impairments in diffusing capacity compared with routine bacterial disease.

While the results reported here were analysed from two sites within a larger multicentre randomized equivalency trial where oral amoxicillin was shown to be as efficacious as injectable penicillin, the same conclusion can not be made with regard to this smaller subset of HIV-infected and uninfected children because of insufficient power to show equivalence. Another limitation of the APPIS trial was the use of a clinical case definition and clinical outcome that is not very specific for bacterial pneumonia. We attempted to minimize the proportion of participants with a non-bacterial cause for severe pneumonia by excluding children who resolved their lower chest wall indrawing after a course of bronchodilators. However, other non-

Table 2. **Multivariate logistic regression of the risk of treatment failure at day 2 and cumulative failure by day 14 in children aged 3–59 months with WHO-defined severe pneumonia**

	Failure rate	Model 1[a]	Model 2[a]	Model 3[a]
Failure at day 2				
HIV infection status				
Postive	20/106 (18.9%)	2.02 (1.11–3.65)	1.97 (1.06–3.66)	2.07 (1.07–4.00)
Negative	37/358 (10.3%)	1	1	1
Site				
Ndola	27/98 (27.6%)		4.39 (2.44–7.91)	3.24 (1.73–6.08)
Durban	30/366 (8.2%)		1	1
Treatment group				
Amoxicillin	24/234 (10.3%)		0.67 (0.37–1.20)	0.68 (0.37–1.25)
Penicillin	33/230 (14.4%)		1	1
Age group				
3–5 months	35/108 (25.4%)			22.71 (3.00–171.9)
6–11 months	11/97 (11.3%)			10.17 (1.27–81.63)
12–17 months	5/79 (6.3%)			5.45 (0.61–48.36)
18–23 months	5/60 (8.3%)			7.38 (0.83–65.90)
24–59 months	1/90 (1.1%)			1
Sex				
Male	40/259 (15.4%)			2.14 (1.11–4.10)
Female	17/205 (8.3%)			1
Cumulative failure by day 14				
HIV infection status				
Postive	34/106 (32.1%)	1.75 (1.08–2.83)	1.79 (1.08–2.94)	1.88 (1.11–3.17)
Negative	76/358 (21.2%)	1	1	
Site				
Ndola	43/98 (43.9%)		3.49 (2.16–5.66)	2.94 (1.76–4.91)
Durban	67/366 (18.3%)		1	1
Treatment group				
Amoxicillin	57/234 (24.4%)		1.10 (0.70–1.72)	1.12 (0.70–1.78)
Penicillin	53/230 (23.0%)		1	1
Age group				
3–5 months	55/138 (39.9%)			3.72 (1.76–7.83)
6–11 months	17/97 (17.5%)			1.35 (0.58–3.14)
12–17 months	18/79 (22.8%)			1.86 (0.80–4.33)
18–23 months	9/60 (15.0%)			1.19 (0.45–3.15)
24–59 months	11/90 (12.2%)			1
Sex				
Male	75/259 (29.0%)			2.09 (1.28–3.39)
Female	35/205 (17.1%)			1

[a] Data are odds ratio (95% confidence interval).

bacterial causes (e.g. viral) for tachypnea and lower chest wall indrawing were certainly present in our participants.

Other limitations of our findings were the lack of identification of specific bacterial causes of ARI in participants who failed treatment, the change in exclusion criteria part-way through the study, and the fact that the trial lacks sufficient power to show differences in failure rates between the HIV-infected and uninfected children aged 12–59 months.

We believe that our findings have important implications for the wide application of the WHO ARI treatment recommendations. The increase in treatment failure associated with asymptomatic or even mildly symptomatic HIV infection suggests that standard empiric therapy for severe pneumonia with injectable penicillin or oral amoxicillin in severe pneumonia is inadequate where HIV prevalence is high. However, this observation seems to apply only to infancy, which includes the period (age 6–9 months) of peak PCP prevalence.[21] This finding is supported by a 2002 autopsy study of HIV-infected children with fatal pneumonia which showed that PCP was the most common cause of illness in children aged 0–5 months and second most common cause in the 6–11 month age group.[9] The same authors report that beyond infancy either tuberculosis or pyogenic pneumonia are more common, indicating that oral amoxicillin could be used alone without significant additional risk for treatment failure if tuberculosis was not considered likely or was ruled out. In the interim, it is prudent to add cotrimoxazole coverage for PCP during initial empiric treatment of pneumonia in areas of high HIV prevalence, especially for

infants. Alternatively, a low threshold for the early addition of pneumocystis coverage seems warranted. For older children, coverage with cotrimoxazole may be less important, and antimicrobial medication with greater Gram-negative bacterial activity and anti-tuberculosis therapy should be considered for initial empiric treatment.

In areas of high HIV prevalence the best policy would be to minimize mother-to-child transmission of HIV, thus decreasing the population at risk of PCP. Alternatively, PCP prophylaxis for all infants exposed to HIV is an option, but this approach is controversial in areas where HIV testing is limited.[22,23] ■

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Competing interests: none declared.

Résumé

Échec du traitement antimicrobien standard chez des enfants de 3 à 59 mois présentant une infection à VIH peu virulente ou asymptomatique, ainsi qu'une pneumonie grave

Objectif Déterminer si le taux d'échec du traitement OMS standard utilisant la pénicilline par voie parentérale ou l'amoxicilline par voie orale de la pneumonie grave chez les enfants de 3 à 59 mois est plus élevé chez ceux présentant une infection à VIH peu virulente ou asymptomatique que chez ceux non contaminés par le VIH.

Méthodes La présente étude consistait en une sub-analyse planifiée d'un essai randomisé sur des enfants de 3 à 59 mois présentant une pneumonie grave selon la définition de l'OMS (étude APPIS). Elle a porté sur deux sites de forte prévalence du VIH à Durban, en Afrique du Sud, et à Ndola, en Zambie. Les principales mesures de résultat étaient l'échec du traitement aux jours 2 et 14.

Identifiant ClinicalTrials.gov : CT00227331http: //www.clinicaltrialsgov/show/NCT00227331).

Résultats On connaissait le statut VIH de 464 des 523 enfants recrutés et parmi les enfants de statut connu, 106 (23 %) étaient contaminés par le VIH. On a relevé 57 échecs thérapeutiques (12,3 % des enfants) au jour 2 et 110 (23,7 % des enfants) au jour 14. Vingt des enfants contaminés par le VIH (18,9 %) ont présenté un échec thérapeutique au jour 2 contre 37 (10,3 %) des enfants non infectés [odds ratio (OR) ajusté 2,07 ; intervalle de confiance à 95 % (IC) : 1,07 - 4,00. Trente-quatre (32,1 %) des enfants infectés par le VIH ont présenté un échec thérapeutique au jour 14 contre 76 (21,2 %) des enfants non infectés (OR ajusté 1,88; IC à 95 % : 1,11-3,17). L'analyse stratifiée par âge a fait apparaître que l'écart entre les taux d'échec thérapeutique au jour 2 et au jour 14 est maximal pour les enfants de 3 à 5 mois.

Conclusions Le traitement OMS standard de la pneumonie grave utilisant la pénicilline par voie parentérale ou l'amoxicilline a échoué plus souvent aux jours 2 et 14 chez les enfants contaminés par le VIH que chez ceux non infectés, en particulier dans le cas des jeunes enfants. La prise en charge standard des cas d'infection respiratoire aiguë (IRA) selon les directives de traitement OMS est inadéquate dans les zones de forte prévalence du VIH et il est urgent de réévaluer le traitement antimicrobien empirique des pneumonies graves associées au VIH-1.

Resumen

Fracaso de la terapia antimicrobiana estándar entre los niños de 3 - 59 meses con infección leve o asintomática por VIH y neumonía grave

Objetivo Determinar si los niños de 3 - 59 meses con infección leve o asintomática por el virus de la inmunodeficiencia humana (VIH) y neumonía grave según la definición de la OMS presentan una mayor tasa de fracaso terapéutico que los niños no infectados por el VIH al ser sometidos al tratamiento estándar de la OMS a base de penicilina parenteral o amoxicilina oral.

Métodos El estudio consistió en un subanálisis planificado de un ensayo aleatorizado de niños de 3 a 59 meses que desarrollaron neumonía grave según la definición de la OMS (estudio APPIS). Incluimos dos sitios con alta prevalencia de infección por VIH de Durban, Sudáfrica, y Ndola, Zambia. Las medidas de resultado principales fueron el fracaso del tratamiento clínico al cabo de 2 y 14 días.

Identificador ClinicalTrials.gov: CT00227331http://www.clinicaltrialsgov/show/NCT00227331).

Resultados De los 523 niños estudiados, se conocía la serología VIH de 464 participantes; de éstos, 106 (23%) estaban infectados por el virus. A los dos días, 57 niños (12,3%) no habían respondido al tratamiento, y a los 14 días éste había fracasado en 110 (23,7%). A los dos días, veinte (18,9%) niños infectados por el VIH no habían respondido al tratamiento, en comparación con 37 niños no infectados (10,3%) (razón de posibilidades (OR) ajustada: 2,07; intervalo de confianza (IC) del 95%: 1,07 - 4,00). Treinta y cuatro (32,1%) niños infectados por el VIH no habían respondido al tratamiento a los 14 días, en comparación con 76 (21,2%) entre los niños no infectados (OR ajustada de 1,88; IC95%: 1,11 - 3,17). El análisis estratificado por edad mostró que la mayor diferencia en cuanto a fracaso terapéutico en los días 2 y 14 se dio en los niños de 3 - 5 meses.

Conclusión Los niños seropositivos con neumonía grave responden al tratamiento estándar de la OMS con amoxicilina o penicilina parenteral a los 2 y 14 días con menos frecuencia que los seronegativos, sobre todo en el caso de los lactantes de corta edad. El tratamiento estándar de los casos de infección respiratoria aguda (IRA) conforme a las directrices terapéuticas de la OMS es inadecuado en las zonas de alta prevalencia de infección por VIH, lo que aconseja reevaluar urgentemente la terapia antimicrobiana empírica contra la neumonía grave asociada al VIH-1.

ملخص

فشل المعالجة المعيارية بمضادات المكروبات لدى أطفال تــتراوح أعمارهم بين 3 و59 شهراً مصابين بعدوى فيروس العوز المناعي البشري غير المصحوبة بالأعراض مع التهاب رئوي وخيم

الهدف: معرفة فيما إذا كان الأطفال الذين تــتراوح أعمارهم بين 3 و59 شهراً والمصابين بعدوى خفيفة أو غير مصحوبة بأعراض بفيروس العوز المناعي البشري مع التهاب رئوي وخيم وفقاً لتعريف منظمة الصحة العالمية، لديهم معدلات مرتفعة لفشل المعالجة أكثر من غيرهم من غير المصابين بالعدوى بفيروس العوز المناعي البشري، إثر المعالجة المعيارية التي توصي بها منظمة الصحة العالمية أو بالبنسيلين حقناً أو بالأموكسيسيلين الفموي.

الطريقة: خططنا لإجراء تحليل تلوي لدراسة معشاة شملت الأطفال الذين تــتراوح أعمارهم بين 3 و59 شهراً ممن ظهرت لديهم أعراض التهاب رئوي وخيم وفقاً لتعريف منظمة الصحة العالمية (وهي دراسة APPIS). وقد تضمَّنت دراستنا موقعين يرتفع فيهما معدل انتشار العدوى بفيروس العوز المناعي البشري في ديربان، في جنوب أفريقيا، وفي ندولا، في زامبيا. وتناولت القياسات الحصائل الأولية لفشل المعالجة في اليومين الثاني والرابع عشر.

الدليل التعريفي الحكومي للتجارب السريرية (الإكلينيكية): CT00227331http://www.clinicaltrialsgov/show/NCT00227331

الموجودات: من بين الأطفال الذين انخرطوا في الدراسة، عرفت حالة 464 أطفال منهم من حيث العدوى العوز المناعي البشري، فقد كان 106 منهم (23%) مصابين بعدوى فيروس العوز المناعي البشري. وبحلول اليوم الثاني من المعالجة، فشلت المعالجة لدى 57 طفلاً منهم (12.3%) فيما فشلت المعالجة لدى 110 أطفال منهم (23.7%) بحلول اليوم الرابع عشر. وقد فشلت المعالجة في اليوم الثاني لدى 20 طفلاً (18.9%) من الأطفال المصابين بعدوى فيروس العوز المناعي البشري بالمقارنة مع 37 طفلاً من غير المصابين بعدوى فيروس العوز المناعي البشري (10.3%) وكان معدل الأرجحية المصحَّح 2.07، فيما كانت فترة الثقة 95% إذْ تراوح معدل الأرجحية المصحَّح بين 1.07 و4.00. وفي اليوم الرابع عشر فشلت المعالجة لدى 34 طفلاً مصاباً بعدوى فيروس العوز المناعي البشري (32.1%) وذلك بالمقارنة مع 76 طفلاً من غير المصابين بفيروس العوز المناعي البشري (21.2%)، وكان معدل الأرجحية المصحَّح 1.88، فيما كانت فترة الثقة 95% ، إذْ تراوح معدل الأرجحية المصحح بين 1.11 و3.17. وقد أظهر التحليل ذي الطبقات الموزعة حسب العمر أن أكبر التفاضل في فشل المعالجة في اليوم الثاني واليوم الرابع عشر قد حدث لدى الأطفال الذين تــتراوح أعمارهم بين 3 و5 سنوات.

الاستنتاج: تفشل المعالجة بالبنسيلين حقناً أو بالأموكسيسيلين الفموي لدى الأطفال المصابين بعدوى فيروس العوز المناعي البشري مع التهاب رئوي وخيم وفقاً لمعايــير منظمة الصحة العالمية في اليومين الثاني والرابع عشر أكثر مما تفشل لدى الأطفال غير المصابين بعدوى فيروس العوز المناعي البشري، ولاسيَّما بين صغار الأطفال. إن التدبير المعياري للالتهاب التنفسي الحاد باستخدام الدلائل الإرشادية لمنظمة الصحة العالمية للمعالجة غير كاف في المناطق التي ترتفع فيها معدلات انتشار العدوى بفيروس العوز المناعي البشري، وتمس الحاجة إلى إعادة تقيــيم المعالجات التجريبية بمضادات المكروبات للالتهاب الرئوي المتصاحبة بعدوى فيروس العوز المناعي البشري.

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