Randomised, controlled trial of effectiveness of ampicillin in mild acute respiratory infections in Indonesian children.

Permalink
https://escholarship.org/uc/item/2dq9j3hc

Journal
Lancet (London, England), 338(8765)

ISSN
0140-6736

Authors
Sutrisna, B
Frerichs, RR
Reingold, AL

Publication Date
1991-08-01

DOI
10.1016/0140-6736(91)90544-y

Peer reviewed
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
the findings obtained in necropsy studies. Information collated from five independent necropsy studies indicated that mean prostate weight reaches 20 g in men between the ages of 21 and 30 years and remains essentially constant at this weight with increasing age unless BPH develops. Table II summarises the prevalence rates of BPH and prostatic weights of patients with BPH in the survey in comparison with necropsy findings among men in similar age-groups with histologically confirmed BPH. A surprising finding is that prostatic weights from these two sources are remarkably similar despite the differences in self-selection between the community survey and necropsy sources, the absence of prior knowledge of urinary dysfunction in the necropsy cases, and the absence of pathological confirmation of the diagnosis in the community survey. What is also of interest are the higher age-specific rates for BPH in the necropsy than in the community survey. This difference suggests that a substantial reservoir of BPH may exist below the “threshold” of signs and symptoms of urinary dysfunction that were used in the survey. The operational definition adopted for this survey will probably change over time as knowledge of the natural history of BPH increases, in the way that perception of what level of blood pressure constitutes hypertension has changed over the past several decades.

Whether the total urinary symptom score and \( \frac{Q_{\text{max}}}{Q_{\text{voided}}} \) cut-off points used are ideal for enabling early cases of BPH to be picked up through screening cannot be established from this survey. This issue can be determined only in a study that sets out to assess prostate size in a representative sample of men who have not been selected on the basis of their likelihood of having BPH. The validity of symptom scores and voiding flow rate as preliminary screening criteria will eventually be required for identifying those men most likely to benefit from treatment should non-surgical therapy for BPH be shown to be effective in the community.

We thank the consultant urologists and other staff of Stirling Royal Infirmary, the general practitioners and their staff at Bridge of Allan Health Centre, the Forth Valley General Practitioner Research Group, and all other members of the BPH Natural History Study Group for their advice, cooperation, and support. Funding for this work was provided by Merck, Sharp & Dohme.

REFERENCES
1. Graves EJ. Detailed diagnosis and procedures. National Hospital Discharge Survey. 1987. National Center for Health Statistics, Washington DC. Vital and Health Statistics 1989; 13: 295.
2. Jensen KM-E, Jorgensen JB, Morgensen P, et al. Some clinical aspects of uroflowmetry in elderly males. A population study. Scand J Urol Nephrol 1986; 20: 93–97.
3. Glynn RJ, Campion EW, Bouchard GR, et al. The development of benign prostatic hyperplasia among volunteers in the Normative Aging Study. Am J Epidemiol 1985; 121: 78–90.
4. Meyhoff HH, Hald T. Are doctors able to assess prostatic size. Scand J Urol Nephrol 1978; 12: 219–21.
5. Fowler FJ, Wenneberg JE, Timothy RP, et al. Symptom status and quality of life following prostatectomy. JAMA 1988; 259: 3018–22.
6. Rowan D, McKenzie AL, McNeice SG, et al. A technical and clinical evaluation of the Disa uroflowmeter. Br J Urol 1977; 49: 285–91.
7. Griffiths CJ, Murray A, Ramsden PO. A simple uroflowmeter tester. Br J Urol 1983; 56: 21–24.
8. Jensen KM-E, Jorgensen JB, Morgensen P. Reproducibility of uroflowmetry variables in elderly males. Urol Res 1985; 13: 237–39.
9. Abu-Yousef MM, Narayana AS. Transabdominal ultrasound in the evaluation of prostate size. J Clin Ultrasound 1982; 10: 755–78.
10. Berry SJ, Coffey DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. J Urol 1984; 132: 474–79.
11. Watanabe H. Natural history of benign prostatic hypertrophy. Urolntrn Med Biol 1986; 12: 567–71.

Randomised, controlled trial of effectiveness of ampicillin in mild acute respiratory infections in Indonesian children

BAMBANG SUTRISNA  RALPH R. FRENCHS  ARTHUR L. REINGOLD

The recommended treatment for mild acute respiratory infections (ARI) in children is supportive care only, but many physicians, especially in developing countries, continue to prescribe antibiotic treatment because they believe it prevents progression to more severe ARI. To find out whether ampicillin treatment conferred any benefit over supportive care alone, a randomised, controlled trial was carried out among 889 children (under 5 years) with mild ARI in Indonesia. 447 were randomly allocated ampicillin (25–30 mg/kg body weight three times daily for 5 days) plus supportive care (continued breastfeeding, clearing of the nose, and paracetamol to control fever); 442 were allocated supportive care only. The treatment groups were almost identical after randomisation in terms of age, sex, level of parental education, history of measles immunisation, and fever. After 1 week the percentages cured were nearly identical (204 [46%] ampicillin; 209 [47%] control), as were the percentages of cases progressing to moderate ARI (56 [13%] vs 53 [12%]). The effect of treatment was not modified by age, sex, measles immunisation status, or the educational level of the parents. At the 2-week follow-up, the percentages cured were 62% (277) in the ampicillin group and 58% (256) in the control group; 14% of both groups had progressed to moderate ARI; and 24% (107) and 28% (123), respectively, still had mild ARI. None of the differences in outcome between the ampicillin and control groups was statistically significant. Thus, ampicillin plus supportive care offers no benefit over supportive care alone for treatment of mild ARI in young Indonesian children.

Lancet 1991; 338: 471–74.

Introduction

Acute respiratory infections (ARI) are common in children throughout the developing world. The infection...
may start in the upper respiratory tract and progress to a more severe lower respiratory infection, such as pneumonia or bronchiolitis. In less developed countries, pneumonia is a major cause of death in young children. Antibiotics such as procaine penicillin, ampicillin, or co-trimoxazole are useful for treatment of pneumonia which is most commonly caused by bacterial agents, mainly Streptococcus pneumoniae and Haemophilus influenzae. Antibiotics are not recommended for treatment of upper respiratory infections, which are believed to be caused mainly by viruses, most likely rhinoviruses and coronaviruses.

The World Health Organisation (WHO) has promoted case-management as the appropriate approach to control of ARI in children. Part of this recommendation is that supportive care by the mother rather than antibiotics be used to treat mild ARI. Inappropriate treatment of mild ARI in developing countries wastes the resources of government-sponsored health services and is believed to increase the occurrence of drug-resistant bacterial strains in the population.

When the WHO case-management programme was introduced in Indonesia, many physicians were reluctant to stop giving antibiotics to children with mild ARI, because they believed that antibiotic treatment prevents the progression of mild ARI to moderate or severe ARI. This belief is not supported by any objective evidence. We decided to test the effectiveness of antibiotics for treatment of mild ARI in Indonesian children. We now present the results from a randomised, controlled comparison of supportive care alone and ampicillin plus supportive care as treatment for mild ARI in children under 5 years of age.

Subjects and methods

900 children under 5 years of age with mild ARI, who attended government health clinics in two regions of East Jakarta, Indonesia, were included in the trial. Mild ARI was defined by WHO criteria: mild upper respiratory signs such as cough or runny nose, and/or fever (>37°C), and breathing at a rate less than 50 breaths per minute. We excluded children with asthma or infections that required antibiotics, those who did not live in a defined service area, and those who had recently been treated by medical personnel in other locations. Parental consent was obtained for all eligible children.

Through random allocation, 451 children were offered ampicillin powder and supportive care and 449 were offered only supportive care. Parents in both groups were advised to provide supportive care at home including continuation of breastfeeding, clearing of the nose as needed, and control of mild fever by means of paracetamol, an inexpensive analgesic and antipyretic drug (30 mg/kg body weight daily; 3 doses per day for 5 days). In addition to the supportive care, children in the ampicillin group received ampicillin powder (age-dependent treatment packets of 25-30 mg/kg body weight per dose every 6 h [except midnight] for 5 days).

Parents were asked to bring their child back to the health centre after 5 days. Home visits were made by nurses or midwives within 2 days to children who did not appear at the clinic on the scheduled day. Based on the clinic or home examination the health status was classified as: cured or recovered; static (no change); worse (moderate or severe ARI); or dead. Moderate and severe ARI were defined according to WHO and Ministry of Health criteria. Moderate ARI was diagnosed if there was a respiratory rate greater than 50 breaths per minute but no chest indrawing, and severe ARI if the child had a respiratory rate greater than 50 breaths per minute and chest indrawing, with or without cyanosis. Children not cured after 1 week were either referred to the health clinic for further medical care or sent home with instructions for additional supportive care. All children were observed by a nurse or midwife 1 week later either at the clinic or at home.

Results

The randomisation procedure successfully achieved two nearly identical groups in terms of the potential confounding variables of age, sex, level of parental education, history of measles immunisation, or fever at the time of enrolment (table I). After 1 week, the percentages of children who were cured, still had mild ARI, or had progressed to moderate ARI in the two groups were almost identical (table I). There was no significant difference in the course of the disease between the ampicillin-treated and control groups at either 1-week follow-up (χ² = 0.25, 2 df; p = 0.64) or 2-week follow-up (χ² = 1.91, 2 df; p = 0.38) (table II). After 1 week the percentage cured was similar at all ages, in both sexes, at various education levels for fathers and mothers, and by measles immunisation status (table III). Amoxicillin appeared beneficial only among a few subgroups, but in each case the 95% confidence intervals included 1.0, so the risk ratios are more likely to reflect variation inherent in the sampling process rather than a real benefit of amoxicillin.

Table I: Characteristics of children with mild ARI at baseline

| Age (mo) | Ampicillin (n = 451) | Control (n = 449) |
|---------|---------------------|------------------|
| 0-11    | 173 (38)            | 155 (35)         |
| 12-23   | 118 (26)            | 121 (27)         |
| 24-35   | 66 (15)             | 93 (21)          |
| 36-59   | 94 (21)             | 80 (18)          |

Table II: Clinical outcome of mild ARI

| Day 5-7 | Day 14 |
|---------|-------|
| Cured   | 204 (46) | 277 (62) |
| Static  | 187 (42) | 107 (24) |
| Worse (moderate ARI) | 56 (13) | 63 (14) |

The World Health Organisation (WHO) has promoted case-management as the appropriate approach to control of ARI in children. Part of this recommendation is that supportive care by the mother rather than antibiotics be used to treat mild ARI. Inappropriate treatment of mild ARI in developing countries wastes the resources of government-sponsored health services and is believed to increase the occurrence of drug-resistant bacterial strains in the population.
TABLE III—MILD ARI CASES CURED AT 1-WEEK FOLLOW-UP

|                | Ampicillin | Control |
|----------------|------------|---------|
|                | No (%)      | No (%)  |
|                | cured at    | cured at|
|                | day 5-7     | day 5-7 |
| **Risk ratio* (95% CI)** |            |         |
| **Age (mo)**   |            |         |
| 0-11           | 65 (38)    | 52 (26) |
| 12-35          | 96 (53)    | 86 (46) |
| 36-59          | 43 (46)    | 81 (51) |
| **Sex**        |            |         |
| Male           | 102 (45)   | 101 (46)|
| Female         | 102 (46)   | 101 (48)|
| **Father’s education (yr)** |      |         |
| <9             | 54 (41)    | 56 (41)|
| ≥9             | 150 (48)   | 128 (44)|
| **Mother’s education (yr)** |      |         |
| <9             | 101 (46)   | 112 (48)|
| ≥9             | 103 (46)   | 97 (47)|
| **Immunised for measles** |   |         |
| Yes            | 91 (52)    | 74 (43)|
| No             | 109 (42)   | 131 (50)|

*Likelihood of being cured in ampicillin group compared with control group; 95% CI = confidence interval

Excludes 21 cases with unknown measles immunisation history (12 ampicillin, 9 control)

The percentage of cases of mild ARI that progressed to moderate ARI at the 1-week follow-up was also similar in the various subgroups (table IV). In some subgroups the control cases were more likely to progress, whereas in others the ampicillin-treated cases were more likely to become worse. The width of the confidence intervals makes it unlikely that any of the group-specific values are truly different.

After 2 weeks, 24% of ampicillin-treated and 28% of control children still showed signs of mild ARI (table II). 14% in each group had progressed to moderate ARI and were referred to the health clinic for additional care. The remaining 58% of controls and 62% of ampicillin-treated children were cured of ARI, and nearly three-quarters of them had recovered during the first week.

TABLE IV—PROGRESSION TO MODERATE ARI AT 1-WEEK FOLLOW-UP

|                | Ampicillin | Control |
|----------------|------------|---------|
|                | No (%) with moderate ARI at day 5-7 | No (%) with moderate ARI at day 5-7 |
|                |            | Risk ratio* (95% CI) |
| **Age (mo)**   |            |         |
| 0-11           | 19 (11)    | 155 (18) |
| 12-35          | 22 (12)    | 207 (14) |
| 36-59          | 15 (16)    | 80 (9)   |
| **Sex**        |            |         |
| Male           | 26 (12)    | 231 (23) |
| Female         | 30 (11)    | 211 (24) |
| **Father’s education (yr)** |      |         |
| <9             | 14 (11)    | 148 (10) |
| ≥9             | 42 (13)    | 39 (10)  |
| **Mother’s education (yr)** |      |         |
| <9             | 24 (11)    | 234 (22) |
| ≥9             | 32 (14)    | 208 (25) |
| **Immunised for measles** |   |         |
| Yes            | 17 (10)    | 172 (18) |
| No             | 31 (14)    | 261 (33) |

*Risk of progression to moderate ARI in ampicillin group compared with control group

Excludes 21 cases with unknown measles immunisation history (12 ampicillin, 9 control)

Discussion

The randomisation process in our study effectively created two groups with the same inherent risk of ARI outcome independent of treatment. Thus, we were able to assess the unconfounded effect of ampicillin plus supportive care compared with supportive care alone on mild ARI. We conclude that there is no beneficial effect of ampicillin on the clinical course of mild acute respiratory infections among young Indonesian children. For children breathing less than 50 times per minute and showing minor signs such as a cough or runny nose, addition of ampicillin to simple supportive care supplemented with paracetamol conferred no benefit.

Since mild ARI is primarily or entirely caused by viruses, our finding that ampicillin is of no benefit for such illnesses is hardly surprising, and readers might wonder why we undertook this study. In our previous work on ARI in Indonesia (unpublished), we observed that many children with mild ARI were being treated with ampicillin by physicians at Government clinics despite the Ministry of Health guidelines (which accord with WHO recommendations) that only supportive care is required.14 In our discussions with physicians, it became clear that many believed antibiotics were effective at preventing the progression of mild ARI to pneumonia or other forms of severe ARI, which are frequently bacterial in origin. When challenged to present data refuting this notion, we were unable to find support in the Indonesian medical or public health literature. Thus, we felt it necessary to assess in Indonesia the effect of antimicrobial therapy on progression of mild ARI to more severe forms. Clinical studies of antibiotic effectiveness have been carried out in other nearby countries—for example, Thailand and Australia.15,16 These studies of children with upper (or mild) respiratory infections showed no therapeutic value for ampicillin, erythromycin, penicillin, or tetracycline.

Although our data clearly show that the use of ampicillin for mild ARI had no beneficial effect, what is not evident is the potential harmful effects of inappropriate antibiotic use. First, ampicillin used for mild ARI will not be available to treat moderate or severe ARI. If there is a limited supply of antibiotics, as is the case in many government health clinics, the resultant shortage could lead to the use of less effective treatment and higher case-fatality for moderate and severe ARI. Even if antibiotics are widely available, use of ineffective treatment for many mild ARI cases will substantially reduce the cost-effectiveness of ARI treatments in general. Second, routine use of antibiotics for common disorders such as mild ARI may contribute to the emergence of drug-resistant bacterial strains, which may become difficult, if not impossible, to treat. In a study of susceptibility of Haemophilus species to antimicrobial drugs, 6% of 426 isolates from around the world were resistant to ampicillin.6 Although this percentage is not great, continued indiscriminate use of antibiotics for minor respiratory ailments can only lead to more resistance.

In summary, our results show that there is no justification for use of ampicillin to treat mild ARI among Indonesian children. This practice is both expensive and potentially harmful and is not in the interests of the medical community, the Ministry of Health, or the Indonesian people.

This study was supported by the United States Agency for International Development through subcontractual agreements with the Center for Human Services (PRICOR); Center for Child Survival, University of...
Indonesia; and the Western Consortium for Public Health, Inc. We thank Prof M. C. Steinhoff for helpful comments.

REFERENCES

1. Stansfield SK. Acute respiratory infections in the developing world: strategies for prevention, treatment and control. Pediatr Infect Dis J 1987; 6: 622-29.
2. Kalter HD, Gray RH, Black RE, Gultiano SA. Validation of postmortem interviews to ascertain selected causes of death in children. Int J Epidemiol 1990; 19: 380-86.
3. Spika JS, Munshi MH, Wojtyniak B, et al. Acute lower respiratory infections: a major cause of death in children in developing nations. Am J Trop Med Hyg 1986; 35: 1-2.
4. Weinberg GA, Spitzer ED, Murray PR, et al. Antimicrobial susceptibility patterns of Haemophilus isolates from children in eleven developing nations. BOSTID Haemophilus Susceptibility Study Group. Bull WHO 1990; 68: 79-84.
5. Campbell H, Bypass P, Forgie IM, O'Neill KP, Lloyd-Evans N, Greenwood BM. Trial of co-trimoxazole versus procaine penicillin with ampicillin in treatment of community-acquired pneumonia in young Gambian children. Lancet 1988; ii: 1182-84.
6. Spika JS, Munshi MH, Wojtyniak B, et al. Acute lower respiratory infections: the leading cause of death in children in developing countries. Am J Trop Med Hyg 1986; 35: 1-2.

Phylogeny of the Whipple's-disease-associated bacterium

KENNETH H. WILSON
RHONDA BLITCHINGTON
RICHARD FROTHINGHAM
JOANNE A. P. WILSON

Efforts to culture and identify the intracellular bacteria associated with Whipple's disease have been unsuccessful. Nucleotide sequencing and amplification by the polymerase chain reaction was done on the bacterial 16 S ribosomal DNA present in a small-bowel biopsy specimen taken from a patient with Whipple's disease. A search by computer for the bacterial 16 S ribosomal DNA present in a biopsy specimen taken from a patient with Whipple's disease has not been identified previously in a patient with Whipple's disease.

Whipple's disease is a systemic infection associated with a small, largely intracellular bacillus of uncertain identity.

The nature of the Whipple's bacillus has not been established because efforts to culture the organism have been unsuccessful. We report the results of sequencing the ribosomal DNA of the predominant bacterium associated with a biopsy taken from the small bowel of a woman with Whipple's disease. Comparison of 16 S rRNA sequences is a powerful approach to phylogenetic analysis, and had led to a new phylogenetic tree of all life forms. It was thus possible to place the Whipple's-associated bacterial organism (WABO) phylogenetically by comparing its 16 S rRNA sequence with known sequences.

A 70-year-old woman presented with a 1-year history of diarrhoea, a 9 kg weight loss, and iron-deficiency anaemia. She complained of abdominal distension, arthralgia, fatigue, and myalgia. On physical examination the patient was cachectic with a distended abdomen and thickening of the metacarpals and wrists. X-ray examination of the small bowel suggested malabsorption, and an abdominal computed tomography scan revealed paracaval and periaortic lymphadenopathy. Upper gastrointestinal endoscopy showed a bowel mucosa with a granular infiltrated pattern. Histologically, the small bowel lamina propria was expanded by foamy macrophages and had prominent lymphatic dilatation. Material in the macrophages stained periodic acid-Schiff-positive and did not contain acid-fast organisms. Electron microscopy showed large numbers of intracellular and extracellular bacilli characteristic of those found in Whipple's disease.