Antibiotic Strategies for Developing Countries: Experience with Acute Respiratory Tract Infections in Pakistan

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The Pakistan program for control of acute respiratory tract infections (ARIs) adopted the standard ARI-case-management strategy of the World Health Organization and recommended co-trimoxazole for the management of nonsevere pneumonia. Reports in that country of high in vitro antimicrobial resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* to co-trimoxazole prompted the program to reevaluate its treatment policy. Two community-based studies during 1991–1993 showed in vivo efficacy of co-trimoxazole in 92% and 91% of children with nonsevere pneumonia. A third double-blind trial showed co-trimoxazole and oral amoxicillin to be equally effective in vivo in cases of nonsevere pneumonia, despite high in vitro resistance. Country-wide surveillance from 1991 to 1994 revealed 78.3%–79.9% in vitro resistance to co-trimoxazole among *S. pneumoniae* isolates and 59.5%–61.0% among *H. influenzae* isolates. Co-trimoxazole is still recommended by the Pakistan ARI control program. The fact that amoxicillin is three times more expensive and must be administered more frequently is a big impediment to recommending it as a first-line drug for nonsevere pneumonia.

Etiologic studies of acute lower respiratory tract infections carried out in Pakistan during the late 1980s documented the important role of *Streptococcus pneumoniae* and *Haemophilus influenzae* as the causative agents of pneumonia in hospitalized children [1–4]. There were two important findings reported. First, there were very high rates of *S. pneumoniae* and *H. influenzae* bacteremia in children hospitalized with pneumonia. Second, a high proportion of these invasive isolates were resistant to co-trimoxazole [2–4]. Forty-three percent of blood isolates of *H. influenzae* and 31% of those of *S. pneumoniae* had reduced in vitro susceptibility to co-trimoxazole, with an MIC of >4 µg/L. In 1989 the government of Pakistan implemented a national acute respiratory infection (ARI) control program based on the standard ARI-case-management guidelines of the World Health Organization (WHO) [5]. The program selected oral co-trimoxazole to treat outpatient nonsevere pneumonia.

Pediatricians expressed concerns about the program’s recommendation of co-trimoxazole for nonsevere pneumonia, because of the reported resistance rates for *H. influenzae* and *S. pneumoniae*. In considering whether to change its recommendations, the program considered the following factors. (1) There was no evidence that in vitro resistance to co-trimoxazole resulted in failure of therapy in cases of nonsevere pneumonia. (2) Amoxicillin, the alternative antibiotic, was 3 times more expensive and needed to be administered 3 times a day (instead of 2 times for co-trimoxazole). (3) Changing national recommendations would mean retraining health care workers, which would be time-consuming, difficult, and expensive. Prior to making a decision and because of concerns that the effectiveness of the national ARI control program might become compromised because of increasing microbial resistance to co-trimoxazole, the program launched several focused applied-research projects. These included four studies of clinical efficacy as well as surveillance activities for documenting antimicrobial resistance patterns of *S. pneumoniae* and *H. influenzae* nasopharyngeal isolates. In one clinical efficacy study, antimicrobial resistance patterns of *S. pneumoniae* and *H. influenzae* blood isolates were also tested. The objectives of these research activities were to document changes in the patterns of antimicrobial resistance of *S. pneumoniae* and *H. influenzae* and to establish the relationship between in vitro resistance and clinical failure rates with ARI case management.

The objective of this article is to review the data from Pakistan ARI studies and discuss the implications for national ARI control programs and future ARI research.

Methods

We reviewed six clinical efficacy and antimicrobial resistance surveillance studies conducted after 1989 in Pakistan in collaboration with or under the auspices of the Pakistan ARI control program to answer the research questions outlined above. Two published studies [6, 7] and other scientific work...
Table 1. Comparison of data from trials of the clinical efficacy of co-trimoxazole in children with pneumonia who were 2–59 months old.

<table>
<thead>
<tr>
<th>Year(s) of study, reference</th>
<th>Setting</th>
<th>WHO ARI category: no. (%) of patients</th>
<th>In vitro resistance of isolates to co-trimoxazole (%)</th>
<th>In vivo response (%)</th>
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<tbody>
<tr>
<td>1991–1992 [7]*</td>
<td>Hospital (double-blind, randomized, controlled trial)</td>
<td>Pneumonia, nonsevere: 293 (49.2) Pneumonia, nonsevere: 302 (50.8)</td>
<td>Pneumonia, nonsevere: (H.) influenzae, 2/12 (16.7); (S.) pneumoniae, 3/13 (23.1)</td>
<td>Pneumonia, nonsevere: 169/195 (86.7); amoxicillin, 86/98 (87.8)</td>
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<td>1995–1996 [10]</td>
<td>Outpatient and community (double-blind, randomized, controlled trial)</td>
<td>Pneumonia, nonsevere: 1,040</td>
<td>Not tested</td>
<td>Double dose, 405/510 (79.4); standard dose, 428/530 (80.8)</td>
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NOTE. ARI = acute respiratory infection; WHO = World Health Organization.
* The resistance level MIC was \(\geq 1\) \(\mu g/mg\).
\(^{\dagger}\) Only 242 nasopharyngeal isolates were tested by the disk-diffusion method; for co-trimoxazole, the resistance level (zone of inhibition) was <10 mm.

Results

Clinical Efficacy Studies

Four clinical studies conducted from 1991 to 1996 have been summarized in table 1. All these studies primarily used the ARI diagnostic categories developed by the WHO for standard ARI-case management [5]. The first study was conducted over a 4-month period in rural Islamabad, where special clinics were established, and all children with ARI during that period were followed up at the clinics or at home [6]. For a further 18 children (3.7% of 491) assessed initially as not having pneumonia, pneumonia was diagnosed on follow-up visits, and they were successfully treated with co-trimoxazole.

Clinical failure was defined by the following factors: the respiratory rate did not improve after 48 hours of treatment; breathing became more difficult or faster; or one or more of the following was noted: chest indrawing, inability to drink, convulsions, stridor in a calm child, abnormal sleepiness, and death. The clinical failure rate was defined as the number of children needing a change of therapy or dying, among those who had WHO-defined nonsevere pneumonia at the time of initial assessment. The clinical failure rate was only 8.4%, with no deaths. No bacteriology was carried out in this study.

The second study, a double-blind, randomized, controlled trial, was carried out in Islamabad/Rawalpindi during the 1991–1992 ARI season (October–April). It included children whose illness was diagnosed according to the WHO ARI diagnostic categories of nonsevere pneumonia (49.2%) and severe pneumonia (50.8%) [7]. One-hundred thirty-one children (22.0%) were bacteremic. Therapy failure in cases of nonsevere pneumonia was defined by oxygen saturation of <87% for >30 minutes when the child was calm; prolonged tachypnea when calm (a respiratory rate of >20 above the age-specific WHO cut-off point for 2 hours); chest indrawing; convulsions, drowsiness, inability to drink, and/or stridor at rest; either lack of improvement or deterioration clinically, in the opinion of the senior pediatrician; and death. For severe pneumonia, therapy failure was defined by any of the above except chest indrawing. The therapy failure rate was the proportion of enrolled children who required a change of therapy while in the hospital, had a recurrence of pneumonia symptoms within 1 week of discharge from the hospital, or died.

The clinical failure rate with co-trimoxazole for nonsevere pneumonia was 13.3%, whereas for severe pneumonia it was 32.5%. Only one child (0.17%) died. There was no significant difference in the treatment outcome by drug in nonsevere pneumonia cases. A subanalysis of 89 bacteremic patients who received co-trimoxazole showed that of 54 \(H.\) influenzae–infected patients, 29 had nonsevere and 25 had severe pneumonia; of 35 \(S.\) pneumoniae–infected patients, 17 had nonsevere and 18 had severe pneumonia. The therapy failure rate among patients infected with \(H.\) influenzae against which the MIC was
$\leq 2 \ \mu g/L$ was 15.4% (4 of 26) in nonsevere cases and 55.5% (10 of 18) in severe cases; for those infected with $S. \ pneumoniae$ with the same MIC, the respective rates were 20.0% (2 of 10) and 30.0% (3 of 10).

The third investigation was an open study in Gilgit in which trained community health workers (CHWs) assessed and managed all pneumonia cases in the villages [8, 9]. Trained physicians supervised them. Nasopharyngeal swab specimens were obtained from all patients with pneumonia, but only 242 isolates survived transport to the reference laboratory. Sixty nine percent of these isolates had some degree of antimicrobial resistance, as tested by the disk-diffusion method.

Clinical failure was defined when, after 2 days, the respiratory rate was the same ($\leq 5$) as at the time of initial assessment; the respiratory rate had increased ($>$5); and/or one or more of the following occurred: chest indrawing, convulsions, drowsiness, inability to drink, stridor at rest, and death. The clinical therapy failure rate was the proportion of children requiring a change of therapy or dying after enrollment. The clinical failure rate was only 8.8%, with no deaths.

The data from a pharmacokinetic study of co-trimoxazole in children suggested that a higher dose of oral co-trimoxazole might result in sustained drug levels, which may increase the clinical success rate [10]. In an outpatient-based, multicenter, double-blind, randomized trial, a standard dose of trimethoprim (4 mg/kg, twice a day) or a double dose (8 mg/kg) was administered to an equal number of children with community-acquired nonsevere pneumonia [11]. Clinical failure was defined when, after 2 days, the respiratory rate was the same ($\leq 5$) as at the time of initial assessment; the respiratory rate had increased ($>$5); and/or one or more of the following occurred: chest indrawing, convulsions, drowsiness, inability to drink, stridor at rest, and death. For 80% of the enrolled children therapy did not fail, but no significant difference was observed between the two therapeutic regimens. Only one child (0.01%) died.

**Antimicrobial Resistance Surveillance**

In vitro resistance levels (as reflected by MICs) of $S. \ pneumoniae$ and $H. \ influenzae$ are summarized in table 2. There were high levels of resistance of both organisms to co-trimoxazole: 78.3% in 1991–1992 (A. Kumar, personal communication) and 79.9% in 1993–1994 for $S. \ pneumoniae$ ([12] and A. Kumar, personal communication) and 61.0% in 1991–1992 and 59.5% in 1993–1994 for $H. \ influenzae$. There was relatively less resistance of $S. \ pneumoniae$ to penicillin: 27.3% in 1991–1992 and 51.5% in 1993–1994.

**Discussion**

Over a period of 8 years the clinical therapy failure rate with co-trimoxazole increased from 8.4% to 20%. Fortunately, this condition was adequately treated by a second-line antibiotic (oral amoxicillin), and the mortality rate for pneumonia in these studies has been negligible. However, the Pakistan ARI control program has been criticized for not changing its recommendations from co-trimoxazole to amoxicillin, in light of the high in vitro resistance and increase in failure of therapy in vivo.

Before the antibiotic-change recommendation is discussed, the limitations of the studies summarized in the results sections need to be addressed. First, only two clinical trials were randomized, controlled studies; the other two were open studies. However, community studies done in this manner are useful, as they are closer to the real situation. Second, in all the studies a very good follow-up of patients was managed, but this might not be possible in reality. This might result in a situation in which a patient with nonsevere pneumonia whose therapy with oral co-trimoxazole fails may become sicker and die at home. Although this hypothetical situation is quite possible, data show that when a child becomes sicker or doesn’t get better in 2–3 days, the parents or guardians seek immediate health care [13, 14].

Third, although the basic criteria for therapy failure in all studies were based on the WHO standard ARI-case-management guidelines, there were subtle differences between the criteria. In particular, the hospital-based study used more sensitive criteria for clinical therapy failure [7]. This might have resulted in the categorizing of more cases as therapy failures.

In the antimicrobial resistance surveillance studies, there were a couple of limitations. First, the number of isolates lost during transport between the isolation site/regional laboratories and the reference laboratories (where susceptibility was tested) might have resulted in a bias. Second, the surveillance results

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<td>Co-trimoxazole ($\geq 1 \ \mu g/mL$)</td>
<td>562 (78.3)</td>
<td>183 (79.9)</td>
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<tr>
<td>Penicillin ($\geq 0.12 \ \mu g/mL$)</td>
<td>196 (27.3)</td>
<td>118 (51.5)</td>
</tr>
<tr>
<td>Chloramphenicol ($\geq 8 \ \mu g/mL$)</td>
<td>109 (15.2)</td>
<td>40 (17.5)</td>
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* Personal communication from A. K. Tanwani; urban and rural sites included.
are for nasopharyngeal isolates, which may have greater resistance levels than invasive isolates.

The data from these studies can be interpreted in different ways. First, low clinical failure rates for nonsevere pneumonia may be explained by low sensitivity of the WHO criteria for identifying cases of bacterial pneumonia. Alterations in the WHO classification need to be considered to improve specificity for identifying cases of bacterial pneumonia. Second, achievable blood and lung levels of co-trimoxazole may be high enough to effectively treat pneumonia, despite in vitro resistance. This means that in vitro resistance does not correlate with in vivo failures in cases of nonsevere pneumonia.

Third, we can try to predict the percentage of resistance from the clinical failure rate. Following is a hypothetical analysis. For example, for cases of nonsevere pneumonia, one can estimate that probably 40% of the cases will be bacterial pneumonia with *S. pneumoniae* and *H. influenzae*. If one assumes that 33% of the isolates are resistant, the failure rate associated with co-trimoxazole would be 13.2%. One could refine this analysis a bit by saying that 70% of the 40% of cases of pneumonia that are bacterial are due to *S. pneumoniae* with a 33% rate of resistance to co-trimoxazole, while the other 30% of bacterial pneumonia cases are due to *H. influenzae* with a 40% rate of resistance. Analysis reveals a failure rate of 14%.

Given the fact that from 1991 to 1995–1996 the clinical failure rate increased from 8.4% to 20.0% (table 1), and if one assumes again that 40% of the cases of nonsevere pneumonia are bacterial in nature, it is possible to calculate the projected proportion of resistance. This means 0.4 × proportion of resistance equals the clinical failure rate. For 1991 the proportion of resistance would be estimated at 21%. Similarly, in 1995, 0.4 × proportion of resistance strains equals 0.2, for a 50% rate of resistance. This analysis suggests that the clinical failure rates correlate with the observed proportion of bacterial strains that are resistant. However, it seems that the bacteremic patients who have severe pneumonia are more likely to fail to respond to therapy, even if they have relatively susceptible organisms.

The Pakistan ARI program cited several reasons for not changing the first-line antibiotic therapy for nonsevere pneumonia, after these study results were available. First, Pakistan is a large country with a big population (140 million) [15]. It is estimated that 22 million episodes of pneumonia occur each year in the population of children <5 years old. Only 2%–3% have severe pneumonia; the rest have nonsevere pneumonia that responds well to oral antibiotics and can be managed at home. The estimated cost (in United States dollars) for just antibiotic therapy (at a hypothetical weight of 10 kg) for all pneumonia episodes in children would be as follows: oral co-trimoxazole, $7.7 million; oral amoxicillin, $25.3 million; and oral co-trimoxazole for all nonsevere pneumonia children, with a 20% therapy failure rate and a change to amoxicillin therapy, $12.8 million. The total health budget for Pakistan at present is only $66 million.

Second, besides being three times more expensive, amoxicillin requires administration three times a day, rather than the two times a day for co-trimoxazole; this might lead to poor compliance. Third, in 8 years, 3,000 physicians and 34,000 CHWs have been trained in standard ARI case management; retraining them all is going to be logistically difficult, very expensive, and time-consuming. Fourth, at present there are no data showing that clinical failure with co-trimoxazole is resulting in a higher mortality. Nearly all cases in which clinical failure of co-trimoxazole occurred were successfully treated with oral amoxicillin.

Although the above-mentioned reasons justify the Pakistan ARI program’s decision not to change the first-line antibiotic, a couple of issues like failure to follow up and missed opportunities need to be addressed. The condition of a child with nonsevere pneumonia not responsive to oral co-trimoxazole, if not followed up or assessed properly at follow-up, may progress to severe pneumonia and possibly death.

Some factors that may have led to high in vitro antimicrobial resistance and increased in vivo failure of therapy for pneumonia need discussion. First is the increasing use of antibiotics, particularly co-trimoxazole, in Pakistan. A study in a major city in Punjab showed that 43% of general-practice prescriptions for treatment of cough and cold episodes included an injectable antibiotic and 83% included an oral antibiotic [16]. In a couple of hospitals, more than 80% of prescriptions for ARI included antibiotics, and co-trimoxazole was the most commonly prescribed antibiotic.

A couple of other studies have reported that antibiotics were included in 53% [17] and 57% [18] of all prescriptions for childhood illnesses. There is some evidence that CHWs have a tendency to overprescribe co-trimoxazole and to use it in inappropriate doses and durations [19]. Besides misuse by health care workers, antibiotics are also easily available over the counter and are self-prescribed by the public.

The Pakistan ARI control program has taken a few steps to address the issue of antibiotic misuse. First is coordination with the national essential drugs program and nongovernmental organizations to promote rational use of drugs. Second is a 3-day training program for general practitioners. Third is having trained physicians visit general practitioners in their clinics/surgery to promote standard ARI case management. Finally, the program is working with the Pakistan CHW program to improve supervision of CHWs and to retrain them when necessary.

Conclusions and Recommendations

First, it is clear that despite high rates of in vitro antimicrobial resistance, the rates of in vivo response of ambulatory pneumonia to the first-line antibiotic (co-trimoxazole) were acceptable to the Pakistan national ARI control program. Although co-trimoxazole is still being used in most developing countries for treatment of ambulatory pneumonia, very few countries have antimicrobial resistance and clinical efficacy data from their own setting. Simple methodology and tools are
needed to help developing countries collect data needed for decision-making. Guidelines are also needed to help countries decide when to change the treatment protocol from use of the first-line antibiotic to use of a second-line antibiotic.

Second, the WHO diagnostic clinical criteria have a specificity of only ~80% [20]. Children presenting with wheezing and fast breathing may not have pneumonia, and the fast breathing may be due to just wheezing. Third, many children with pneumonia diagnosed by the WHO criteria and treated with antibiotics may have viral rather than bacterial pneumonia. Research is needed to make WHO ARI diagnostic criteria more specific.

Research is needed to define alternative antibiotic regimens that are inexpensive and associated with good compliance. Less frequent dosing and shorter courses of antibiotic need to be studied (e.g., oral amoxicillin twice a day and a shorter course of oral amoxicillin [3 days vs. 5 days]). Shorter courses and more specific ARI diagnostic criteria may result in less antibiotic use, thus reducing antimicrobial resistance.

References