Evaluation of the resistance induction in enteric flora in children caused by oral ampicillin plus sulbactam

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To evaluate the effect on bacterial resistance of a β-lactamase inhibitor, resistance patterns of predominant bacteria in enteric flora were evaluated before and after a 7-day course of oral ampicillin (100 mg/kg/day, qid, in 16 patients) and ampicillin–sulbactam (50 mg/kg/day of ampicillin, bd, in 32 patients) therapy. Ampicillin and ampicillin–sulbactam MICs for Escherichia coli, the predominant bacteria in all cases, and resistance rates of E. coli species to both antibiotics were 51.20 ± 13.80 mg/L, 87.5% and 4.84 ± 2.11 mg/L, 21% before the treatment respectively. Post-treatment MICs and resistance rates were 106.51 ± 14.05 mg/L, 100% and 15.89 ± 5.76 mg/L, 37.5% respectively, indicating a significant increase in MICs of both antibiotics (P < 0.05), being more prominent in the case of ampicillin–sulbactam (about four-fold). We concluded that oral ampicillin–sulbactam could also decrease the susceptibility of the enteric flora to ampicillin.
bacterial strains to be tested were prepared for inocula to a density of 0.5 on the McFarland scale. MICs were determined after incubating the plates at 37°C for 18 h.

Statistics
Wilcoxon signed rank and paired Student’s t-test were used for paired groups, and a chi-square test for non-parametric comparisons.

Results
E. coli was the dominant bacterium in enteric flora in all cases. The resistance rates of E. coli were 87.5% (14/16) and 100% (16/16) for ampicillin and 21% (6/32) and 37.5% (12/32) for ampicillin–sulbactam before and after antibiotic treatment, respectively. The difference between resistance rates before and after treatment, were not statistically significant in either group (P > 0.95 and P > 0.5 respectively) (Table).

Before antibiotic treatment there was a significant difference (P < 0.01) between ampicillin and ampicillin–sulbactam resistance rates in E. coli; after treatment this difference was not significant (P ≤ 0.1) (Table).

The mean MICs were significantly higher after treatment than before treatment (P < 0.05) (Table).

Discussion
UTIs are usually caused by enteric flora contaminating the perianal region and colonizing the bladder via the ascending route, E. coli being the most common agent. It has been known for a long time that antibiotic treatment for any reason could lead to the development of resistance in the flora of the host. Penicillin and its derivatives are the most frequently prescribed antibiotics owing to their efficacy and safety in childhood, and thus it is possible that bacteria might gain significant resistance to this group of antibiotics.

In the present study, the pretreatment resistance rate of E. coli was found to be 87.5% and 21% in ampicillin and ampicillin–sulbactam groups, respectively; this difference was statistically significant. E. coli strains isolated from UTIs were found to have a resistance rate of 50% and 21% for ampicillin and ampicillin–sulbactam groups, respectively, in an epidemiologic study performed in Malaysia. Denguchi et al. reported that the ratio of β-lactamase-producing strains had been 100% in E. coli. They also concluded that the antimicrobial activity of sulbactam–ampicillin against many bacteria, including E. coli, was higher than that of ampicillin. Pfaller et al. had reported that ampicillin–sulbactam had an effect on 74–84% of E. coli strains. In one local epidemiological study, the resistance rates of E. coli strains isolated in children with UTIs has been found to be 92% and 40% to ampicillin and ampicillin–sulbactam respectively. Our findings are in accordance with these results.

The difference between the resistance rates mentioned above indicates the importance of β-lactamase inhibition. However, it is not known what the potential of resistance development in predominant enteric bacteria is when this combination is used for treatment of UTIs.

In our study, after the completion of antibiotic treatment, E. coli strains isolated were still more resistant to ampicillin than to ampicillin–sulbactam (100% and 37.5% respectively), but the difference was not statistically significant. Furthermore, although post-treatment MICs were significantly higher than the pretreatment values in both ampicillin and ampicillin–sulbactam groups, this evaluation was more pronounced (approximately fourfold) in the ampicillin–sulbactam group. However, this difference is not statistically significant (P > 0.05).

It is also clear that combination of ampicillin with sulbactam enhances its inhibitory effect on Gram-negative bacteria.

In conclusion, the results of this study imply that therapy with oral ampicillin–sulbactam could cause the development of resistance to ampicillin in enteric bacteria, as seen here with a two-fold increase in MICs. This finding may have significance to physicians when prescribing antibiotics containing sulbactam as a β-lactamase inhibitor for recurrent UTIs in childhood.

References

<table>
<thead>
<tr>
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<th>Before treatment resistance (%)</th>
<th>After treatment resistance (%)</th>
<th>P value resistance rate</th>
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<tbody>
<tr>
<td>Ampicillin</td>
<td>51.20 ± 13.80</td>
<td>87.5 (14/16)</td>
<td>&lt;0.05</td>
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<tr>
<td>Ampicillin–sulbactam</td>
<td>4.84 ± 2.11</td>
<td>21 (6/32)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
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Table. Comparison of the resistance rates of E. coli to ampicillin and ampicillin–sulbactam and comparison of the MICs of these antibiotics for E. coli before and after treatment.
Ampicillin/sulbactam resistance in UTI flora


Received 17 June 1996; returned 5 August 1996; revised 10 October 1996; accepted 23 November 1996