Trimethoprim resistance in the 21st century: It is commoner than perceived

K. HAJIBAGHERI, M. PRIESEMANN,
N. LESSOF, I. MORRISON, E. PRICE, DEVESH MISRA

The Royal London Hospital

INTRODUCTION:
This study aims at comparing persistence of symptoms when trimethoprim resistant and trimethoprim sensitive paediatric urinary tract infections (UTIs) are treated with trimethoprim, prior to availability of sensitivity results.
It also compares the present local incidence of trimethoprim resistant paediatric UTIs with previous results.

PATIENTS AND METHODS:
In 2003 over a 3 month period, notes were reviewed from children with a positive urine culture from Paediatric A&E. After 3 days of trimethoprim treatment, symptoms were recorded and sensitivities reviewed.

The same study was repeated over a 12 month period in 2005.

RESULTS:

Children who presented to A/E with a proven UTI

- Clean catch specimens
- Trimethoprim started
- 3 days later, review of symptoms and microbiology

- At 3 days, 83% of patients with resistant organisms were still symptomatic
- Only one patient with sensitive organisms was still sympt at 3 days

1999- Trm resistance - 30%

2005- Trm resistance - 41%
- NFT resistance- 10%
- cephalexin resist- 15%

CONCLUSION:

When trimethoprim was used as initial therapy for trimethoprim resistant infections, significant treatment failures occurred. Trimethoprim resistance in paediatric UTI has increased more than resistance to some other antibiotics. This may relate to its frequent use for treatment and prophylaxis, as well as to intra-familial spread of resistant organisms. It is also possible that children with resistant UTIs may be over-represented in this study as they are more likely to attend hospital.

Discussion

Antibiotic resistance has been around ever since antibiotics were first discovered. Since antibiotics are often the derivatives of natural products, resistance genes already exist as the bacteria and the producer often live cheek by jowl in the same ecological environment. As antibiotics evolve, so do the bugs. Nature abhors a vacuum, so when an effective antibiotic eliminates susceptible members of a flora, resistant varieties soon fill the niche.

But even if the bacteria do not have innate primary resistance to antibiotics, this can be acquired by any of the following methods- (1) Some bacteria can absorb naked DNA molecules from the environment and incorporate them across regions of homology in their chromosome(s). (2) Resistance can be acquired from other bacteria, even from a different genus, by transfer of plasmids. Plasmids are extra-chromosomal replicative DNA forms which can encode a large variety of genes. (3) Or there may be spontaneous genetic mutations.

These genes or plasmids then bestow resistance by one of the following techniques- (1) Production of enzymes by the bacteria capable of destroying the antibiotic, eg, beta-lactamase production by staphylococcal species and certain gram negative bacilli. (2) Reducing the permeability of the cell wall to the antibiotic. (3) The receptor on the bacteria on which the antibiotic attaches, is altered. (4) In trimethoprim resistance, an alternative dihydrofolate reductase is manufactured which is resistant to the action of trm. Or there may be an excess of this enzyme produced.

The transferability of these plasmids and the frequent association with other resistance genes, explains the widespread nature and persistence of resistance in the community. Sometimes, even when the antibiotic is discontinued, as in the case of streptomycin 25 years ago, recent testing still shows the same high level of resistance.

Resistance to trm and sulfonamides

Trimethoprim inhibits the enzyme dihydrofolate reductase while sulfonamides inhibit the enzyme dihydrofolate synthase. Thus both drugs act at different levels of folate synthesis and are synergistic, explaining their coupling in co-timoxazole.

Some bacteria like enterococci are naturally resistant to trm because they can absorb exogenous folate.

Trm resistance- global phenomenon

- Rare till 1980, now being increasingly recognised
- Guy's hosp 2002
  - Trm resist 1/3 in primary UTI
  - 2/3 if underlying anomaly

Globally, there is a rise in antibiotic resistance for which many factors are associated. Humans are vectors in spread of resistance bacteria across international borders. In hospital environment, poor hygienic practices and a concentration of very sick patients results in an environment where the most virulent bacteria are concentrated and often pass resistance genes to one another.

It has also been shown that the widespread use of antibiotics like fluoroquinolones in farm animals has resulted in a greater prevalence of resistant E Coli in the community.

Factors assoc with Trm resistance

- Previous hospitalisation
- Recent antibiotics
- Underlying disease- VUR, neurogenic bladder, CRF
- Pts on prophylaxis
- Crowded places with children- nurseries, hospitals

Reducing Trm resistance

- Stricter indications for prophylaxis
- Reduce duration of prophylaxis
- Adults- 1 or 3 day Rx for cystitis
- Use NFT, Ceph (Cefdinir) more often
- Minimise antibiotic usage in the community
- ?Double antibiotic proph- Trm am/NFT PM

At present, antibiotic prophylaxis is used in the following conditions, some of these could be reassessed-

- Following a first UTI, while awaiting investigations
- Antenatally diagnosed VUR
- Symptomatic VUR
- Recurrent UTI with no underlying anomaly
- Infants with imperforate anus awaiting anorectoplasty, etc