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AMPICILLIN AND SULPHADIMIDINE IN TREATMENT OF URINARY TRACT INFECTION

J. C. GOULD and ELIZABETH EDMOND

Central Microbiological Laboratories, Edinburgh, 4.

FROM the bacteriological point of view there is a great difference between the "primary" case of urinary tract infection such as occurs in the young adult with bacteriuria, and the "secondary" or chronic case such as the chronic pyelonephritic who has had much investigation and treatment. In the former the flora is almost invariably simple consisting of *Esch. coli*; in the latter the flora is frequently complex and many of the infecting strains are resistant to the antibacterial agents commonly used in treatment. The treatment of such cases is less satisfactory, particularly with the sulphonamides.

The primary type of case is however important since successful treatment of such early cases should reduce the incidence of chronic infection. It is important that these early cases be treated effectively to eradicate the infection before irreversible damage has been caused to renal tissue and chronic pyelonephritis becomes inevitable.

The general practitioner and the obstetrician most frequently come into contact with this type of early case. Many use sulphonamides

in the treatment of infections of the urinary tract with good results, and since sulphonamides are relatively cheap and familiar to them they tend to be the drugs most frequently used. Some workers have suggested that these results are more apparent than real, and failure to eradicate the infection leads to relapse and the development of chronic disease.

Diagnosis

The diagnosis of urinary tract infection is particularly important in the young woman, for in our opinion there are more such women treated for non-existent urinary tract infection than who fail to have treatment for an infection which has not been diagnosed. Important in this context is a proper appreciation of quantity and quality of the urinary microflora and the examination of the urine by the bacteriologist should involve an assessment of the following factors:

1. Serial specimens of urine must be examined before treatment to establish that a significant bacteriuria exists. In a number of patients intermittent bacteriuria may lead to

TABLE I

Types of Bacteria

No. of strains	Esch. coli	N.L.F.* Ex. Proteus and Pseudomonas	Enterococcus
55	41 (74%)	10 (19%)	4 (7%)

Number of patients examined 893

Number with significant bacteriuria 55 (6.2%)

*N.L.F.=non-lactose fermenting coliform bacilli.

false negative results.

2. A quantitative estimation of viable bacteria present in the urine to the order of ten.

3. A full qualitative assessment of the flora isolated. In cases of significant bacteriuria the pathogens outnumber the contaminating flora by at least ten to one. When the proportion is less than this the significance of *Esch. coli* and other species even when present in numbers approximating to 100,000 per ml. must be regarded as doubtful.

4. No estimation to establish significant bacteriuria can be carried out in the presence of antibacterial substances in the urine. This is such a frequent occurrence in specimens sent to the laboratory that routine assay should be carried out on all specimens of urine at the time of culture.

5. All results must be interpreted in the light of methods of sampling of the specimen, and the time interval elapsing between sampling and examination, as well as previous knowledge of the case if any.

Present Series

Eight hundred and ninety-three cases have been examined in this way, and represent consecutive patients presenting themselves at the ante-natal clinic of an Edinburgh maternity hospital. On the basis of at least two pre-treatment urine bacteriological examinations, those patients with significant bacteriuria were allocated at random to a course of treatment with sulphadimidine, 1 g. three times a day, or ampicillin 0.25 g., four times a day, each for 14 days. Further urine specimens were taken at the end of this course of treatment, and at two- or four-weekly intervals thereafter until delivery of the child. A number of cases have also been followed up at post-natal clinics.

Of 893 consecutive patients examined, over a three month period, 55 (6.2%) were

TABLE II

Antibiograms of Strains Isolated from the Present Series.

	No. of strains	AS	SuS	SS	TS	KS	CyS
Esch. coli	41	36 (88)	30 73	41 100	37 90	41 100	37 90
N.L.F.	10	10	6	10	5	8	8

*AS = Ampicillin sensitive

SuS = Sulphonamide sensitive

SS = Streptomycin sensitive

TS = Tetracycline sensitive

KS = Kanamycin sensitive

CyS = Cycloserine sensitive

found to have a significant bacteriuria with the types of flora as shown in Table I, which conform to those most commonly isolated from this type of case. The predominance of *Esch. coli* will be noted. (Table I).

Determination of the antibiotic sensitivity of this flora is of interest since it shows that the majority of the coliforms were sensitive to both ampicillin and sulphonamide, as well as to most of the other antibiotics tested (Table II).

Further, these figures correspond very closely to the antibiograms of 1,000 strains of coliforms isolated from cases of urinary tract infection contracted outside of hospital, which we have studied during the previous six months, but are in marked contrast to those strains isolated from hospital contracted urinary tract infections where the majority of strains are resistant to both sulphonamide and tetracyclines.

A limited number of coccal strains which were isolated proved to be both sulphonamide and ampicillin resistant *in vitro*, but this does not conform to our general findings, as two thirds of the strains of *Streptococcus faecalis* isolated from urinary tract infections have been ampicillin-sensitive and only a minority resistant to sulphonamide.

Of some importance is the level of sensitivity which is taken to divide the "sensitive" from the "resistant" strains. Shown in Table II is the more detailed sensitivity of the coliform bacilli isolated in the present series to both sulphonamide and ampicillin. All of the strains were sensitive to amounts of ampicillin less than the average amount found in the urine, following 0.25 g. four times a day, but is this the standard to go by? Is it not more correct to be guided by the average plasma level of the antibiotic, e.g. 5 $\mu\text{g./ml.}$? Ninety per cent of our strains were sensitive to less than 25 $\mu\text{g./ml.}$ and 78% to less than 5 $\mu\text{g./ml.}$ Further, what kind of *in vitro* tests should be used?

TABLE III
Results of Treatment

	Total	Number of Patients Treated with Sulphadimidine 1 g. t.i.d.	Number of Patients Treated with Ampicillin 0.25 g. q.i.d.
Success	45	24	21
Failure	32	14	18
	13	10	3

10 withdrawals, including 1 because of sulphonamide toxicity and 1 of ampicillin hypersensitivity

We have carried out both plate diffusion and serial dilution tube tests and found them to correlate reasonably well: however, by using very heavy inocula in both types of test and the replica plate technique following initial diffusion plate tests, it has been possible to show the presence of ampicillin-resistant mutants occurring in a number of strains, but so far their appearance has not been correlated with failure of treatment.

In the case of the sulphonamides there is perhaps greater reason to question our interpretation of the *in vitro* tests: these are difficult to carry out by serial dilution tests and we have relied entirely upon diffusion plate studies, but our level of 100 $\mu\text{g./ml.}$ may be too high; thus, taking 25 $\mu\text{g./ml.}$ as the critical level of sensitivity the proportion of sensitive strains would be considerably reduced and this would correlate better with the results of therapy.

Results

The results of treatment are shown in Table III and indicate that in the majority of the treated cases infection was suppressed following cessation of therapy and during the follow-up period which has not been less than three months in any case. Ampicillin has been more effective in this respect than sulphadimidine, although the series is as yet rather small to draw outright conclusions. Failure in the ampicillin cases may have been due to relative ampicillin resistance and in one case is correlated with the presence of small num-

TABLE IV
Relationship of Antibiotic Sensitivity to
Results of Treatment

	Initial Sensitivity of Strain			
	SuS Treated with Su	SuR	AS Treated with A	AR*
	16	8	18	3
Success	10	4	16	2
Failure	6	4	2	1

*Su=Sulphonamide
A=Ampicillin

S=sensitive
R=resistant

1 failure associated
with change
SuS $\rightarrow$ SuR

In no other case of
failure was there any
change in sensitivity

bers of resistant mutants in the original population although significant resistance after treatment was not measured. Failure in the sulphonamide treated cases was due in four instances to relatively high sulphonamide resistance but not to any known cause in the remaining cases (Table IV). In one patient the original sulphonamide-sensitive population was replaced by a sulphonamide-resistant population, presumably by selection. However, the bacteriological result of therapy could not be absolutely related to *in vitro* sensitivity.

Summary

Care is required in the diagnosis of urinary tract infection particularly in the young female where there may be difficulty in distinguishing relatively heavy growths of skin and vaginal contaminating flora. A quantitative method is necessary and must be supported by full qualitative analyses including estimation of antibacterial products in the urine.

Treatment with sulphonamide and ampicillin has shown the latter to be more effective in the elimination of the bacteria normally found in early urinary tract infections: this may be related to the relative resistance of the infecting bacteria to sulphonamide in concentrations normally found in the plasma as opposed to the more usually accepted urine concentrations.