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AN ANALYSIS OF THE MICRO-ORGANISMS RESPONSIBLE FOR PELVIC INFECTION IN PRETORIA: THEIR SENSITIVITY AND RESISTANCE TO ANTIBIOTICS*

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Because of the current interest in bacterial resistance we decided to review the situation in Pretoria regarding the organisms responsible for pelvic infection and their sensitivity to the various antibiotics. As will be seen, a number of interesting facts emerged and we were able to draw certain conclusions.

During the 6-month period from 20 May to 20 November 1960, 501 smears (excluding sputum, blood, urine and faeces) were submitted for bacteriological examination by the Department of Obstetrics and Gynaecology of Pretoria University. Of these 200 (38·2%) were negative, i.e. either no growth (23·2%) or mixed vaginal flora (15%).

In the 301 positive smears the following organisms were represented:

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E. coli 33·2%, coagulase-positive staphylococci 30·3%, beta-haemolytic streptococci 6·4%, enterococci 5·4%, alpha-haemolytic streptococci 5·1%, proteus group 4·2%, coagulase-negative staphylococci 4·2%, *B. subtilis* 2·9%, parakolon 2·2%, *Cl. welchii* 1·3%, aerobacter 0·9%, *Ps. pyocyaneus* 0·9%, diphtheroids 0·9%, achromobacter 0·6%, and anaerobic streptococci 0·6%.

It will be seen that *E. coli* and coagulase-positive staphylococci accounted for 63·5% of the organisms found.

To ascertain the antibiotic sensitivity of these organisms, we selected 100 specimens of the 7 most common bacteria at random from the files of the bacteriology department. The results can be seen in Tables I - VI.

If these figures are combined into one graph, the degree of sensitivity of these organisms to the various antibiotics can be seen at a glance (Fig. 1).

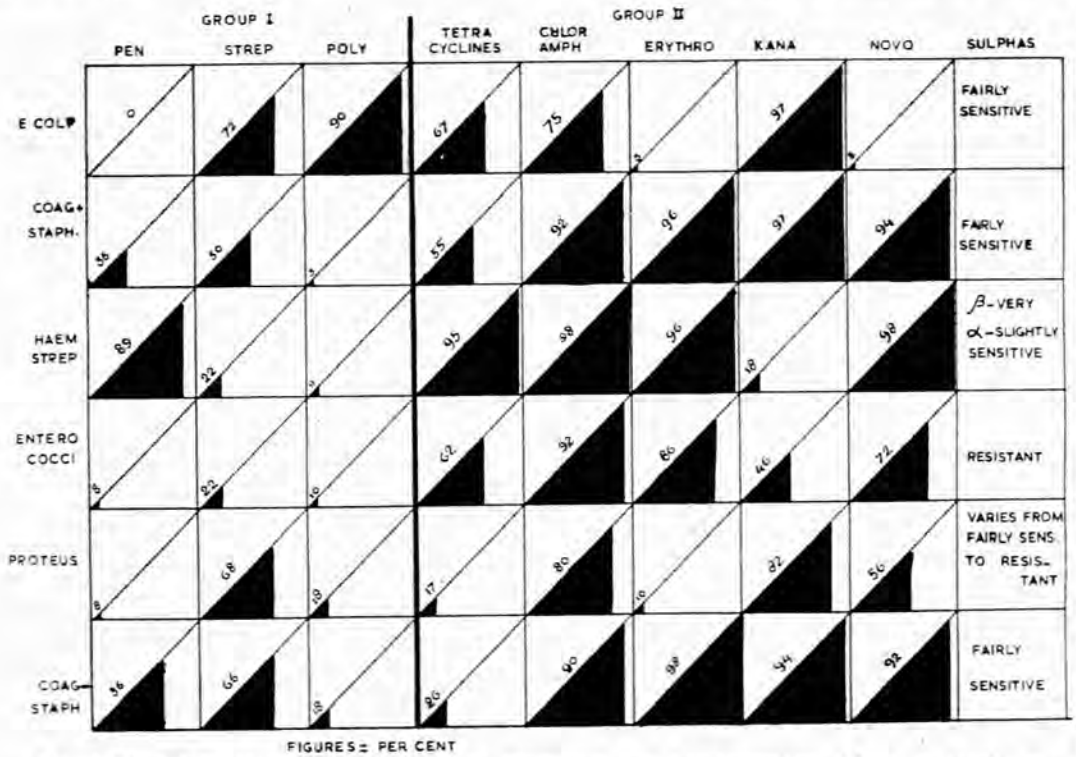

Fig. 1. Sensitivity of various organisms to antibiotics and sulphonamides. (Coag + staph. = coagulase-positive staphylococci, haem. strep = haemolytic streptococci, coag − staph = coagulase-negative staphylococci, pen = penicillin, strep = streptomycin, poly = polymyxin, chloramph = chloramphenicol, erythro = erythromycin, kana = kanamycin, novo = novobiocin, sulphas = sulphonamides.)

SENSITIVITY

Penicillin: We see that this drug is effective only against the haemolytic streptococcus and that the sensitivity of this organism is only 89%. Even the coagulase-negative staphylococcus, besides becoming more pathogenic, is losing some of its sensitivity to penicillin.

Streptomycin: Although it has lost its place as the drug of choice for *E. coli* infections, it is still effective against 72% of these organisms. Two-thirds of proteus organisms and coagulase - negative staphylococci are sensitive, and only 50% of the coagulase-positive staphylococci.

The tetracyclines: The 'terramycin' drip is favoured by

TABLE I. PERCENTAGE SENSITIVITY OF *E. coli* TO VARIOUS ANTIBIOTICS

Organisms		*Penicillin*	*Streptomycin*	*Chlortetracycline*	*Oxytetracycline*	*Tetracycline*	*Chloramphenicol*	*Erythromycin*	*Kanamycin*	*Novobiocin*	*Polymyxin*
E. coli	sensitive to	0	72	66	67	67	75	3	97	2	90
	insensitive to	100	28	34	33	33	25	97	3	98	10

E. coli are very sensitive to kanamycin **97%**, and polymyxin 90%; partly sensitive to tetracyclines 67%, chloramphenicol **75%**, and streptomycin 72%; insensitive to penicillin 0%, erythromycin 3%, and novobiocin 2%.

TABLE II. PERCENTAGE SENSITIVITY OF COAGULASE-POSITIVE STAPHYLOCOCCI TO VARIOUS ANTIBIOTICS

Organisms		*Penicillin*	*Streptomycin*	*Chlortetracycline*	*Oxytetracycline*	*Tetracycline*	*Chloramphenicol*	*Erythromycin*	*Kanamycin*	*Novobiocin*	*Polymyxin*
Coagulase-positive staphylococci	sensitive to	36	50	55	55	55	92	96	97	94	3
	insensitive to	64	50	45	45	45	8	4	3	6	97

Coagulase-positive staphylococci are very sensitive to kanamycin **97%**, erythromycin 96%, novobiocin **94%**, and chloramphenicol **92%**; partly sensitive to penicillin 36%, streptomycin 50%, and tetracyclines 55%; insensitive to polymyxin 3%.

TABLE III. PERCENTAGE SENSITIVITY OF ALPHA- AND BETA-HAEMOLYTIC STREPTOCOCCI TO VARIOUS ANTIBIOTICS

Organisms		*Penicillin*	*Streptomycin*	*Chlortetracycline*	*Oxytetracycline*	*Tetracycline*	*Chloramphenicol*	*Erythromycin*	*Kanamycin*	*Novobiocin*	*Polymyxin*
Beta-haemolytic streptococci	sensitive to	80	24	98	98	98	98	96	24	98	10
	insensitive to	20	76	2	2	2	2	4	76	2	90
Alpha-haemolytic streptococci	sensitive to	98	20	94	92	92	98	96	12	98	12
	insensitive to	2	80	6	8	8	2	4	88	2	88

Alpha- and beta-haemolytic streptococci taken together are very sensitive to chloramphenicol **98%**, tetracyclines 95%, penicillin 89%, erythromycin 96%, and novobiocin 98%; insensitive to streptomycin 22%, kanamycin **18%**, and polymyxin 11%.

TABLE IV. PERCENTAGE SENSITIVITY OF ENTEROCOCCI TO VARIOUS ANTIBIOTICS

Organisms		*Penicillin*	*Streptomycin*	*Chlortetracycline*	*Oxytetracycline*	*Tetracycline*	*Chloramphenicol*	*Erythromycin*	*Kanamycin*	*Novobiocin*	*Polymyxin*
Enterococci	sensitive to	8	22	64	62	62	92	86	46	72	10
	insensitive to	92	78	36	38	38	8	14	54	28	90

Enterococci are very sensitive to chloramphenicol **92%**, and erythromycin 86%; partly sensitive to novobiocin 72%, tetracyclines 62%, and kanamycin **46%**; insensitive to penicillin 8%, streptomycin 22%, and polymyxin 10%.

TABLE V. PERCENTAGE SENSITIVITY OF PROTEUS TO VARIOUS ANTIBIOTICS

Organisms		*Penicillin*	*Streptomycin*	*Chlortetracycline*	*Oxytetracycline*	*Tetracycline*	*Chloramphenicol*	*Erythromycin*	*Kanamycin*	*Novobiocin*	*Polymyxin*
Proteus	sensitive to	8	68	18	16	18	80	10	82	56	18
	insensitive to	92	32	82	84	82	20	90	18	44	82

Proteus is very sensitive to chloramphenicol **80%**, and kanamycin **82%**; partly sensitive to streptomycin 68%, and novobiocin 56%; insensitive to penicillin 8%, tetracyclines 17%, erythromycin 10%, and polymyxin 18%.

TABLE VI. PERCENTAGE SENSITIVITY OF COAGULASE-NEGATIVE STAPHYLOCOCCI TO VARIOUS ANTIBIOTICS

Organisms		*Penicillin*	*Streptomycin*	*Chlortetracycline*	*Oxytetracycline*	*Tetracycline*	*Chloramphenicol*	*Erythromycin*	*Kanamycin*	*Novobiocin*	*Polymyxin*
Coagulase-negative staphylococci	sensitive to	56	66	26	26	26	90	98	94	92	18
	insensitive to	44	34	74	74	74	10	2	6	8	82

Coagulase-negative staphylococci are very sensitive to chloramphenicol **90%**, erythromycin 98%, kanamycin **94%**, and novobiocin 92%; partly sensitive to penicillin **56%**, streptomycin 66%, and tetracyclines 26%; insensitive to polymyxin 18%.

some gynaecologists in the treatment of severe infections. It will be seen that it is very effective against the haemolytic streptococci only, and 67% and 55% effective against *E. coli* and coagulase-positive staphylococci respectively. However, since the tetracyclines can conveniently be administered by the continuous-drip method, they still have a place in these infections, especially if they can be combined with another group-II antibiotic.

Chloramphenicol: This is the antibiotic *par excellence* in this series, most probably because it is prescribed only occasionally for pelvic infection. It is effective against 75% of *E. coli* and against 80% or more in each of the other groups.

Erythromycin: This has a spectrum not unlike that of penicillin, except that it is still very effective against the staphylococci and the enterococci. It is known, however, that resistance to erythromycin develops rapidly unless it is combined with another group-II antibiotic. When it was combined with novobiocin in a series of 108 patients, no resistance developed against erythromycin and only twice against novobiocin.[1]

Kanamycin: This is almost 100% effective against the 2 most common organisms, and very effective against proteus organisms and coagulase-negative staphylococci.

Novobiocin: This has, for practical purposes, the same spectrum as erythromycin. For that reason these 2 antibiotics form an ideal combination, especially against the coagulase-positive staphylococci.

Polymyxin: This is of use only against *E. coli* in the form of local application or bladder instillations.

The sulphonamides: Unfortunately sensitivity tests cannot be performed because some of the culture media inhibit sulphonamides.[5] Therefore the susceptibility of these organisms is not known and the spectrum included here (Fig. 1) has been supplied by Messrs. May and Baker. It will be seen that the alpha-haemolytic streptococci and the enterococci are resistant, but that the rest are fairly sensitive.

Although no figures are available (anaerobic cultures are not performed as a routine) the incidence of anaerobic streptococcal infections seems to be increasing.[10]

RESISTANCE

Let us apply these observations to the subject of antibiotic resistance. Antibiotics can be divided into 2 groups:

Group I (bactericidal): Penicillin, streptomycin, neomycin, bacitracin, polymyxin, vancomycin, and ristocetin.

Group II (bacteriostatic): Tetracyclines, chloramphenicol, erythromycin, novobiocin, kanamycin, and the sulphonamides.

This division is of great practical importance because of the existence of synergism and antagonism between the 2 groups.[7,8] The following facts concerning synergism and antagonism are important:

1. Combinations of group-I antibiotics are often synergistic, but seldom antagonistic.

2. Combinations of group-II antibiotics are neither synergistic nor antagonistic, but merely additive.

3. Combinations of group I and II can be either synergistic or antagonistic. If the organism is sensitive to a group-I antibiotic, the addition of a group-II antibiotic will have an antagonistic effect. If, however, the organism is resistant or partly sensitive to a group-I antibiotic, a group-II antibiotic will be synergistic. It follows that group I and II antibiotics should not be combined without testing the sensitivity to at least one of the two. Because the sulphonamides belong to group II, and because the majority of organisms (except the beta-haemolytic strep-

tococci) are either partly sensitive or resistant to them, these drugs can be safely combined with both group-I and group-II antibiotics.

The application of genetics to bacteria established that bacterial resistance is either natural or acquired.[4,7,8]

Natural Resistance

1. Certain bacteria possess a primary natural resistance, e.g. proteus and pseudomonas.

2. Others produce enzymes which inactivate antibiotics, e.g. most hospital staphylococci produce penicillinase.

Acquired Resistance

1. One natural variant exists in 10^7 organisms. If one considers that a generation of bacteria is formed every 20 minutes, it becomes clear that, by selection, these mutants can replace the entire population in one night. The strain then becomes resistant.

2. Mutation of sensitive organisms can occur by the use of biochemical processes other than those eliminated by the antibiotic. If only one step is involved, as in the case of streptomycin and INH, a rapid mutation can take place, even in one generation. Because other antibiotics eliminate more than one step in the biosynthesis, mutation is required in two or more genes and this may take several generations.

Combined Therapy

The rationale of the use of combined antibiotic therapy is as follows:[1,2,4]

1. To suppress mutants resistant to one antibiotic by another.

2. To prevent the selection of resistant strains, especially in hospital practice. By such means chloramphenicol can be protected against the fate which befell penicillin in its early years.

3. In the treatment of mixed infections.

4. To obtain an additive or synergistic effect in the case of partial sensitivity.

If an organism develops resistant mutants to one antibiotic at the rate of 1 per 10^7 and to another at the rate of 1 per 10^6 cell divisions, the chance of developing resistance to both simultaneously will be 1 in 10^{13} cell divisions. Because the occurrence of 10^{12} viable organisms in one patient is extremely uncommon, the development of a doubly resistant mutant is unlikely.[4] Combined antibiotic therapy has become the established practice of such people as Barber, McClure Brown, Ian Donald, Lacey, Coetzee and others.[11]

CONCLUSION

In conclusion we should like to put forward the following suggestions:

1. Bacterial cultures and sensitivity tests should be performed whenever possible.

2. If this is impossible, or while awaiting the results, chloramphenicol and kanamycin should be administered together in severe infections.

3. The terramycin drip still has a place in fulminating infections if it is combined with another antibiotic.

4. Combined antibiotic therapy is strongly recommended.

5. Penicillin should not be used in pelvic infections unless the organism has been proved sensitive and the penicillin can be combined with another antibiotic. This, however, does not justify the indiscriminate use of penicillin-streptomycin combinations.[12] The possibility of reversal of resistance to penicillin should be entertained, as happened when 'chloromycetin' was practically abandoned some years ago.[3]

6. Only those antibiotics that are unsuitable for systemic administration should be used for local application.

7. Patients receiving antibiotics should be isolated.[6]

8. Although sulphonamides belong to group II, they can, for practical purposes, be combined with either group-I or group-II antibiotics.

9. The use of prepared antibiotic combinations is condemned.[9]

10. Finally, it is suggested that antibiotics should be prescribed only by the senior staff of a hospital.

SUMMARY

The frequency of occurrence of the organisms responsible for pelvic infection in Pretoria is discussed. *E. coli* and the coagulase-positive staphylococci together are responsible for 63·5% of cases.

Culture and sensitivity tests of the organisms show that chloramphenicol and kanamycin are the two antibiotics which, when used in combination, are most effective in the majority of pelvic infections.

Certain aspects of resistance against antibiotics are discussed, and a plea is made for combined antibiotic therapy. Penicillin should be used only in exceptional circumstances, and the sulphonamides can be used with the antibiotics more frequently.

OPSOMMING

Die veelvuldige voorkoms van die organismes wat bekkeninfeksie in Pretoria veroorsaak, word bespreek. *E. coli* en die koagulase positiewe stafilokokke is saam verantwoordelik vir 63·5% van die gevalle.

Kulture en sensitiwiteitstoetse van die kieme het getoon dat chloramphenicol en kanamisien die twee antibiotika is wat, indien hulle saam gebruik word, die meeste van die infeksies sal bekamp.

Sekere aspekte van weerstand teen antibiotika word bespreek en 'n pleidooi word gelewer vir gekombineerde antibiotiese behandeling. Penisillien behoort slegs in uitsonderlike gevalle gebruik te word, en die sulfonamides kan meer dikwels saam met die antibiotika toegedien word.

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