Epidem. Inf. (1989), **102**, 391–400
Printed in Great Britain

Beta-haemolytic streptococci from the female genital tract: clinical correlates and outcome of treatment

R. F. M. LEWIS*

Microbiology Department, Worthing Hospital, Worthing, West Sussex BN11 2DH

(*Accepted 12 January 1989*)

SUMMARY

Clinical features, treatment and outcome were assessed retrospectively by means of a questionnaire in 174 patients in general practice whose vaginal swabs yielded beta-haemolytic streptococci. These were compared with 96 patients whose swabs yielded no recognized microbial pathogens. Patients with group B streptococci did not differ in any of these parameters from the control group, but those with group A streptococci were more likely to have vaginal soreness, a purulent discharge, and to respond to anti-streptococcal antibiotics. Implications for laboratory reporting are discussed.

INTRODUCTION

A wide variation in microflora of the female genital tract occurs both between individuals and with time in the same individual. This has been documented both in pregnancy (Goplerud, Ohm & Galask, 1976; de Louvois *et al.* 1975*b*) and during the normal menstrual cycle (Wilks & Tabaqchali, 1987). The relationship between these organisms and the presence of disease states has proved harder to define, as the continuing debate over *Gardnerella vaginalis*, now in its 33rd year, testifies (Gardner & Dukes, 1955; Kerr *et al.* 1988; O'Dowd & West, 1988). Beta-haemolytic streptococci (BHS) of various Lancefield groups may be pathogenic in the genital tract after childbirth or surgery, and are readily isolated by laboratories on routine media. Although the available evidence is that group B streptococci are not linked to other forms of genital tract morbidity, less is known about BHS of other groups, and microbiology laboratories may be tempted to report the presence of all BHS isolated from the genital tract, in the belief that clinical significance is best left to the clinician to determine.

This study attempts to examine the effect of this policy for a general practice population served by one district general hospital laboratory.

METHODS

Bacteriological methods

The bacteriological methods were those used routinely in the laboratory at the time. Swabs were received in Charcoal-Amies Transport medium ('Transwab',

* Present address: Bacteriology Department, Victoria Infirmary, Glasgow, G42 9TY.

Medical Wire & Equipment Co., Corsham, Wilts.). A wet film was examined for the presence of leucocytes, yeasts and *Trichomonas vaginalis* and the swab then inoculated on to the following media.

(1) Bilayer plates consisting of a base of nutrient agar (Oxoid) overlain with Columbia agar (Oxoid) containing 10% human blood (HB agar).

(2) Thayer-Martin medium (Oxoid) with Oxoid GC supplement SR56 (TM agar).

(3) Malt Extract agar (Oxoid) with potassium tellurite 35 mg/l and chloramphenicol 100 mg/l (ME agar).

(4) Cysteine Lactose Electrolyte-deficient agar (Oxoid) (CLED agar). HB agar plates had disks of metronidazole 5 μg and penicillin 1·5 units applied, and were read after 1 and 2 days' incubation at 37 °C anaerobically. TM plates were incubated at 37 °C in air plus 7% CO_2 and were read after 1 and 2 days. CLED and ME plates were read after aerobic incubation at 37 °C overnight. In addition to *Trichomonas vaginalis*, the presence or absence of the following organisms were reported on the basis of culture as follows.

Yeasts (identified by Gram film of colonies on ME agar).

Gardnerella vaginalis (identified by Gram film of typical weakly-haemolytic, metronidazole-resistant colonies on HB agar).

β-haemolytic streptococci other than group D (where > 10 β-haemolytic colonies were present on HB agar and were sensitive to penicillin, subculture was performed for Lancefield grouping ['Streptex', Wellcome Laboratories, Beckenham] and sensitivity).

Anaerobic pathogens (where there was judged to be an abnormal excess of metronidazole-sensitive colonies on HB agar after 48 h).

Epidemiological methods

During a period of about 6 months, reports on those bacteriological swabs submitted by general practitioners from which a β-haemolytic streptococcus was isolated were issued to the requesting doctor accompanied by an explanatory letter and a questionnaire requesting the following details.

Nature of clinical symptoms and signs referable to the genital tract, including specifically the presence and nature of any vaginal discharge, and vaginal pH. Details of vaginal tampon usage were not sought; this information appears seldom to be routinely recorded by doctors.

Age, stage of reproductive life, contraceptive usage, history of antibiotic therapy during the previous 2 weeks.

Nature of any treatment given, and doctor's assessment of the degree of patient's response to treatment (as complete, partial, or none) at follow-up visit.

Hospital in-patients and out-patients, and patients whose swabs yielded trichomonas, yeasts, gardnerella or anaerobes in addition to BHS were not included in the study.

During the early part of the study, an equal number of negative reports was sent out on a daily basis accompanied by the same questionnaire. These were taken at random from the negative HVS reports as they were issued to general practitioners, and no attempt was made to match them individually with BHS-

positive reports in respect of any of the features mentioned. Where (as occurred frequently) no data were given regarding a follow-up visit, the surgery was telephoned 1–8 months later to establish whether there had been a subsequent consultation during this time and whether any genital tract symptoms and signs had been recorded. Search of microbiology laboratory records during the follow-up period was also carried out as a further check.

Results were analysed by chi-squared test (Wang 2200 General Library Statistics/Engineering).

RESULTS

A total of 322 questionnaires was issued, and 273 adequately completed returns received. Three patients were excluded because of documented co-existent urinary tract infections. The 270 remaining questionnaires related to 241 high vaginal swabs, 12 vulval swabs, 11 endocervical swabs and 5 low vaginal swabs. Culture results showed the group to comprise 96 controls (no pathogens isolated), 114 with group B streptococcus (GBS), 41 with group A streptococcus (GAS) and 19 with haemolytic streptococci other than group A, B and D. This latter group proved too small and heterogeneous for evaluation, comprising 13 strains of groups G, 3 of group C, 1 of group F and 2 ungroupable. Only two of the patients had cervical swabs taken for chlamydia, both with negative results.

Clinical features

Not all features about which information was specifically sought were recorded on all questionnaires, and no patient had vaginal pH measured. No significant difference was found between patients with GBS and controls in respect of stage of reproductive life (Table 1), contraceptive usage (Table 2), or symptoms and signs related to the genital tract (Tables 3 and 4); however, patients from whom GAS were isolated were significantly more often premenarchal, complained of vaginal soreness or irritation, and had inflamed vaginal mucosa. These patients were also more likely to have numerous pus cells present on microscopy of their vaginal swabs (Table 5). The use of antibiotics during the 2 weeks prior to presentation was similar in all groups of patients (Table 6).

Treatment and outcome

No recommendations as to treatment were given on the reports issued by the laboratory, although sensitivities of BHS to penicillin and erythromycin were reported. Treatment regimes were extremely varied, and were often begun empirically before the results of laboratory tests were known. Combinations of drugs were often used at the outset, and the numbers who in effect received combination therapy were increased by those whose empirical therapy was changed to another drug after 2 or 3 days, as the swab result became known. Sixteen patients with BHS thus completed two consecutive different courses of therapy, and these patients were included twice in the assessment of outcome (11 in GBS group, 5 in GAS). Table 7 attempts to summarize the diverse treatments used.

In assessing outcome, two further categories of patient had to be excluded from the study. These were those who had subsequently moved away or been referred

https://doi.org/10.1017/S0950268800030107 Published online by Cambridge University Press

Table 1. *Stage of reproductive life in relation to swab culture results*

Stage of reproductive life	Culture results: No pathogens isolated	Streptococcus group B	Streptococcus group A
Post-menopausal	18	25	6
Pre-menarchal	2	2	16*
Postnatal (< 6 months from delivery)	2	7	2
Pregnant	7	2	0
Other than above	67	78	17
Total	96	114	41

* $P < 0{\cdot}001$ compared with control group ($\chi^2 = 34{\cdot}35$, 1 D.F.)

Table 2. *Method of contraception in relation to swab culture result*
(Patients with streptococcus group A excluded as only 19 were of reproductive years.)

Method of contraception	Culture result: No pathogens isolated	Streptococcus group B
Oral contraceptive	18	27
Barrier method	9	15
Inter-uterine contraceptive device	4	7
Sterilization (male or female)	5	7
None	14	16
Not known	17	6
Total	67	78

to hospital departments or private clinics (nine in GBS group, eight in control group), and those given non-antibiotic forms of therapy, e.g. local oestrogen cream for atrophic vaginitis or removal of IUCD (six in GBS group, one in GAS group, two in control group). The remaining patients could be divided into three groups.

(*a*) Those who were actively assessed at a follow-up visit, usually within a week or two, and categorized as 'completely improved', 'partially improved' or 'not improved' in respect of their symptoms.

(*b*) Those who attended surgery during the follow-up period, but had no record of relevant symptoms made ('no recorded symptoms').

(*c*) Those who are known not to have attended surgery during the follow-up period ('no further attendance').

For groups (*b*) and (*c*), follow-up period was between 1 and 8 months (see methods).

For patients in group (*a*) with no pathogens isolated from their swabs, 13/20 (65%) treated with antibiotics were judged improved, compared with 10/21 (48%) not treated ($\chi^2 = 0{\cdot}67$ with Yates' correction, $P > 0{\cdot}5$). Taken as a whole, this group provides an average rate of spontaneous improvement of 56% for 'non-microbiological' disease.

For patients with GBS or GAS, antimicrobial treatments could be grouped on the basis of *in vitro* susceptibility into 'inappropriate' (antifungals, metronidazole

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Table 3. *Genital tract symptoms and signs (specifically sought in questionnaire) in relation to swab culture results*

	Culture result (No. for which feature present / No. for which data available)		
	No. pathogens isolated ($n = 96$)	Streptococcus group B ($n = 114$)	Streptococcus group A ($n = 41$)
Vaginal discharge	36/89	35/105	11/40
Absent physiological			
Colour			
White/cream	25/89	31/105	4/40
Yellow	18/89	30/105	19/40*
Other colour	10/89	9/105	6/40
Consistency			
Homogeneous	42/53	52/70	26/29
Curdy	11/53	18/70	3/29
Appearance of vaginal mucosa			
Inflamed	18/87	35/107**	22/33***
Not inflamed	69/87	72/107	11/33
Appearance of cervix			
Abnormal	13/58	11/77	2/17
Normal	45/58	66/77	15/17

* $0{\cdot}02 < P < 0{\cdot}05$ *v.* control group ($\chi^2 = 5{\cdot}19$, 1 D.F.).
** $0{\cdot}05 < P < 0{\cdot}1$ *v.* control group ($\chi^2 = 3{\cdot}49$, 1 D.F.).
*** $P < 0{\cdot}001$ *v.* control group ($\chi^2 = 22{\cdot}76$, 1 D.F.).

Table 4. *Other recorded clinical features in relation to swab culture result*

	Culture result		
	No pathogens isolated ($n = 96$)	Streptococcus group B ($n = 114$)	Streptococcus group A ($n = 41$)
Vaginal soreness or irritation	19	30	20*
Abnormal bleeding	7	8	0
Abdominal pain or diagnosis of pelvic inflammatory disease	14	17	2

* $P < 0{\cdot}001$ *v.* control group ($\chi^2 = 11{\cdot}86$, 1 D.F.).

or none) and 'inappropriate' (β-lactam agent or erythromycin, given alone or in combination with other agents); four patients treated solely with agents difficult to classify (co-trimoxazole, oxytetracycline, betadine) were excluded.

No significant difference was found in the proportion of patients with GBS showing documented improvement or between appropriately and inappropriately treated patients ($\chi^2 = 0{\cdot}68$, 1 D.F.). (Table 8). For GAS patients, numbers were too small for χ^2 analysis. If the inference is made that the 'no further attendance' and

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Table 5. *Microscopy of HVS in relation to culture result*

	Culture result		
	No pathogens isolated ($n = 96$)	Streptococcus group B ($n = 114$)	Streptococcus group A ($n = 41$)
Number of leucocytes*			
'none' or 'very occasional'	28	37	4**
'occasional' or '±'	48	51	16
'+'	17	19	12
'++' or '+++'	3	7	9***

* Arbitrary grading based on high-power microscopy of wet preparations.
** $0{\cdot}01 < P < 0{\cdot}02$ *v.* control group ($\chi^2 = 6{\cdot}04$, 1 D.F.).
*** $P < 0{\cdot}001$ *v.* control group ($\chi^2 = 12{\cdot}74$, 1 D.F.).

Table 6. *HVS culture result in relation to previous antimicrobial treatment.*

	Culture result			
Antimicrobials received during the preceding 2 weeks	No pathogens isolated ($n = 96$)	Streptococcus group B ($n = 114$)	Streptococcus group A ($n = 41$)	Haemolytic streptococcus not group A, B, D ($n = 19$)
None	79	99	30	17
Local antifungal agent	7	5	4	0
Oral β-lactam	4	3	1	1
Oral erythromycin	0	2	2	0
Oral metronidazole	2	3	3	1
Miscellaneous	4*	2**	1***	0

* Tetracycline 1; trimethoprim, 1; sultrim pessary, 1; Vioform cream, 1.
** Tetracycline, 1; trimethoprim, 1.
*** Benzalkonium pessary, 1.

'no recorded symptoms' groups also represent a successful outcome following treatment, then again no benefit is associated with appropriate treatment in GBS patients ($\chi^2 = 0{\cdot}50$ 1 D.F.), but significant benefit in GAS patients ($\chi^2 = 23{\cdot}44$ with Yates' correction, $P < 0{\cdot}001$). Comparison of appropriately and inappropriately treated patients in the GBS group for factors that might have influenced decisions to treat revealed a non-significant excess of patients with abdominal pain or tenderness in the treated group (13/83 *v.* 1/25, $\chi^2 = 1{\cdot}39$ with Yates' correction), but no difference in stage of reproductive life, presence of clinical inflammation of the lower genital tract, or presence of leucocytes in the vaginal swab.

DISCUSSION

Morris & Morris (1967) first examined isolation rates for BHS vaginal swabs in symptomatic and asymptomatic women. Group B streptococci were significantly more common (6·2%) in their asymptomatic patients, who were attenders at a family planning clinic, than in women attending their general practitioners with a complaint of vaginal discharge (1·8%). No difference was noted for isolation

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Table 7. *Antimicrobial therapy in relation to HVS culture results*

Antimicrobial therapy	Culture results: No pathogens isolated	Streptococcus group B	Streptococcus group A	Haemolytic streptococcus other than groups A, B, D
None	56	20	1	2
Local anti-fungal agent alone	17	8	2	3
Oral β-lactam alone*	5	65	22	12
Erythromycin alone	5	19	7	2
Metronidazole alone	10	0	2	0
Combinations of the above	2	11	8	0
Miscellaneous	1 Betadine pessary	1 Betadine pessary 1 cotrimoxazole + metronidazole	1 oxytetracycline 1 cotrimoxazole + erythromycin 1 cotrimoxazole 1 penicillin V + Betadine pessaries	0
Total	96	125 46	19	

* Comprises: Penicillin V, ampicillin, amoxycillin, augmentin, cephalexin (2 patients), flucloxacillin (2 patients), mecillinam (1 patient).

Table 8. *Outcome of antimicrobial therapy in patients with β-haemolytic streptococci*

Outcome	Group B streptococcus (108 treatment courses in 97 patients)		Group A streptococcus (43 treatment courses in 39 patients)	
	Appropriate treatment	Inappropriate treatment	Appropriate treatment	Inappropriate treatment
Improvement (Complete/partial)	30	10	17	1
No improvement	9	2	2	4
No record of symptoms at next attendance	23	5	9	0
No further attendance during follow-up period	21	8	10	0
Total	83	25	38	5

rates of streptococci of other groups (including D), which ranged from 0·3% to 3·4% using non-selective media. No correlation was found between isolation of BHS and use either of vaginal tampons or oral contraceptives. However, in the 'symptomatic' group, no details of microbiological results other than BHS are given, and no further details of symptom or treatment are supplied. De Louvois *et al.* (1975*a*) divided 280 ante-natal clinic attenders into those with 'healthy' and those with 'morbid' lower genital tracts on the basis of standardized clinical criteria, in a prospective study. Isolation rates of BHS using Nalidixic Acid Blood Agar did not differ significantly between the two groups (11% in 'morbid' and 8% in 'healthy' group). Very full clinical details are given in an accompanying paper (Stanley *et al.* 1975) which notes a lack of correlation between the patient's and the clinician's assessment of vaginal discharge and also interobserver variations between clinicians. Finch, French & Phillips (1976) studied only group B streptococci, and using a selective broth enrichment medium achieved isolation rates of 17·1% from family planning clinic attenders and 36% from women attending a sexually transmitted diseases clinic. No correlation was noted with vaginal discharge, but details of other symptoms were not given.

The present study confirms the results of the earlier ones in respect of the non-pathogenicity of group B streptococci, no correlation being found between isolation of these organisms and recorded clinical symptoms and signs. (Interestingly, none of the general practitioners taking part measured vaginal pH, even though this is arguably the most useful supplementary test in differentiating the microbial causes of vaginal discharge in situations where sexually transmitted disease is unlikely (Blackwell *et al.* 1983).) Review of the outcome of treatment reinforces this view, although the lack of standardization of treatment used makes interpretation more difficult. It must also be conceded that assessment of treatment was not made 'blind', but by those who had prescribed it, and who were in possession of the microbiological results. Nevertheless, any resulting bias might be expected to be towards a favourable assessment of the effects of anti-streptococcal therapy, and the fact that no such favourable assessment emerges overall with GBS is notable. The presence of leucocytes in the vaginal swabs does

not, in our hands, indicate pathogenicity on the part of GBS. However, some selection bias in antibiotic treatment is evident towards patients with GBS who had abdominal pain or tenderness, and it cannot be assumed from this study that treatment is ineffectual in this group.

A syndrome of group A streptococcal vulvo-vaginitis in pre-pubertal girls has long been recognized (Christie, 1980), and 16 cases were noted during the 6 months of the present study. However, GAS were isolated from women of all ages and results of antibiotic therapy suggest that here too they are capable of causing significant inflammation, and should be treated. Thirteen of the 19 other haemolytic streptococci found were Lancefield group G, and all of these patients were given anti-streptococcal treatment. In view of the absence of data on the natural history of group G streptococci at this site (Gaunt & Seal, 1987), a separate study of this group would be useful.

As well as revealing the extremely variable prescribing antibiotic habits of general practitioners with genital tract disease in women, this study suggests that reporting of organisms by the laboratory is still often seen as an instruction to treat them. In view of this it is likely to be counterproductive for laboratories to report the presence of group B streptococci in genital tract specimens, unless there is strong clinical evidence of upper genital tract infection. However we will continue to report group A streptococci and, pending further work, haemolytic streptococci of groups C, G and F when growth is heavy.

ACKNOWLEDGEMENT

I am grateful to Mr N. Kramer for statistical advice.

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