A simple scoring system for evaluating symptoms, history and urine dipstick testing in the diagnosis of urinary tract infection

F.F. DOBBS, MRCOG, MRCGP General Practitioner Trainee, Birmingham

D.M. FLEMING, FRCGP
Deputy Director, Royal College of General Practitioners' Birmingham Research Unit

SUMMARY. Patients presenting with symptoms suggestive of urinary tract infection were recruited in a general practice survey aimed at measuring the predictive value of symptoms, history and urine dipstick testing for diagnosing the presence of bacterial infection. Urine specimens were obtained from 87% of the 521 patients recruited. A diagnosis of infection was established by urine culture producing a colony count in a pure culture exceeding 100 000 organisms per ml or between 10 000 and 100 000 organisms per ml plus a minimum of 100 leucocytes per mm³.

Occurrence rates for symptoms and other items of information in infected and non-infected groups were used to derive their positive and negative predictive values in making the diagnosis. The predictive value of volunteered symptoms was compared with that of elicited and volunteered symptoms combined. The positive predictive value of symptoms was increased where elicited symptoms were included but this was achieved at the cost of diminishing the negative predictive value. The occurrence rates were used to derive a mathematical model for diagnosing infection. The symptoms-history-urinalysis (SHU) score generated in this model compared well with a computer predicted probability. Both were substantially better than the assessment and action (decision to prescribe an antibiotic) of the recording doctor.

The scoring method described has been demonstrated in urinary tract infection but may be applied to any symptom combination related to a diagnosis for which there is an agreed definition.

Introduction

STUDIES of suspected urinary tract infection in general practice¹⁻⁵ indicate that in approximately 50% of possible cases a bacterial infection with a colony count exceeding 100 000 organisms per ml is not identified. However, a survey on urine culture by the Public Health Laboratory found that 94% of general practitioners start antibiotic treatment before receiving the culture report.⁶ Thus many patients are prescribed antibiotics unnecessarily for this common complaint and perhaps many unnecessary and wasteful cultures of urine specimens are taking place. It may be difficult to differentiate the presence or absence of infection on clinical grounds alone, ^{1,7-9} though O'Dowd⁵ believed it could be done if attention were paid to the psychosomatic features of the case.

Urine dipsticks have been advocated as an aid to diagnosis in the consulting room¹⁰ and in recent years an increasing variety of combinations of dipsticks has become available. Zilva¹¹ reviewed their usefulness in routine screening of urine and drew attention to the correct storage procedures, the need for careful technique using freshly voided urine collected without contamination and the desirability of using the minimum combination of tests to achieve the desired objective. She considered that the urine must be examined by microscopy and microbiological methods if urinary tract infection is suspected. The relative cost of urine microscopy and culture (local private hospital cost £9.25) and dipstick (N-Labstix 10p) must also be borne in mind.

The validity of the conventional criterion for a diagnosis of urinary tract infection (a colony count of 100 000 organisms per ml of urine) has been questioned by several authors.^{3,4,12} Stamm¹² considered a level of 100 organisms per ml may be a sufficient criterion and stressed the need for microbiologists to be given adequate clinical information. In order to minimize the number of urine samples cultured, many laboratories have introduced a preliminary screening of the dipstick type and urines found to be negative are not usually cultured. Support for this action is provided in a hospital based study of 3047 urines tested by N-Labstix¹³ where the predictive value of a negative test was 96% and of a positive test was 32%.

The present study analysed the symptoms and history of suspected cases of urinary tract infection, and the result of urine dipstick tests carried out in the practice using N-Labstix. The aim was to increase the precision with which the infection can be identified, thus leading to more rational use of urine culture and effective utilization of antibiotics. In addition the study provided the opportunity to review the occurrence of antibiotic-resistant organisms.

Method

The study was conducted at Northfield health centre. Birmingham, during the period November 1984 to June 1985. Three practices took part, involving 10 general practitioner principals and three trainees caring for a total registered population of 18 000 people. Patients presenting with symptoms suggestive of urinary tract infection were recruited. A questionnaire for each patient was completed at the time of recruitment, covering the presenting symptoms (frequency, nocturia, dysuria, haematuria, offensive urine, loin pain, abdominal pain, nausea, incontinence, vaginal discharge); the duration of symptoms; items of history (recent increase in sexual activity, previous urinary tract infection, previous intravenous pyelography, recent catheterization, recent pelvic surgery). Symptoms which were volunteered were recorded separately from those elicited on subsequent questioning. For the symptoms of frequency, nocturia and vaginal discharge a reported increase by the patient was accepted.

The assessment of the doctor of the likelihood of urinary tract infection being present (definite, probable, maybe) and his actions (midstream specimen of urine obtained or not, antibiotic prescribed or not) were recorded. Wherever possible the urine specimen was obtained before beginning antibiotic therapy. Urine was tested at the health centre using N-Labstix for the presence of protein, blood and nitrite and for its alkalinity. The specimens

[©] Journal of the Royal College of General Practitioners, 1987, 37, 100-104.

were then forwarded each weekday afternoon to Selly Oak Hospital microbiology laboratory. Specimens from children and pregnant women were all examined by microscopy, culture and sensitivity. All other specimens were first tested using N-Labstix and only examined further if blood, protein or nitrites were present. Further examination included microscopy (cell count in a counting chamber containing mixed but uncentrifuged urine), testing for the presence of bacterial inhibitors and culturing using standard methods and cysteine-lactose electrolyte deficient agar medium. Sensitivity to trimethoprim, ampicillin, sulphonamide, cephalexin, nalidixic acid and nitrofurantoin were assessed routinely when organisms exceeding 100 000 per ml of urine were cultured.

For this study the criteria for infection were either a colony count exceeding 100 000 organisms per ml with a pure urine culture or a count of 10 000-100 000 organisms per ml plus a minimum of 100 leucocytes per mm³. Urines containing bacterial inhibitors and in which mixed growths were cultured were excluded. The remaining urine samples were classified 'not infected'.

Analysis

After excluding any data set with a major omission (for example, no midstream urine specimen report available, uncertainty about patient identification), remaining data were summarized and entered on a computer file. Data sets in which there were minor omissions (for example, details regarding an item of history or practice dipstick test not available) were processed but excluded in those calculations to which the omission related. Analyses were made in six groups — children aged 0–14 years, pregnant women, and men and women respectively in age groups 15–49 years and 50 plus years.

The occurrence of symptoms in patients with infected urines was compared with that in patients with non-infected urines using a chi-square test with Yates correction. The predictive values (positive and negative) of each symptom, item of history and practice urine dipstick test were calculated. The positive predictive value is the percentage occurrence of these factors in infected urines and the negative predictive value is equal to 100

minus the occurrence in non-infected urines. These values were computed for volunteered symptoms and were compared with the values for volunteered and elicited symptoms combined.

The occurrences in infected and non-infected patients of certain symptoms, items of history and urine dipstick results where there were significant differences between infected and non-infected cases were used to develop a mathematical model in which the probability of a positive diagnosis of urinary tract infection could be calculated (Appendix 1). The score generated in this computation was called the symptoms-history-urinalysis (SHU) score. The percentage of cases predicted using this score was compared with those predicted using a computer aided program¹⁴ to process all items of information obtained in the study. The value of this computer model in assessing the predictive value of symptoms in the management of abdominal pain has been demonstrated. Finally results of the scoring system were compared with the assessment and action of the doctor.

Results

Altogether 521 patients were recruited with suspected urinary tract infection. In 456 patients a midstream specimen of urine was obtained and the laboratory results showed 115 (25%) of the samples were infected, the proportion being greatest among females aged 50 or more years. Of the infected samples 102 contained Escherichia coli; other organisms cultured in the 13 other urines were Proteus species (3), Staphylococcus albus (3), Klebsiella species (2), Streptococcus faecalis (2), Staphylococcus aureus (2) and Pseudomonas species (1). Bacterial inhibitors were found in 26 specimens and mixed growths were cultured in a further 25. Two hundred and ninety specimens were classified as not infected.

Of the 115 urine specimens from which organisms were cultured, 67 (58%) contained organisms sensitive to all antibiotics tested. Nalidixic acid was associated with the lowest level of resistance (3%) and ampicillin the highest (28%). The pattern of resistance was broadly similar in all age groups surveyed.

The occurrence of symptoms, items of history and urine dipstick test results in infected and non-infected cases is presented in Table 1 for four of the groups of patients; the numbers of

Table 1. Percentage occurrence of symptoms, items of history and urine dipstick test results by patients' group and infection status.

	Children 0-14 yrs.		Women 15-49 yrs.		Women 50+ yrs.		Men 50+ yrs.		All	
	Infected (n = 16)	Not Infected (n = 59)	Infected (n = 46)	Not Infected (n = 96)	Infected (n = 39)	Not Infected (n = 57)	Infected (n = 9)	Not Infected (n = 32)	Infected (n = 115)	Not Infected (n = 290)
Symptoms								-		
Frequency Nocturia Dysuria Urgency Haematuria Offensive urine Nausea	62* 31 75** 19 6 12 6	28 20 29 17 2 7 20	87* 67** 80*** 39 18 20 4	68 38 50 26 6 15	95** 87** 78* 62 3 30 10	67 49 49 42 7 14 20	58 28 71* 28 29 28 28	67 67 23 20 0 0	83*** 64*** 70*** 43*** 14* 22** 9*	36 40
History										
Symptoms for 9 days or less Previous UTI Previous IVP	93 43 14	67 22 0	89* 52 16	68 47 6	59 76 14	56 54 6	60 43 40	32 34 24	79** 57** 15*	62 40 6
Dipstick test										
Protein Blood Nitrite	56** 44* 38*	10 12 6	40** 74*** 46***	13 29 0	24 72 55***	27 49 7	80 100* 100***	13 25 4	41*** 69*** 54***	15 26 3

^{*}P<0.05, **P<0.01, ***P<0.001. Chi-square test (Yates correction) comparing infected and non infected. UTI = urinary tract infection. IVP = intravenous pyelography. n = total number of patients recruited (denominators vary slightly according to the completeness of the information).

infected urines in pregnant women and men aged 15–49 years were insufficient for inclusion in this table. Items are only shown in the tables where significant differences occurred in one or all of the groups. In the analysis of material relevant to the duration of history a history of nine days or less was found to be the most useful discriminator between the infected and non-infected cases. Table 1 shows that the presence of nitrite in the urine was the single most powerful positive predictor of the presence of urinary tract infection though it was not found in approximately half the infected cases.

The predictive values (positive and negative) of each of these factors among 110 females aged 15–49 years for whom a complete set of data were available were summarized separately for symptoms which were volunteered and for volunteered and elicited symptoms combined (Figure 1). In general, the positive predictive value of a factor improved when elicited symptoms were included but at the cost of a reduction in the negative predictive value. For nocturia and offensive urine there was obvious benefit in including elicited symptoms. Similar results were obtained for children and females aged 50 plus years.

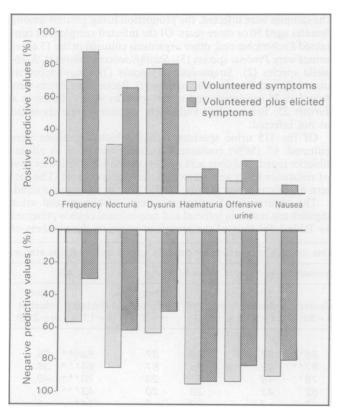


Figure 1. Predictive values of volunteered symptoms compared with volunteered and elicited symptoms combined in 110 women aged 15–49 years.

In 263 cases the results of urine dipstick test in the practice could be compared with that subsequently undertaken in the hospital laboratory (Table 2). For this purpose any abnormal finding (test positive for protein, blood or nitrite) was accepted as a positive test result. Concordance occurred in 199 (76%) cases. Twenty positive results in the practice were negative on hospital screening and 44 practice negatives were positive on hospital screening; cultures of 36 of the latter samples were not infected.

The occurrence rates of the important items of symptoms, history and urinalysis shown on Table 1 were used to derive the

Table 2. Results of dipstick testing in 263 urine samples: comparison of health centre and laboratory.

	Laboratory test					
Practice test	Positive (infected)	Positive (not infected)	Negative	Total		
Positive	66	61	20	147		
Negative	.8	36	72	116		
Total	74	97	92	263		

Table 3. The 'SHU' score factors for the diagnosis of urinary tract infection (see Appendix 1).

	Children 0–14 yrs.			men 9 yrs.	Women 50 + yrs.	
	Present	Absent	Present	Absent	Present	Absent
Symptoms						
Frequency	+ 2	-2	+ 1	-3	+ 1	-3
Nocturia	0	0	+ 2	-2	+ 2	-4
Dysuria	+3	-3	+2	-2	+ 2	-2
Urgency	0	0	+ 1	- 1	+ 1	- 1
Haematuria	0	0	+3	0	0	0
Offensive urine	+ 2	0	+ 2	0	+ 2	– 1
Nausea	-2	0	-2	0	-2	0
History						
Symptoms for						
9 days or less	+ 1	-3	+ 1	-3	0	0
Previous UTI	+ 2	– 1	0	0	+ 1	-2
Previous IVP	+ 2	0	+2	0	+ 2	0
Dipstick test						
Protein	+ 5	-2	+3	- 1	0	0
Blood	+4	– 1	+3	-3	+ 1	-2
Nitrite	+4	– 1	+11	- 2	+ 5	-2

SHU score (Appendix 1). The scoring system is reported for three of the groups of patients (Table 3); the numbers of infected urines in men and in pregnant women were insufficient for this calculation.

In a separate analysis involving all the items of information collected in the survey, the computer assisted diagnostic model¹⁴ was used to calculate the probability of infection in individual cases. Comparison of the probability assessed in this way with the SHU score for 110 females aged 15-49 years showed both methods produced a similar spectrum of results (Figure 2). An SHU score of zero is equivalent to a probability of infection of 50% and in our opinion represents a suitable level for initiating antibiotic treatment in cases of suspected urinary tract infection. Figure 2 shows that 89% of infected cases and 33% of non-infected cases were included in the group of patients with a positive or zero SHU score; 83% and 11% respectively were included in the group having a computer predicted probability exceeding 50%. For the non-infected group the difference in prediction by the SHU score compared with the computer method (33% as against 11%) was due entirely to the high occurrence rate of several minor symptoms (sweating, loin pain, incontinence, vaginal discharge) in the non-infected group. These differences were not statistically significant and were not included

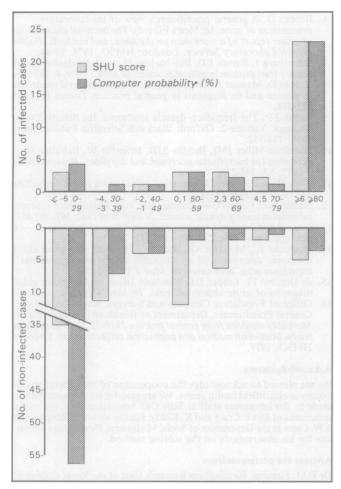


Figure 2. Numbers of infected and non-infected cases for 110 women aged 15–49 years: comparison of SHU score and computer probability.

in the SHU score. The differences corresponded to a score factor of -1 for the presence of each of these systems and a score factor of 0 for the absence of each.

A further comparison of the percentage of infected and non-infected cases predicted as infected by the SHU score, the computer and the general practitioner's assessment and action is presented for three patient groups for whom complete data are available in Table 4. Computer assisted predictions were marginally better than the SHU score but both were better than the doctor's assessment and action.

The SHU score and computer predicted probability in these three patient groups were also measured in 17 cases in which bacterial inhibitors were found and 19 in which mixed growths were cultured and for whom a sufficient data set was present (Table 5). SHU scores exceeded 0 in five of the cultures with bacterial inhibitors and 11 with mixed growths, and the computer predicted probability exceeded 50% in five and nine cases respectively. Table 5 also includes information about the SHU score and computer predicted probability for patients in which there was non-concordance between urine dipstick testing in the practice and at the laboratory.

The incidence of computer prediction of infection in the mixed growth cases (47%) was higher than that identified in all the non-infected cases (16%, P < 0.01) so probability scoring may allow separation of significant mixed growth infection from contamination. In the non-concordant N-Labstix tests, cases found to be positive at the health centre had a higher incidence of computer prediction of infection (38%) than laboratory positive cases (11%), though the difference did not reach statistical significance.

Table 4. Percentage of infected and non-infected cases predicted as infected by various criteria.

Group	SHU score 0 +	Computer predicted probability 50% +	GP opinion	GP action (antibiotic prescribed)
Children 0-14 yrs.				
Infected (n = 16) Not infected	88	81	53	69
(n = 47)	21	19	21	35
Women 15-49 yrs.				
Infected (n = 35) Not infected	89	83	74	69
(n = 75)	33	11	30	40
Women 50+ yrs.				
Infected (n = 27) Not infected	85	85	69	81
(n = 47)	15	22	40	35
All cases				
Infected (n = 78) Not infected	85	83	68	72
(n = 169)	25	16	30	38

Table 5. Percentage of cases with equivocal culture results for which the SHU score exceeded 0 or the computer predicted probability exceeded 50%.

	SHU score 0 +	Computer predicted probability 50% +
Bacterial inhibitors		
present $(n = 17)^a$	29	29
Mixed growths cultured $(n = 19)^a$	58	47
Non concordant dipstick tests		
Health centre positive,		
laboratory negative $(n = 16)^a$ Health centre negative,	50	38
laboratory positive $(n = 36)^a$	18	11

^aCases only shown for which a sufficient data set was available.

Discussion

Medicine is not an exact science, but is based on probability where actions are determined by identifying favourable risk/benefit ratios. On economic grounds and from obvious commonsense, many laboratories have restricted the number of urine samples cultured though it has to be acknowledged that these are submitted for analysis because of the suspicion of urinary tract infection. Although dipstick testing for protein, blood and nitrite is a useful screen and is entirely appropriate for use in practice it carries an appreciable risk of error when used without any clinical appraisal. Urine culture is the only end-point by which a scientific study of urinary tract infection can be judged. This procedure has limitations, however, as not every urine sample arriving at a laboratory is fresh and uncontaminated, patients sometimes take bacteriostatic agents before consulting the doctor, mixed growths cause confusion and the conventional criterion of 100 000 organisms per ml is itself arbitrary and based on probable rather than absolute criteria.

The key decision for the general practitioner concerns the prescribing of antibiotics, which, if the patient is distressed, ought to be prescribed early rather than late in the illness. Appropriate use of urine culture is desirable but this procedure costs much more than most courses of antibiotics and cannot always be organized easily in rural areas or at inconvenient times of the day or week. Nevertheless there is a tendency by some doctors to overstate this problem; we achieved a midstream urine specimen screen in 87% of suspected cases. The incidence of infection (25%) was lower than that seen in many other reports and this largely reflects the lower threshold for testing patients with suspicious symptoms. In the second national morbidity study 1971-72,16 the episode rate of urinary tract infection amounted to 38 per 1000 per annum. Applying this estimate we might have expected to recruit approximately 400 patients in the seven months, which compares with the 521 we actually recruited.

A symptoms-history-urinalysis (SHU) score of zero or more identified 89% of infected cases and included only 33% of non-infected cases. This compares well with the computer predicted probability, taking all factors into account, and is substantially better than both the clinical assessment of the doctor and his action, as judged by the decision to prescribe an antibiotic. At the least therefore the SHU score enhances decision-making in cases of suspected urinary tract infection. O'Dowd and colleagues⁵ reported a survey in which the management of 46 women with urinary tract infection was compared with that of 40 with the urethral syndrome. They believed these groups could be distinguished if attention were given to psychosomatic factors. These findings differ from those of others, 1,7-9 who could not discriminate on clinical grounds between the two.

When planning the study we were concerned that symptoms volunteered by patients might have a different value than those obtained by direct questioning, a matter of particular importance for computer modelling. Although there were some differences between the predictive values of volunteered symptoms compared with volunteered and elicited symptoms, they were in general small. For the symptoms 'offensive urine' and 'nocturia', there were marked differences which in practical terms favour the inclusion of the elicited symptoms.

The scoring system described translates observed probabilities into a simple summation of single digits to derive an overall probability of diagnosis. It is applied specifically here to urinary tract infection though it can equally be applied to any combination of occurrences in relation to a well-defined diagnosis. The quantification of symptoms, history and urinalysis presented here enhances the quality of the clinical diagnosis and hence the quality of care of patients with urinary problems. Before we are in a position to make logical recommendations for widespread use of the SHU score, this method has to be tested in a prospective survey and this is planned. In the interim we would suggest that an SHU score of zero or more gives a useful guide to diagnosis and would welcome an extension of this approach to, for example, the quantification of symptoms in other areas of medical care.

References

- Mond NC, Percival A, Williams JD, Brumfitt W. Presentation, diagnosis and treatment of urinary tract infection in general practice. *Lancet* 1965; 1: 574-576.
- Gallagher DJA, Montgomerie JZ, North JDK. Acute infections of the urinary tract and the urethral syndrome in general practice. Br Med J 1965; 1: 622-626.
- Murphy DM, Cafferkey MT, Faulkiner FR, et al. Urinary tract infection in female patients a survey in general practice in the Dublin area. Ir Med J 1982; 75: 240-242.
 Jordan S, Wilcox GM, Wasson JH. Urinary tract infection in
- Jordan S, Wilcox GM, Wasson JH. Urinary tract infection in women visiting rural primary care practices. J Fam Pract 1982; 15: 427-428.
- O'Dowd TC, Small JE, West RR. Clinical judgement in the diagnosis and management of frequency and dysuria in general practice. Br Med J 1984; 288: 1347-1349.

- Brooks D. A general practitioner's view of the laboratory examination of urine. In: Meers PD (ed). The bacterial examination of urine; report of a workshop on the needs and methods. Public Health Laboratory Service. London: HMSO, 1978: 39-44.
- Steensberg J, Bartels ED, Bay-Nielson H, et al. Epidemiology of urinary tract diseases in general practice. Br Med J 1969; 4: 390-394.
 Brooks D, Maudar A. The pathogenesis of the urethral syndrome
- Brooks D, Maudar A. The pathogenesis of the urethral syndrome in women and its diagnosis in general practice. *Lancet* 1972; 2: 893-898.
- Marsh FP. The frequency-dysuria syndrome. In: Blandy J (ed). Urology. Volume 2. Oxford: Blackwell Scientific Publications, 1976: 734-752.
- Hamilton-Miller JMI, Brooks SJD, Brumfitt W, Bakhtiar M. Screening for bacteriuria: microstix and dip slides. *Postgrad Med J* 1977; 53: 248-250.
- Zilva JF. Is unselected biochemical urine testing cost effective? Br Med J 1985; 291: 323-325.
- Stamm WE, Counts GW, Running KR, et al. Diagnosis of coliform infection in acutely dysuric women. N Engl Med 1982; 307: 463-467.
- Lowe PA. Chemical screening and prediction of bacteriuria a new approach. Med Lab Sci 1985; 42: 28-33.
- Horrocks JC, McCann AP, Staniland JR, et al. Computer aided diagnosis: description of an adaptable system and operational experience with 2034 cases. Br Med J 1972; 2: 5-8.
- 15. de Dombal FI, Leaper DJ, Staniland JR, et al. Computer aided diagnosis of acute abdominal pain. Br Med J 1972; 2: 9-13.
- Office of Population Censuses and Surveys, Royal College of General Practitioners, Department of Health and Social Security. Morbidity statistics from general practice 1971-72. Second national study. Studies on medical and population subjects no. 36. London: HMSO, 1979.

Acknowledgements

We are pleased to acknowledge the cooperation of the general practitioners in Northfield health centre. We are grateful for the contribution made by the laboratory staff at Selly Oak hospital and for the useful comments of Drs I. Craig and K. Kiddy. Finally we are indebted to Dr KW. Cross in the Department of Social Medicine at Birmingham University for his observations on the scoring method.

Address for correspondence

Dr D.M. Fleming, Birmingham Research Unit of the Royal College of General Practitioners, 54 Lordswood Road, Harborne, Birmingham B17 9DB.

Appendix 1 - Derivation of symptoms-history-urinalysis (SHU) score
The computer based system for combining probabilities of symptoms¹⁴
uses the occurrence rate of each symptom in the infected and non-infected
groups. The occurrences of each symptom in the infected group are
multiplied together to obtain a product representing the probability that
the patient belongs to the infected group (pro-infection product). Similarly, the occurrences of each symptom in the non-infected group are
multiplied together giving a product for the probability that the patient
belongs to the non-infected group (con-infection product). The actual
percentage probability of infection is then obtained by calculating the
percentage that the pro-infection product is of the sum of the proinfection product and con-infection product.

The SHU score system is derived from the computer system to allow simple mental arithmetic calculation of probabilities. SHU-score factors (see Table 3) are derived from the logarithm of the occurrence of the factor in each group, thus allowing addition instead of multiplication of the factor for each symptom. In addition the ratio of occurrence rates in the infected and non-infected groups is used to avoid separate pro and con factors.

SHU score = 2 x log₂ (percentage occurrence in infected cases) (percentage occurrence in non-infected cases)

To allow easy mental addition of the scores, logarithms to base 2 are used, and the log value is doubled and rounded to the nearest whole number. This decreases rounding errors and gives scores in the range 0 to \pm 11. Scores for absence of symptoms are calculated in the same way, using '100 minus percentage occurrence' instead of 'percentage occurrence'.

The final sum is approximately equal to the odds for or against infection for values ± 2 , ± 3 , ± 4 , (for example, a sum of -4 is equivalent to odds of 4 to 1 against infection or a probability of infection of $1/5 \times 100 = 20\%$). For other values, the odds can be calculated as the square root of 2 to the power of the sum (for example for a sum of +6, the odds for infection = $\sqrt{2^6} = 2^3 = 8$ to 1). The final sum is obtained by adding the 'present' factor for any symptom present, and the 'absent' factor for any symptom absent (Table 3). A sum of zero corresponds to a probability of infection of 50%.