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# Infective complications of open-heart surgery and the monitoring of infections by the NBT test

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**Freeman, R., King, B., and Hambling, M. H. (1973). *Thorax*, 28, 617–621. Infective complications of open-heart surgery and the monitoring of infections by the NBT test.** Seventy-four consecutive patients undergoing open-heart surgery were extensively investigated, preoperatively and postoperatively, for evidence of infection. The incidence of the infective complications encountered is presented, together with discussion on the aetiology of these complications. A previously unrecognized infective complication is described, this being a high incidence of infection with *Mycoplasma pneumoniae*.

The series also reports an assessment of the nitroblue tetrazolium (NBT) test in these patients, and it is concluded that the system evolved in this series, of minimal chemoprophylaxis and constant monitoring of infection, affords a logical alternative to conventional methods using massive prophylaxis.

Open-heart surgery is now a well-established procedure. One of the most feared complications which can arise is postoperative infection. A group of patients undergoing open-heart surgery have been studied, and the results and techniques are reported.

## PATIENTS

The series consists of 74 consecutive patients who underwent open-heart surgery. There is no case selection, the sole criterion being that the operation involved cardiopulmonary bypass and was elective.

## METHODS

Patients' progress was divided into three stages for the convenience of description: (1) preoperative assessment; (2) postoperative period A—intensive care unit; (3) postoperative period B—convalescence.

PREOPERATIVE ASSESSMENT Each patient had a bacteriological survey, the following specimens being obtained: mouth swab, throat swab, nasal swab, axilla swab and groin swab; midstream urine for microscopy and culture; 1·0 ml venous blood for nitroblue tetrazolium (NBT) test; and 10 ml serum for baseline serological studies.

All the swabs were examined for the presence of *Staphylococcus aureus*, and the urine was examined microscopically for casts and cells. Culture of the urine was by a semiquantitative method, using a commercial dip-inoculum method. Significant bacteriuria was taken to be the isolation of 100,000 organisms or more per millilitre of urine. All organisms isolated throughout the study were identified by routine methods.

Each patient then received a preoperative treatment of the skin and external nares. The skin preparation consisted of daily baths using chlorhexidine soap, beginning three days before the operation, and painting of the operation field with an iodine-based solution. Skinfolds were treated with antiseptic powder, and the nose was treated with a neomycin-based cream twice daily for three days before the operation.

Each patient was given prophylactic antibiotics for 48 hours, starting 12 hours before the operation and ceasing after eight doses had been given at intervals of six hours. Each injection consisted of 1·0 g of ampicillin and the same dose of cloxacillin.

POSTOPERATIVE PERIOD A—INTENSIVE CARE UNIT Immediately after operation each patient was sent to the intensive care unit. At the time of transfer the patient was intubated (endotracheal) and had in place several intravenous and intra-arterial catheters. An indwelling bladder catheter was also in place. Following the end of the period of prophylaxis, no antibiotic was given without a specific indication. During this period of intensive care the following specimens were taken: daily mouth swab, daily bronchial secretion or sputum, daily urine specimen, and daily blood for NBT test; blood cultures were taken from a noncatheterized vein for the first two days, or until all the intravascular catheters had been removed, whichever was the shorter period.



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As each catheter was removed the tip was severed under aseptic conditions and sent for culture. This procedure was also followed for the urinary catheters. Two policies were followed regarding the intravascular catheters. In the early part of the series the intravascular catheters were left in place for as long as was thought necessary, often for up to eight days. Analysis of the early results suggested that this practice was unwise, and in the later part of the series every effort was made to remove these catheters as early as possible, if necessary continuing any intravenous therapy by infusion into a peripheral vein.

POSTOPERATIVE PERIOD B—CONVALESCENCE Assuming an uneventful recovery from the operation the patient was returned to the convalescent ward after three to four days of intensive care. During the period of convalescence NBT monitoring continued. Any suspicious signs, for example, pyrexia and increase in the white blood count, were immediately investigated, the following specimens being routinely obtained: blood for NBT test, sputum, midstream urine for microscopy and culture, and white blood count and differential, looking especially for 'atypical lymphocytes'; 10 ml serum was taken and serology was performed for viral antibodies, comparing the results with those obtained on the preoperative sample. Blood cultures were performed in some cases.

Any other relevant specimen was obtained, for example, wound swab and chest aspirate.

Significant serological results were taken to be those in which a fourfold, or greater, rise in specific antibody was shown in successive samples.

## NITROBLUE TETRAZOLIUM (NBT) TESTS

The test was performed using the procedure of Park (Park, Fikrig and Smithwick, 1968) with the subsequent modification of Freeman and King (1971). Any value greater than 11% was taken to be positive, that is indicating active bacterial infection. In this context the phrase 'bacterial infection' included infection with *Mycoplasma pneumoniae* (Freeman and King, 1972b).

## RESULTS

The results of the tests were assessed retrospectively when all the other data had been assembled. We have assessed each test result for the occasion on which it was performed. For each test result we assessed the patient concerned for evidence of active bacterial infection on the day that the result was obtained. We then placed each assessment into one of the following two categories:

1. Proven active infection: This means that on the day on which the test was performed the patient could be shown to have had an uncontrolled bacterial infection, the diagnosis being established by conventional criteria. These criteria were bacterial culture, radiology, and serology.

2. No active infection: This is a group of patients without proven infection on the criteria stated. A small group of patients who were known to be infected but who were on effective chemotherapy at the time that the test was performed are also included here. However, they are included only if the chemotherapy which they were receiving could be shown to be effective by conventional parameters, such as return of a previously elevated temperature to normal and control of the white cell count.

It must be emphasized that this classification was made using all available information, which included the results of necropsy where appropriate. Since the test is claimed to be negative in viral infections, these were included in the second group.

The results are presented separately, each dealing with specific aspects of the work (Tables I to V).

TABLE I

PREOPERATIVE ISOLATION OF *STAPH. AUREUS* AND POSTOPERATIVE INFECTION WITH THE ORGANISM

| Site | Isolation Rate | |
|---|---|---|
| Nose .. .. .. | 20/74 | 27% |
| Throat .. .. .. | 3/74 | 4% |
| Axilla .. .. .. | 5/74 | 7% |
| Groin .. .. .. | 10/74 | 13% |

Postoperative infection: No cases due to *Staph. aureus*

TABLE II

URINARY TRACT INFECTION

*Preoperative investigation*

| No. of Patients | Microscopy Abnormal +Significant Growth | Microscopy Abnormal-sterile |
|---|---|---|
| 74 | 3/74 | 1/74 |

Significant growth was taken to be 100,000 or more organisms/ml

*Isolation of organisms from tips of urinary catheters*

| No. of Catheter Tips Received | Isolation Rate | |
|---|---|---|
| 61 | 28/61 | 46% |

*Postoperative urinary tract infection*

| No. of Patients | No. Developing Significant Bacteriuria | |
|---|---|---|
| 74 | 21/74 | 28% |

## TABLE III

INTRAVENOUS AND INTRA-ARTERIAL CATHETERS

*Overall isolation rate of organisms from catheter tips*

| No. of Catheter Tips Sampled | No. from which Organisms Isolated | |
|---|---|---|
| 149 | 24/149 | 16% |

*Results prior to early removal policy*

| No. of Patients | No. of Catheters Sampled | Mean Time *in situ* | Isolation Rate | |
|---|---|---|---|---|
| 36 | 37 | 3·9 days | 13/37 | 35% |

*Results after early removal policy*

| No. of Patients | No. of Catheters Sampled | Mean Time *in situ* | Isolation Rate | |
|---|---|---|---|---|
| 38 | 112 | 1·75 days | 11/112 | 8% |

*Types of organisms isolated from catheter tips before and after early removal policy*

| Organism | No. Isolated | |
|---|---|---|
| | Prior to Early Removal | After Early Removal |
| Micrococcus .. .. .. | 4 | 6 |
| Faecal streptococcus .. .. | 2 | 1 |
| Aerobic sporing bacillus .. | 2 | 6 |
| Coliform bacillus .. .. | 2 | Nil |
| Candida .. .. .. | 4 | Nil |

All blood cultures were sterile

## TABLE IV

RESULTS OF SEROLOGICAL INVESTIGATION

| Antigen | No. of Patients showing Four-fold or Greater Rise in Complement-fixing Antibody Titre | |
|---|---|---|
| Cytomegalovirus .. .. | 3 | 4% |
| *Myocoplasma pneumoniae* .. | 14 | 19% |

In those instances in which a significant rise in complement-fixing antibody to *Mycoplasma pneumoniae* or cytomegalovirus was shown, the sera were tested against a panel of complement-fixing antigens, including influenza A and B, mumps, psittacosis-LGV group of agents, and *Coxiella burneti*, together with normal yolk-sac antigen. In no case was a fourfold rise in antibody titre shown, and no evidence of a significant anamnestic response was found.

## TABLE V

ASSESSMENT OF NITROBLUE TETRAZOLIUM TEST

| | |
|---|---|
| Total number of tests performed .. .. .. | 535 |
| Number of tests positive (greater than 11%) .. | 144 |

*Analysis of* 144 *instances in which the test was positive*

| No. of Positive Tests | Active Bacterial Infection Found | No Infection Found |
|---|---|---|
| 144 | 106 (75%) | 38 (25%) |

TABLE V (Continued)

ASSESSMENT OF NITROBLUE TETRAZOLIUM TEST

*Analysis of* 391 *instances in which the test was negative*

| No. of Negative Tests | Active Bacterial Infection Found | No Infection Found |
|---|---|---|
| 391 | Nil | 391 (100%) |

*Analysis of* 38 *instances in which the test was positive but no evidence of bacterial infection was found*

| No. of Positive Tests | Comments |
|---|---|
| 12 test results .. | All come from patients undergoing intensive care in the period before catheters were removed early, and in whom no catheter tips were sent for culture |
| 10 test results .. | All come from patients suspected of having had infection with *Mycoplasma pneumoniae*, but in whom paired sera were not obtained for testing |
| 16 test results .. | All come from one patient, who had an undiagnosed febrile illness which responded to antibiotics, but no definite cause could be found |

The results of the work on the specimens of bronchial secretion have been considered separately and will form the basis of a further report.

## DISCUSSION

Open-heart surgery is a procedure in which infection is a hazard for two separate reasons. First, patients undergoing open-heart surgery are liable to infection in the same way that patients undergoing any surgical procedure would be at risk, that is, postoperative wound sepsis or pulmonary infection may occur.

Secondly, it is commonly accepted that open-heart surgery patients incur additional risks due to the specialized nature of the operation. Thus, they are liable to develop infective endocarditis, and there appears to be at least one infective complication peculiar to cardiopulmonary bypass or, more correctly, the fresh blood transfusions which bypass requires (Caul *et al.*, 1971).

For these reasons, and for some other less scientific reasons, it is common to include open-heart surgery with those procedures which should have prophylactic antibiotic cover (Garrod and O'Grady, 1971). Recent evidence would seem to contradict this view (Sallam, Mackey, and Bain, 1970), and there are those who would argue that such prophylaxis might even produce positive harm (Price and Sleigh, 1970). We therefore elected to pursue a policy of very brief chemoprophylaxis, combining it with vigorous local treatment in the preoperative stages. Using *Staph. aureus* as an indicator of the success of this scheme, no

infections were encountered with this organism in the postoperative period despite the detection of a substantial carriage rate in the preoperative assessment. It would be interesting to speculate, in the light of others' experience (Sallam *et al.*, 1970), how much was due to the chemoprophylaxis and how much was due to the local treatment.

Having elected for such a policy, it is important that a system be available which will detect infection efficiently, reliably, but above all quickly. To this end the system described earlier in this paper was devised. The daily specimens on the intensive care unit are the key, since it is at this stage that infection can be overlooked in a patient who may not be displaying the usual signs and symptoms because of other problems.

URINARY TRACT INFECTION The routine examination of urine preoperatively is very common and has two uses. First, it screens the patients for asymptomatic infection, and secondly it may contribute towards the overall assessment of renal function necessary in these patients, for example by the finding of casts and red cells. This study revealed that a small number of patients had urinary tract infections, and the importance of this was shown when one such patient developed Gram-negative septicaemia in the postoperative period despite being treated beforehand. It is also important to note that 28% of the patients developed significant bacteriuria sometime in the postoperative period. Not all of these patients had symptoms and signs other than a low-grade pyrexia. It became clear that examination of the urine was a necessary routine test in the investigation of postoperative pyrexia. The aetiology of this substantial incidence of bacteriuria is almost certainly related to the very high rate of colonization found in culture of the bladder catheter tips. Our figures are unfortunately insufficient to elucidate the connection more precisely.

INTRAVENOUS AND INTRA-ARTERIAL CATHETERS The association of infection and indwelling intravascular catheters has been reported previously (Freeman and King, 1972a), and the same situation was found in this series. What was, however, additionally found was the effect on this complication of simply adopting a policy of early catheter removal. This has resulted in a dramatic fall in the infection rate and has also produced a trend away from resistant organisms to more sensitive bacteria. This latter statement is based on a small number of cases, but it is gratifying to note the absence of *Candida albicans* when the catheters are removed early. It is also important to note that the organisms isolated from these catheters are the very organisms commonly found to cause endocarditis in open-heart surgery. The recognition and control of this complication are important.

RESULTS OF SEROLOGICAL INVESTIGATIONS In the postoperative period the practice of routinely sending serum for detection of complement-fixing antibodies to cytomegalovirus was adopted in cases of postoperative pyrexia. A surprise finding was the low incidence, since we had previously assessed this to be 15%, but since that time the procedure used for bypass has been modified, and very little fresh blood is used. The explanation may therefore be that the low incidence of cytomegalovirus infection is merely a reflection of the reduction in the amount of fresh blood transfused (Caul *et al.*, 1971).

During this series it was noticed that several patients developed a characteristic picture postoperatively. They became pyrexial but claimed to be feeling well, and they all exhibited a strongly positive NBT test. All cultures and other investigations for a bacterial cause were negative, but each patient so affected recovered completely in three to four days and the NBT test became negative. From the sera sent for cytomegalovirus antibodies it was found that serological evidence of infection with *Mycoplasma pneumoniae* could be shown in every case. Having thus been alerted, further cases with the same presentation were similarly investigated, and we recorded an overall incidence of infection with *Mycoplasma pneumoniae* in 19% of patients, this figure being the minimum since several patients escaped serum samples being taken due to accidents and oversights.

The association of infection with *Mycoplasma pneumoniae* and open-heart surgery has not apparently been previously described and it is intended to produce a full account of this disease in the future. At the moment it can be stated that the clinical picture is characteristic, and the infection is initially detected by the NBT test. No specific treatment has been necessary and all the affected patients show no residual effects after more than six months.

ASSESSMENT OF NBT TEST The NBT test has been reported to be efficient and reliable in detecting bacterial infection (*Lancet*, 1971). A subsequent report indicated its use in a serial manner to control chemotherapy (Freeman, King, and Kitt, 1973). Such a procedure, if shown to be applicable to open-heart surgery patients, would be

worthwhile. The sensitivity and specificity of the test have been assessed in this series, using all the other data gathered, since these patients comprise a group in which infection has been looked for intensively. The results show that if the test is negative, bacterial infection can be virtually excluded from consideration. There are many situations in open-heart surgery where such information is invaluable.

Equally important is the finding that if the test is positive, bacterial infection is very likely. It is important to emphasize that a positive result may indicate infection with *Mycoplasma pneumoniae*. The sensitivity of the test in this assessment was found to be 75%, but in some of the instances of 'false positive' results, the explanation put forward would indicate that they were valid cases of bacterial infection. It cannot be claimed that the 16 unexplained positive results which came from a single patient with an obscure febrile illness can be accepted without further proof, but it is considered that the 12 positives in the patients with intravascular catheters, and the 10 positives which came from patients who probably had mycoplasma infection, are almost certainly true positive results. If these are accepted the sensitivity of the test is probably of the order of 90%. It is thus felt that the NBT test is a valuable aid in the management of open-heart surgery patients, particularly in detecting those infections which have no specific symptoms, such as catheter infections, urinary tract infection, and the mycoplasma infection referred to earlier. As previously stated, this test can also be used to follow the treatment of a case, once diagnosed, and it has proved to be of value in such instances.

Finally, it has been shown that by adopting the techniques described in this study, antibiotic treatment becomes infrequent. Quite apart from the great saving in cost, the possibility of masking endocarditis by using inadequate chemotherapy has been eliminated. These comments, however, apply only to endocarditis developing in the immediate postoperative period, of which this series contains none. Endocarditis developing after discharge from hospital may well have a different aetiology, quite unrelated to the immediate postoperative management.

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