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Life-threatening surgical infection: its development and prediction

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Summary

A number of clinical, investigational, immunological, and peroperative host factors are identified which will predispose the patient to a serious postoperative infection that may endanger his life. The degree of the risk and the severity of the infection can be predicted, but only fairly crudely at present. The future holds a more precise identification of these risk factors and thus greater accuracy in predicting operative risk. The methods of preventing life-threatening postoperative infections, both those currently used and those projected for the future, are discussed.

Introduction

> Know then thyself, presume not God to scan,
> The proper study of mankind is man.
> *An Essay on Man* II:1,
> Alexander Pope (1688–1744)

The introduction of antisepsis and asepsis and later the discovery of antibiotics, as well as the principles of careful surgical technique, have greatly decreased surgical infections and advanced the scope of surgery. Serious surgical infections such as septicaemias and large abscesses still occur, however, and some, such as Gram-negative infections and hospital surgical infections, are on the increase[1].

No new major concepts have been developed in recent years regarding antisepsis, asepsis, and antibiotics. We have therefore turned to the patient to determine whether there are any factors in the host which will predispose it to the development of a serious infection. This lecture deals with postoperative surgical infections as seen in the human. Attention is focused on infections which could endanger the patient's life, such as a septicaemia or an abscess which may lead to a septicaemia.

Retrospective study

MATERIAL

The subjects of this survey were 917 patients on whom an elective abdominal operation was performed by me in the past 10 years. Patients who required urgent surgery, those in whom an infection, such as a liver abscess, was the main reason for surgery, and those who were operated on by residents or registrars under my supervision were excluded. Retrospective surveys have a number of shortcomings, the most important of which is that the data one eventually seeks may not have been systematically recorded in every case. The redeeming feature of this retrospective survey is that I had kept careful records of each patient's preoperative clinical condition and of the findings at operation. Also, a precise record of the postoperative course was made, including the nature and severity of complications.

As may be seen from Table I, there was a large bias towards biliary tract and pancreatic

TABLE I *Postoperative infections in 917 abdominal operations*

Type of operation	*No of cases*	*Infections*	%
Biliary tract surgery	516	48	9·3
Pancreatic surgery	77	20	26
Large-bowel resection	68	16	23·5
Malignant lymphoma surgery	42	13	31
Other abdominal operations	214	25	11.7
Total	917	122	13·3

Hunterian Lecture delivered on 8th June 1977

TABLE II *Retrospective study of clinical risk factors in 917 patients*

Risk factor	*No of cases*	*Infections*	%
Weight loss, malnutrition	271	47	17.3
Malignant disease	193	64	33.2
Drugs (steroids, cytotoxics)	49	9	18.4
Diabetes	68	28	41.2
Alcoholism	61	19	31.1
Peroperative contamination	108	22	20.4

surgery because of my personal interest. The biliary tract operations were mostly cholecystectomies for gallstones, but they also included bile duct explorations and operations for biliary stricture and biliary tract carcinomas. Half the pancreatic surgery was performed for carcinoma and the other half for chronic pancreatitis. Large-bowel resection was mainly performed for carcinoma. The operations for malignant lymphoma involved either a splenectomy only or a splenectomy combined with a staging laparotomy procedure. There were 214 miscellaneous abdominal operations involving diseases of the liver, stomach, and duodenum and other less common gastrointestinal problems.

FINDINGS

There were 122 postoperative surgical infections in the 917 patients, an incidence of 13.3%. Chest infections and urinary tract infections were excluded. The incidence of infection following the various types of surgery varied, as may be seen from Table I.

When the records were further examined it became apparent that there were a number of factors which were associated with a much higher incidence of infection than that seen for the whole group (Table II). Gross weight loss and malnutrition, the presence of malignant disease, the previous use of steroids or cytotoxic drugs, and the presence of diabetes or alcoholism in the patient, as well as moderate or gross peroperative bacterial contamination, were all associated with a high incidence of postoperative infection. An examination of Table III makes it clear that when one or more of the factors mentioned in Table II were present the incidence of infection was 21.7%, and when none of these factors were present it was only 5.8%. Retrospective surveys do not deserve the dignity of statistical analysis; nevertheless, the figures in Table III are statistically significant. Further analysis showed that the greater the number of these risk factors present in any one patient the greater is the risk of a postoperative infection. Thus if only one risk factor was present the incidence of infection was 17%, but patients with 4 risk factors had an incidence of 39%.

NATURE OF POSTOPERATIVE INFECTION

The survey showed that there are four main patterns of postoperative infection: (1) bacteraemia; (2) abscess formation often associated with bouts of bacteraemia; (3) abscess formation followed by multiple abscesses and often resulting in septicaemia; and (4) septicaemia without previous abscess formation.

In a retrospective survey of this type it is difficult to ascertain the incidence of bacteraemia and septicaemia because a systematic search was not made postoperatively. Also some patients were treated empirically on the assumption that a septicaemia might be developing, and blood cultures were not taken in every case. However, when the available information was correlated with the previously mentioned clinical and peroperative risk factors it was noted that when only 1 or 2 of these factors were present there was a scatter of different types of infection, though bacter-

TABLE III *Infections in relation to presence or absence of risk factors in 917 patients*

Factors present	*No of cases*	*Infections*	%
One or more	433	94	21.7
None	484	28	5.8
Total	917	122	13.3

aemias and abscesses predominated. When 3, 4, or 5 risk factors were present there was again a scatter of infections, but in these patients abscesses and septicaemias predominated. Thus it was noted that as the risk factors increased in number more severe infections were more likely to develop and particularly that septicaemias occurred almost exclusively in the group with multiple risk factors.

MORTALITY

There were 34 postoperative hospital deaths in the 917 patients, an incidence of 3.7%. There were only 3 deaths in patients who had no clinical risk factors associated with their operation, an incidence of 0.6%, but if one or more risk factors were present, then the overall mortality was 7.2%, and again this difference is statistically significant. Also, as the number of risk factors increased the mortality rose very sharply.

CONCLUSION

This retrospective survey provides some evidence that there are certain clinical and peroperative factors present in the patient which predispose to the development of a serious postoperative infection and increase the risk of postoperative mortality. The factors enumerated have traditionally been associated with a greater risk of infection and mortality following operation and this survey was a crude attempt to elaborate on this and to calculate the actual degree and nature of this risk.

Prospective study

A prospective pilot study was undertaken on 30 patients who were about to undergo an abdominal operation to see whether there were any trends in the preoperative and peroperative state of the patient which are predictive of a serious postoperative infection. In this pilot study 112 factors were looked at and included a diverse and comprehensive range of clinical factors such as malnutrition or alcoholism and investigative factors such as the blood picture, liver function and renal function tests, and an extensive immunological survey including immunoglobulin estimation, function of the white cells, and delayed hypersensitivity skin tests. Also an array of peroperative factors were looked at, including the degree of bacterial contamination, duration of the operation, severity of blood loss, complexity of the operation, use of preventive antibiotics, and others.

The pilot study indicated that of the 112 factors considered there were 11 which showed a trend that suggested that they may be predictive of a serious postoperative infection. These factors were: malnutrition, the presence of malignant disease, diabetes, or alcoholism, exposure to steroids and/or cytotoxic drugs, hypoalbuminaemia, anaemia, lymphopenia, abnormal immunoglobulins, abnormal results of delayed hypersensitivity skin tests, and the presence of peroperative bacterial contamination. Clearly, some of the factors which we investigated and which did not show such a trend may well prove to be significant in the future, with larger numbers, and should not be neglected.

THE PROTOCOL

On the basis of this pilot study we embarked on a prospective study of 50 patients who were about to undergo an elective abdominal operation, looking closely at the 11 factors mentioned. There was a precise protocol and each factor was carefully defined. For example, a patient was regarded as malnourished if she or he did not have 5 protein meals per week and did not eat vegetables, fruit, or greens 5 times a week. An alcoholic was defined as a person who habitually took more than 500 g of alcohol per week. Of previous medication, only steroids and cytotoxics were regarded as of any significance and these needed to have been administered for a period of at least 2 weeks before surgery. Lymphopenia of less than $1 \times 10^9/l$ ($1000/mm^3$) was regarded as abnormal, and anaemia was defined as a haemoglobin level below 10 g/dl. Hypoalbuminaemia and abnormality of immunoglobulins were defined according to our hospital laboratory standards. The delayed hypersensitivity skin tests used were for 5 antigens—mumps, trichophyton, streptokinase, tuberculin, and candida; the reactions were read after 48 h and a positive response recorded if there was induration of 6 × 6 mm or greater.

We had also carefully defined the various infections, and the decision whether an in-

TABLE IV *Postoperative infections in relation to risk factors in prospective study of 50 patients*

Risk factor	*Factor present (infections/cases)*	*Factor absent (infections/cases)*
Malnutrition	11/21	5/29
Malignant tumour	10/24	6/26
Anaemia	6/8	11/42
Hypoalbuminaemia	7/12	9/38
Abnormal immunoglobulins	9/19	7/31
Skin test 0	13/19	3/31
Skin test 0 or 1	16/35	0/15
Skin test 2 or more	0/15	16/35
Contamination nil	5/18	11/32
Contamination + +	4/9	12/41

fection had or had not occurred was made not by me but by the surgical registrar and ward sister. Wound abscesses were diagnosed only if culture-positive pus was obtained from the wound; mild wound inflammation and stitch infections were excluded. Intra-abdominal infection was defined as the presence of pus requiring drainage at a further operation or draining in large quantities (> 100 ml) through the drain tube. The diagnosis of septicaemia required a positive blood culture *and* a rise of temperature *and* one or more of a number of the features of septicaemic shock, which were all previously defined also.

RESULTS

According to these definitions 23 serious infections occurred in 16 of the 50 patients. There were 12 wound abscesses, 6 intra-abdominal abscesses, and 5 septicaemias.

Analysis of the relation of the various risk factors to postoperative infection is presented in Table IV. This table requires some explanation. For example, malnutrition was present in 21 of the 50 patients and 11 of these developed a postoperative infection. Malnutrition was absent in 29 patients and only 5 of these developed a postoperative infection. Thus malnutrition appears to be a significant factor. It was interesting that hypoalbuminaemia paralleled malnutrition fairly closely. The presence of a malignant tumour was also associated in many cases with an infection and is a significant factor.

Of the 19 patients in whom all the skin tests were negative, a situation described as anergy, 13 developed a postoperative infection, while only 3 of the 31 patients with one or more positive skin tests developed an infection and all 3 were among the 16 with only one positive reaction. Indeed, I believe that anergy or reduced response to delayed hypersensitivity skin testing is a very significant indicator of the likelihood of infective complications following surgery. A similar finding was recently reported by MacLean and his group in Canada[2].

Anaemia was also predictive of a postoperative infection, as was the presence of abnormal immunoglobulins to some extent, but we will have to go further into an analysis of the various types of immunoglobulin abnormality in the future to see whether any more significant patterns arise.

The degree of bacterial contamination, which was judged subjectively during surgery, also had a bearing on the development of a postoperative infection. However, one should note that in the apparent absence of bacterial contamination 5 out of 18 patients still did develop an infection. Four out of 9 patients with moderate or gross contamination developed an infection, whereas only 12 of the 41 who had lesser degrees of contamination or none at all developed an infection. Thus there is a correlation, but this is not as close as one would expect.

Our numbers were too small for the effects of steroid and cytotoxic therapy, diabetes, alcoholism, and lymphopenia to be assessed, but the results were sufficiently suggestive to justify their inclusion as risk factors in the prediction of postoperative infection.

Again we found that the risk increases

TABLE V *Postoperative infections in relation to number of risk factors in prospective study of 50 patients*

No of factors present	*Infections/No of cases*
Nil	0/11
One or two	2/13
Three or four	8/18
Five or more	6/8

with an increase in the number of risk factors present in any one patient (Table V). Thus no infections occurred in the 11 patients who had no risk factors, while 6 of the 8 patients in whom 5 or more risk factors were present did develop a serious postoperative infection. Similarly, when we looked at the nature of the infections we saw that the most severe infections—that is, the 5 septicaemias—all occurred in the group with at least 4 risk factors. It is again interesting that the 5 patients with a septicaemia were all completely anergic to delayed hypersensitivity skin testing.

CONCLUSION

A number of clinical, investigational, immunological, and peroperative factors have been identified which, alone or combined, will predispose a patient to the development of a serious postoperative infection. The degree of this risk can be measured and predicted, though at present only within very crude limits.

The future

The evidence is mounting that host factors can be identified preoperatively and peroperatively to predict postoperative infections. Also, probably closely allied to these, there are factors which determine the healing characteristics of a patient after surgery or trauma.

We are most enthusiastic about our initial results and are continuing and expanding the present prospective survey to include, among other tests, lymphocyte and phagocyte function tests and a test of the reticuloendothelial system by liver–spleen scanning and incorporating HLA typing.

Future investigations will pinpoint mechanisms responsible for serious infections and problems of healing so that we can more precisely identify the patient at risk. Once this can be done we may then be able to institute a number of preventive measures which will alter the preoperative environment of the patient and decrease the risk of a postoperative infection.

ESTIMATION OF RISK

Clearly we need to study our patients preoperatively in a prospective way in more detail in order to be able to pinpoint all the factors which may cause problems postoperatively. Eventually we may be able to have enough data to be able to calculate a 'risk index', a process which we in fact do now, using our personal cerebral computer relying heavily on subjective observations and bias rather than on accurate data. We may then be able to determine just how risky an operation is and whether the risk is too high and contraindicates surgery. In other cases we may find that the risk is high only temporarily and that, for example, it can be reduced by discontinuing the administration of certain drugs for a time before surgery.

PREVENTIVE MEASURES

At present we appear to have two major weapons as preventives, the first being an improvement in the nutrition of the patient before surgery and the second the correct use of preventive antibiotics during surgery. Stimulation of the immune mechanism and the use of adjuvant hyperimmune vaccines may prove to be preventive measures of the future.

The nutritional factor Improvement in the preoperative nutritional status of the patient appears to be one of the most important ways of decreasing the risk of postoperative infection[3, 4]. When we began to take accurate nutritional histories we were surprised by the number of patients who were malnourished before surgery. Malnutrition is common in patients who have a malignant tumour anywhere in the body, and especially when the tumour is in the gastrointestinal tract or in

one of its appendages. It is also commonly seen in diabetics and alcoholics, as well as in patients who are receiving medication with cytotoxics or other treatment which makes them anorexic. We therefore took 12 patients, all of whom were malnourished and who also had at least 3 other risk factors present as determined in our prospective survey. In these the expected incidence of a serious postoperative infection was about 50%. We gave these patients total parenteral nutrition preoperatively for a period of 2 weeks. Parenteral nutrition consists of amino acids administered with 25% dextrose as well as sodium, chloride, potassium, calcium, and magnesium ions. Approximately 1000 kcal (4.2MJ) are given per litre of solution and approximately 3000 kcal (12.6MJ) are given each day. All solutions are infused into the superior vena cava through a subclavian vein catheter.

After operation, instead of the 6 serious infections we had expected only one relatively minor wound infection developed in these 12 high-risk patients. It was also of great interest to find that the negative skin-test reactions which were present in all of these patients converted to a variable number of positives in some of them, implying that, at least in some cases, the immunological deficit is an acquired one and related to malnutrition rather than to the underlying disease, such as a malignant tumour. Clearly we will have to do properly conducted scientific trials on the value of total parenteral nutrition in this high-risk group of patients, but the immediate results are encouraging.

Preventive antibiotics In recent years Dr John Burke, of Boston, has focused attention on the correct use of antibiotics in surgery in order to lower the incidence of postoperative infections[5]. He believes that postoperative infections can frequently be prevented by the use of an appropriate antibiotic in those patients who are at high risk. The antibiotic must be in high concentration in the tissues before bacterial contamination occurs and certainly before these organisms have had a chance to multiply. This implies the intravenous or intramuscular use of an appropriate antibiotic given just before or at the beginning of an operation to a compromised host who is at high risk of developing an infection, as calculated, for example, by an estimation of the various risk factors mentioned earlier.

So far this hypothesis has been validated for the reduction of severe wound infections following surgery on patients who have a low host resistance or whose operation has involved massive contamination of the wound, or both. For example, we have shown this to be true in both a retrospective and a prospective survey of patients being operated on for acute cholecystitis[6].

In our prospective study of 50 patients we used preventive antibiotics according to this thesis, particularly on patients who had a good deal of contamination during surgery and who were also thought to be a high-risk group on clinical grounds. Ethically we could not justify withholding antibiotics from 16 of the 50 patients because there is now a good deal of evidence to substantiate the value of preventive antibiotics. It is emphasised that in general the 16 patients were a much higher-risk group than the 34 patients who did not get preventive antibiotics. In spite of this it was seen that of the 16 patients who received preventive antibiotics only 4 developed a postoperative infection compared with 12 of the 34 who did not receive preventive antibiotics. While this was not a properly conducted clinical trial it is very suggestive that an appropriate antibiotic used as a preventive is valuable in decreasing the number of serious postoperative infections in the high-risk group of patients.

Stimulation of immune mechanism In the future agents such as BCG or levimasole or some more specific agents yet to be discovered may well be used to stimulate or potentiate a particular part of the patient's immune mechanism before surgery. Clearly George Bernard Shaw's Sir Ralph Bloomfield Bonnington in 'The Doctor's Dilemma' also had this idea:

> 'Drugs are a delusion. Find the germ of the disease; prepare from it a suitable antitoxin; inject it three times a day, quarter of an hour before meals; and what is the result? The phagocytes are stimulated; they devour the disease and the patient recovers—unless of course he's too far gone.'

Hyperimmune vaccines The use of hyperimmune vaccines in patients at high risk of developing certain types of bacterial infections after burns, trauma, or surgery is another

preventive possibility. The problem is to know the type of organism responsible and to have a wide range of appropriate hyperimmune sera available. I have no personal experience of this, but Dr J Wesley Alexander in Cincinnati was able to decrease the mortality caused by sepsis in severe burns from 40% to 3% with the use of hyperimmune pseudomonas gammaglobulin[7].

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References

1 Alexander, J W (1974) *Surgery, 75,* 934.
2 MacLean, L D, Meakins, J L, Taguchi, K, Duignan, J P, Dhillon, K S, and Gordon, J (1975) *Annals of Surgery, 182,* 207.
3 Copeland, E M, MacFadyen, B V, and Dudrick, S J (1974) *Surgery, Gynecology and Obstetrics, 138,* 377.
4 Copeland, E M, MacFadyen, B V, and Dudrick, S J (1976) *Annals of Surgery, 184,* 60.
5 Burke, J F (1973) *Annual Review of Medicine, 24,* 289.
6 Kune, G A, and Burdon, J G W (1975) *Medical Journal of Australia, 2,* 627.
7 Alexander, J W (1972) *Surgical Clinics of North America, 52,* 1367.