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Infection in Immunodepressed Patients

The Approach to Diagnosis and Treatment

Summary: Infection is an important cause of death in patients receiving cytostatic drugs or with any other impairment of host resistance. Such infections are frequently due to opportunist micro-organisms usually belonging to the endogenous flora of the patient. It is often difficult to obtain an exact diagnosis of the cause and localization of the infection. The problems associated with the prevention of infection are manifold. Exogenous infections can be prevented by proper isolation and a sterile diet. Endogenous infections can only be prevented by eradication of the patient's endogeous flora, so-called decontamination. Special attention should be given to treatment of foci of chronic infection and of the carrier state of certain microorganisms. However, the prophylactic use of antibiotics should be avoided. The curative use of antibiotics should be based on the most probable micro-organism. We consider the inventory of the patient's microflora, repeated weekly, of great help in the choice of antibiotics in cases of septicaemia of unknown aetiology. The initial therapy usually consists of a broad-spectrum combination of antibiotics, which should be bactericidal. When the causative bacteria have been isolated and the sensitivity is known, antibiotic therapy should be adjusted to the narrowest spectrum possible.

Zusammenfassung: Infektion bei Patienten mit Immunsuppression. Der Zugang zu Diagnose und Behandlung. Die Infektion ist eine wesentliche Todesursache bei Patienten, die unter zytostatischer Medikation stehen oder bei denen irgendeine andere Beeinträchtigung der körpereigenen Widerstandskraft vorliegt. Derartige Infektionen sind häufig auf opportunistisch-pathogene Erreger zurückzuführen, die für gewöhnlich zur endogenen Flora des Patienten gehören. Eine exakte Diagnose der Ursache und Lokalisierung der Infektion ist oft schwierig.
Die mit der Infektionsverhütung einhergehenden Probleme sind vielschichtig. Exogene Infektionen können durch geeignete Isolierung und eine sterile Diät verhindert werden. Endogene Infektionen lassen sich nur durch eine Ausrottung der endogenen Flora des Patienten, d. h. durch „Entseuchung" verhindern. Besondere Aufmerksamkeit ist der Behandlung chronischer Infektionsherde und dem Trägerstatus bestimmter Mikroorganismen zu widmen. Die prophylaktische Anwendung von Antibiotika sollte jedoch vermieden werden.
Die therapeutische Anwendung von Antibiotika sollte auf die größtmögliche Wahrscheinlichkeit des zugrundeliegenden Erregers ausgerichtet sein. Wir halten die wöchentlich wiederholte Inventur der Mikroflora des Patienten in Fällen von Septikämie unbekannter Ätiologie für eine große Hilfe.
Die Anfangsbehandlung besteht für gewöhnlich aus einer Breitbandkombination von Antibiotika, die bakterizid wirken sollte. Sobald die ursächlichen Bakterien isoliert wurden und die Empfindlichkeit bekannt ist, sollte das Spektrum der antibiotischen Therapie soweit wie möglich eingeengt werden.

Introduction

Infection is one of the most serious complications in patients with malignant processes treated with cytostatic drugs and in patients with acquired or congenital immunodepression; in such patients infections are often fatal (1–9). This paper deals with the factors leading to increased incidence of infections and with the prevention, diagnosis, and management of infections in these patients, and the principles underlying antibiotic therapy.
The host resistance of the patient is a decisive factor in the outcome of any infection. The defence against micro-organisms is governed by several mechanisms (Table 1) (10—13). The first barrier against micro-organisms is intact skin and mucous membranes. The second line of defence comprises cellular factors, the phagocytic cells, and cell-mediated immunity, which involves the joint action of sensitized T-lymphocytes and macrophages. Thirdly, there are the humoral factors.
Patients with severe immunodepression have impaired function of one or more of these host resistance factors (Table 2). Cytostatic drugs can lead to lesions in the

Table 1: *Host resistance to infection*

Anatomical barries	skin
	mucous membranes
Cellular functions	
Phagocytosis	granulocytes
	macrophages
Cell-mediated immunity	T-lymphocytes + macrophages
Immunoglobulin production	B-lymphocytes, plasma cells
Humoral factors	
Immunoglobulins (i. e. antibodies)	
Complement	
Non-specific factors (e. g. lysozyme, lactoferrin)	

mucous membranes by inhibiting proliferation of the normally rapidly dividing cells of the gastro-intestinal mucosa, and can lead to leukopenia. Glucocorticosteroids can also cause lesions in the mucous membranes. These drugs do not severely impair phagocytosis and intra-

Table 2: *Causes of impaired function of defence mechanisms*

Affected host factors	Cause
Barriers	cytostatic drugs glucocorticosteroids malignant infiltrations infections catheters (e. g. intravascular; urinary) wounds
Cellular factors	cytostatic drugs glucocorticosteroids agranulocytosis leukaemia lymphoma
Humoral factors	hypogammaglobulinaemia paraproteinaemia immunosuppression

Table 3: *Micro-organisms frequently causing infection during severe immunosuppression*

Bacteria	Staphylococcus aureus Pseudomonas spp. Klebsiella spp. Salmonella spp. Other Gram-negative organisms Bacteroides spp. and other anaerobic bacteria Mycobacterium tuberculosis Listeria monocytogenes Nocardia
Viruses	Cytomegalovirus Herpes simplex Herpes zoster-varicella
Fungi, yeasts	Candida Aspergillus Histoplasma Cryptococcus
protoza	Pneumocystis carinii Toxoplasma gondii

cellar killing by phagocytic cells, but cause monocytopenia and lymphocytopenia (15—19). The interaction of the lymphocytes with macrophages is probably also impaired by these drugs, leading to decreased cell-mediated immunity (20). In acute myeloid leukaemia the host defence is affected in another way: many immature granulocytes may be present in the peripheral blood and leukaemic blast cells do not have a normal phagocytic function (21). In this disease granulocytopenia often develops because the differentiation of myeloid cells is impaired. An unequivocal correlation has been found between the severity and duration of granulocytopenia and the frequency of occurrence of infection (22, 23). In lymphatic leukaemia and Hodgin's disease the host resistance may be reduced because the lymphoid cells do not function normally. These patients may show reduced antibody production (24—26) and may also have diminished cell-mediated immunity (26—28). In multiple myeloma and Waldenström's disease, there is a decreased level of normal immunoglobulins and impaired antibody production (24, 25, 29).

Patients with diminished host resistance are more prone to infection than normal individuals. Lesions of skin and mucous membranes resulting from surgery, intravenous canulae, or indwelling vascular and urinary catheters and tracheal tubes provide a route of entry (30, 31). Even normally non-pathogenic micro-organisms may invade the body and cause serious disease, and infections which are rarely seen under normal circumstances can become extremely important (Table 3). It is noteworthy that the bacterial infections (32—35) are often caused by endogenous micro-organisms, which the patient has harboured for some time before infection developed (36). For example, infections with Staphylococcus aureus are seen mainly in patients who already carry staphylococci in the nose or on the skin (1). The high frequency of infections with pseudomonas and klebsiella may be related to the fact that these bacteria occur in the faeces more frequently in hospital patients than in normal individuals. This is especially true of patients on antibiotic treatment (37—45).

Infection with cytomegalovirus is frequently encountered (46, 47) often as the result of reactivation of the carrier state; this may also be the case in overt herpes zoster-varicella (48—53) and herpes simplex (54) infections. In contrast, infections with respiratory viruses are usually aquired directly from the environment. Candida infection too, is often seen in patients with depressed cell-mediated immunity or in those whose bacterial flora has been altered by antibiotic treatment, permitting growth of yeasts already present on the mucous membranes (55 to 57).

Pneumonia caused by infection with Pneumocystic carinii has frequently been described and offers many diagnostic problems (47, 58—63). Infection with more than one micro-organism (e. g. in bacteraemia or severe local infections) are not rare during immunosuppression (64). A combination frequently encountered is cytomegalic inclusion disease accompanied by infection of the lung by Pneumocystic carinii (47).

Prevention of infection

Prevention of infection during severe immunosuppression is a major problem. The most important source of such infection is the endogenous flora. This could be overcome by decontamination of the patient, but this is generally not feasible. Our management for the prevention of infections is outlined in Table 4.

The presence of chronic asymptomatic infections is in-

Table 4: *Management for prevention of infections*

Examination and treatment of chronic asymtomatic infections.
Bacteriological inventory of the patient.
Treatment of carrier state of certain micro-organisms.
Isolated nursing:
    a. conventional isolation room,
    b. ultra-clean ward,
    c. laminar flow isolator; plastic isolator
Isolated nursing with decontamination and sterile diet.

vestigated, for these constitute foci that may become reactivated. Such hidden foci include sinusitis, dental granuloma, chronic bronchitis, chronic urinary tract infection and prostatitis or old tuberculous lesions. Each patient is examined and investigated very thoroughly and antimicrobial treatment is instituted, if possible, before immunosuppressive therapy is started.

It is of great importance to make a systematic investigation of the patient's endogenous flora. The advantage of maintaining a regular bacteriological inventory is that when signs of serious infection develop, information is available for a provisional choice of antibiotic.

A microbiological inventory is done at admission in all patients, nursed in isolation, with a severe immunosuppression or in whom a diminished host resistance due to treatment can be anticipated. Cultures for pathogenic bacteria are then prepared from material taken from the nose, tonsils, pharyngeal wall, hair, axilla, umbilicus, groin, perineum and urine. Faecal samples are investigated for the presence of enterobacteriaceae, other gram-negative organisms, Staphylococcus aureus and Candida. The antimicrobial sensitivity of each micro-organism is determined. These investigations are repeated weekly. In addition a tuberculin skin test is done and in special occasions serological tests for viral or protozoan infections.

If a patient carries Staphylococcus aureus on his nasal mucosa, he is treated with a topical cream containing antiseptics (e. g. chlorhexidine) or antibiotics. We try to eradicate staphylococci on the skin by daily washing with a polyvidone-iodine shampoo or trichlorocarbanilide soap. A heavy growth of Candida in the mouth or faeces should be reduced with fungistatics, preferably before antibiotic therapy is started, especially if bacterial decontamination of the gut is considered. Patients with an old tuberculous lesion on the radiograph or with a positive tuberculin test are routinely given isoniazide.

Isolation

It is generally accepted that patients with diminished host resistance should be nursed in isolation, but the most suitable method of isolation for particular types of patients has not been clearly established. The classical method of nursing in a single room is valuable for management of patients with contagious diseases since it protects the surroundings from contamination. However, the value of this type of conventional room for reversed isolation of immunodepressed patients is probably minimal. Nursing in ultraclean wards gives some reduction and retardation of colonization with micro-organisms (65). This form of isolation might be indicated, for instance, for patients during the first weeks after kidney transplantation. Nursing in a laminar air flow system or plastic isolator should prevent all exogenous infections. This type of isolation can be very useful for treatment of patients with severe burns or patients with severe immunosuppression who do not harbour too large a

number of very pathogenic or resistant micro-organisms (23, 66, 67).

A combination of nursing in laminar air flow systems with decontamination and a sterile diet, offers the optimal means of preventing infections (68, 69). It must be kept in mind that food is an important source of pathogenic micro-organisms capable of colonizing the patient (43). This is especially likely to occur during decontamination. It should be stressed that decontamination should never be applied without strict isolation and a sterile diet, because during the state of decontamination there is no resistance at all to colonization by antibiotic-resistant bacteria (70). Strict isolation and decontamination is indicated for example, in bone marrow transplantation, where there is a total paralysis of cellular and humoral immunity, and a graft-versus-host reaction is almost always complicated by bacteriaemia orginating from the digestive tract. Recontamination of the gastrointestinal tract should be done with a human donor flora, consisting of anaerobic bacteria and aerobic micro-organisms of low pathogenicity (86, 87).

Since facilities for isolation are limited, it is often difficult to decide which patient should be nursed in what type of isolation. The strictest form of isolation is probably indicated for patients with a temporarily severely diminished host resistance and a (relatively) good prognosis, for example, patients with agranulocytosis due to drug dyscrasia, cytostatic treatment, or X-irradiation.

Infection

Even when good isolation of the patient is achieved we frequently diagnose and have to treat an infection. What considerations must we keep in mind in such a situation, and how does the infection present itself? Certain signs may indicate that infection is present, the most important being fever (71—73, 93, 94). According to the literature, two-thirds of all febrile episodes in these patients are caused by an infection; a high fever is particularly likely to be due to infection. Other causes of fever include transfusion of blood products; haemorrhages, especially in the brain; tissue damage (for instance by cytostatic drugs), and agranulocytosis. It is common clinical experience, that fever occuring during agranulocytosis disappears with the reappearance of granulocytes in the peripheral blood.

As with any patient, diagnosis of the presence of infection must be made on the basis of the history, clinical picture, physical examination, and the results of laboratory and radiological investigations. Because infection so often takes an acute and serious course in patients under cytostatic treatment, these data must be evaluated as soon as suspicion of infection has been aroused. Since the clinical signs pointing to the site of an infection are in many cases not clearly expressed, extensive bacteriological and serological investigations must be performed without delay. These tests include multiple blood cultures within the first few hours, and cultures of swabs from

the tonsils and pharyngeal wall as well as of the samples of sputum, urine, faeces and any inflammatory exudate; special attention should be paid to adequate collection and culturing of material for anaerobic bacteria (74 to 76). Since the bacteriological results may not be available for 24—48 hours a microscopic preparation should always be made. In leukopenic patients there may be no granulocytes in these specimens and bacteria alone may indicate the presence of an infection.

Therapy

When a clinically manifest (systemic or localized) infection is present, the patient must be treated (77, 78). Usually, the causative agent is not known at the onset of the infection, but the patient's clinical condition often does not permit postponement of treatment. Therapy must be started as soon as all the possible samples for cultures have been taken. At this stage, the following general principle holds: prior to identification of the infecting bacteria provisional antimicrobial treatment is instituted in cases of strongly suspected infection. The choice of drug depends on the nature of the most probable agent, assessed on the basis of localization of the infection. In the case of a septicaemia without localized infection, data provided by the bacteriological inventory are used. As soon as the causative organism has been isolated and a definite bacteriological diagnosis has been made, the antibiotic treatment should be revised.

We prefer to give bactericidal antibiotics rather than bacteriostatic types. Bacteria whose growth has been merely inhibited by bacteriostasis cannot be dealt with adequately by patients with a reduced number of phagocytic cells and therefore the bactericidal action of the antibiotic is of great importance in helping to overcome infection. For the same reason, these antibiotics must be used in high dosages.

Antibiotics should preferably be administered parenterally. This serves first of all to avoid any defective absorption in the digestive tract and, furthermore, there is less disturbance of the endogenous bacterial flora. For the same reason we prefer to use narrow-spectrum antibiotics when the micro-organism is known.

At present, our initial therapy consists of a combination of a broad-spectrum penicillin (ampicillin or carbenicillin) or one of the cephalosporins with kanamycin or gentamicin, depending on the suspected micro-organism. In case of a suspected infection with anaerobic bacteria high doses of benzyl-penicillin, clindamycine or metronidazole is given in addition. (This scheme will of course have to be reassessed as new antibiotics become available.) The initial antibiotic therapy must be re-evaluated as soon as the causative organisms have been isolated and their sensitivity determined. If another antibiotic has to be substituted, it should have the narrowest possible antimicrobial spectrum.

As a rule, the prophalactic administration of antibiotics, in other words the use of antibiotics in the absence of a demonstrated acute or chronic infection or carrier state of certain bacteria, is not advisable. The use of antibiotics in itself may promote the emergence of resistant strains. We are therefore generally reluctant to institute antibiotic treatment. When fever develops we are governed mainly by the patient's clinical condition. Blind therapy with antimicrobial drugs is only indicated when an infection is strongly suspected in a severely ill patient. Systemic fungal infections are difficult to diagnose, if the patient fails to respond to the antibiotic regimen the possibility of a fungal infection should be kept in mind and therapy with an antifungal agent, e. g. 5-fluorocytosine and amphotericine B, should be tried (79). The same holds for the treatment of a Pneumocystis carinii infection, which can be treated with pentamidine and probably with pyrimethamine plus sulfonamide.

Supplementary treatment

The value of granulocyte transfusions is still a matter of discussion (80—82). Daily transfusion of granulocytes, preferable from HLA identical donors (88), obtained by filtration leukopheresis of blood (89—92), are indicated when during an absolute agranulocytosis septicaemia persists during adequate bactericidal antibiotic therapy.

If the patient suffers from high fever, one can use antipyretics, but this may obscure the clinical picture and make it difficult to evaluate the effectiveness of the antibiotic therapy. It remains to be established whether treatment with (hyperimmune) gammaglobulin (78) and with transfer factor (83) will be effective in certain viral and fungal infections.

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