A New Look at Infectious Diseases

Opportunistic Infection

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The term "opportunistic infection" has come to have several different meanings: some claim that the term should be used to describe infections with rare or exotic organisms not normally pathogenic; others reserve its application to infection in patients in whom impairment in the body's protective mechanisms is demonstrable. Arguments can be raised to support a comprehensive concept. To some extent all infection might be considered opportunistic; take the situation when a patient with a boil—an extremely common local staphylococcal lesion—develops staphylococcal septicaemia—which is a rare event. Such patients who develop generalized staphylococcal infection must have impaired defence mechanisms, but these are rarely demonstrated. Possibly advances in immunology and related subjects will uncover adequate explanations for such phenomena. Clearly for current practice some form of limitation of usage and definition is desirable.

Opportunistic infection can result from micro-organisms normally or traditionally pathogenic, but in many instances the organisms isolated in these infections are unusual, often of low pathogenicity, and may be derived from the patient's own flora. Autoinfection is an important concept when dealing with opportunistic infection. The traditional distinction between pathogenic and non-pathogenic micro-organisms is becoming much less rigid, indeed almost untenable—"show me an organism and I will show you a pathogen" is a more realistic approach. Not only bacteria, but fungi, protozoa, and viruses may assume an opportunistic role; cytomegalovirus infection is particularly prominent in this context.

Patients in whom opportunistic infection is diagnosed may have no demonstrable abnormality in host response, but many will have abnormalities. Some, such as major skin loss (as occurs in burns or exfoliating conditions), are obvious; other defects may be found on testing humoral and cellular defence systems; and subtle changes may be demonstrated or implied in many patients receiving antimicrobial and other drugs.

Opportunistic infections therefore result from micro-organisms, both traditional pathogens and those that in the past might have been considered non-pathogenic. This type of infection is commonest in patients whose immune responses are compromised, but it is not necessarily confined to such patients.

Incidence

With such a comprehensive definition, and because of the varied nature in presentation combined with the near impossibility of establishing a diagnosis in many cases, it is not surprising that any estimate of the overall incidence of opportunistic infections must be speculative. In some particular units or wards major changes in the incidence of opportunistic infections may be observed and documented. As we become more involved with the survival of the unfittest—as it were, putting natural selection in reverse by the use of advanced modern treatments—we must expect an increase in infections due to micro-organisms that will make the most of their opportunities in patients whose defences are lowered.[1 2]

The table is an attempt to link some of the common major disorders with frequently encountered pathogens. It is merely a guide and by no means comprehensive (for a full review see Klainer and Beisel.[3]) A few special situations, important because of the numbers of patients involved or because they represent particular contemporary problems, are now discussed in brief.

INTENSIVE CARE AND THERAPY UNITS

Areas set apart or built with the purpose of concentrating medical and ancillary staff equipped and trained to deal with ill patients requiring simultaneous care by several specialists are now being provided in increasing numbers. It is insufficiently realized that major achievements by advanced anaesthetic, cardiopulmonary, surgical, and other measures may be vitiated by opportunistic infections. In these units opportunistic infections are very closely related to contaminated ventilators, humidifiers, tracheostomy tubes, intravenous lines, and all the related gadgetry that intensive modern management demands.

Three factors may contribute to form a major hazard: a repository of resistant organisms derived from ill patients treated with a multitude of antibacterial agents; the lack of adequate isolation facilities; and staff members who may not have an understanding of preventive measures.

"ROUTINE" ADMINISTRATION OF ANTIBIOTICS

The undoubted success of antibacterial therapy in acute infections has in many doctors' minds been followed by a dogma which might be summed up as, "when bacteria are present antimicrobial agents should be administered." Nothing could be more misleading; on the contrary, when this concept is practised morbidity may be increased and occasionally superinfection with opportunistic organisms may be fatal. Three examples will suffice.

Acute Respiratory Illness

In acute respiratory illness prophylactic antibacterial agents should not be used routinely. This is well exemplified by measles, where routine administration of prophylactic antibiotics may be not only ineffective but positively dangerous.[4] Members of the Royal College of General Practitioners[5] who reported on nearly 5,000 cases of measles concluded that routine administration of antibiotics was largely unwarranted.

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Predisposing Factor	Possible Mechanism	Frequently Encountered Pathogens
Burns: Skin lesions	Altered skin flora.	Pseudomonas. Staphylococci
Trauma	Loss of integument	
Foreign bodies: urinary and intravenous catheters: prostheses	Organisms entering from exterior. Altered from anatomy. Stasis	Staphylococci. Pseudomonas and other Gram-negative bacilli. Fungi
Surgery: Abdominopelvic Urological Cardiac		Gram-negative bacilli: anaerobes Bacteroides. Gram-negative bacilli. Enterococci. *Staph. aureus*, *Staph. albus*
Drugs: Antimicrobial	Altered flora, particularly in skin, chest, bowel. Selection of resistant strains	
Corticosteroids	Depress inflammatory response: stabilization of lysosomal membrane. Depress antibody formation. Others	
Phenylbutazone	May alter phagocytosis	
Irradiation and Immunosuppression	Granulocytopenia. Depresses antibody formation. Cell injury—for example, gastrointestinal tract	
Other diseases and conditions: Diabetes mellitus	Not known or conjectural	(1) Urinary tract infection (2) *Mycobacterium tuberculosis* (3) Mucor (associated with acidosis) (4) Possibly others
Chronic renal failure	Not known	Gram-negative bacilli, hepatitis-B virus jaundice
Liver failure	Not known	Gram-negative bacilli, staphylococci
Hypoparathyroidism	Not known	Candidiasis
Myeloproliferative disorders: Acute leukaemia, chronic myeloid leukaemia, polycythaemia, myelofibrosis, myelosclerosis, fatal granulomatous disease of children, Chediak-Higashi anomaly, other disorders of leucocytes, numerical or functional due to disease or therapy	Disorder of granulocytes	Pyogenic cocci, Gram-negative bacilli, fungi
Lymphoproliferative disorders: Acute leukaemia, chronic lymphatic leukaemia, reticulosis, myeloma, ? post splenectomy, hypogammaglobulinaemia	Disorder of immunoglobulins	Pyogenic cocci, Gram-negative bacilli, *Listeria monocytgenes*, *Pneumocystis carinii*
Hodgkin's disease. Disorder of cellular immunity from therapy or disease	Disorder of cellular immunity.	*Cryptococcus neoformans*, Brucellae, cytomegalovirus, fungi

Urethral Catheterization

When a catheter is placed in the bladder, urinary infection occurs in 98% of patients within 48 hours.[6] In these patients the administration of antimicrobial agents results not in prevention of infection but in an alteration of the bacterial flora of the urine, so that in many cases sensitive strains of *Escherichia coli* are replaced by resistant staphylococci or pseudomonas.[7–9] Acute danger to these patients arises when invasive infection such as septicaemia supervenes, since the pathogens have now been made resistant by unwarranted, previously administered, "prophylactic" chemotherapy.

Acute Leukaemia

Infection in acute leukaemia is common and current methods of managing these patients often favour aggressive use of antimetabolites with severe bone-marrow depression. If the patient can survive infection in this vulnerable phase the prognosis for the leukaemia may be improved. Indeed at this stage the immediate prognosis is related to septicaemia often due to *Pseudomonas aeruginosa*, resistant staphylococci, fungi, and other disquieting pathogens. Should these patients receive "routine" antimicrobial drugs? The failure of chemoprophylaxis in similar situations[10] and the paucity of clear evidence indicating any advantage when prophylactic drugs are used in these patients compel caution.[11 12] The question cannot be considered settled and controlled trials may help to formulate antibiotic management based on fact.

Diagnosis

In the diagnosis of opportunistic infection similar principles obtain as in the diagnosis of any other infection: clinical assessment together with critical evaluation of data from other sources—particularly microbiological, radiological, and histological. In opportunistic infection several special factors make practical application of these diagnostic principles difficult and sometimes impossible. Patients in this category may fail to exhibit many of the expected features of infection, such as pyrexia and rigors; the leucocyte count may be unhelpful or entirely misleading, and the manifestations of multisystem disease so alter or obscure the expression of an infective state that its presence is unrecognized or its severity underestimated. These circumstances emphasize that the physician must be aware of the possibility of infection in vulnerable patients; as Klainer and Beisel[3] put it, " . . . the diagnosis of opportunistic infection must be based upon: (1) an awareness of the circumstances in which it occurs, (2) acceptance of the concept that virtually any micro-organism can cause disease if the host is susceptible, and (3) familiarity with clinical characteristics of opportunistic infections." Some details worthy of special note are:

CULTURES

Isolation of micro-organisms from a single site may be meaningless; repeated positive cultures must be taken seriously. The locus from which the culture is obtained may have important implications in weighing up the relevance of a number of apparently conflicting findings. For instance, the isolation of *Staphylococcus aureus* in a single blood culture can sometimes be dismissed, but the presence of *Candida albicans* in even one blood sample is almost certainly indicative of serious fungal infection, likewise the presence of *Mucor* in the nasopharynx of a diabetic with acidosis has particular relevance. The frequent isolation of the same organism, albeit an unusual one, from multiple sites in the same patient is an important indication of true pathogenicity. The correct interpretation of positive cultures may be impossible, especially when several opportunistic organisms are repeatedly isolated. In practice, those that are known to respond to available therapy are often given preference as the likely pathogen.

When intravascular catheters are removed their tips should be cut off and then cultured even in the absence of definite tissue reaction around the insertion site.[13]

BIOPSY MATERIAL

The examination of material obtained from potentially infected sites both bacteriologically and histologically is an especially useful method in the diagnosis of opportunistic infection. Not only the more accessible sites such as skin lesions, muscle, and lymph nodes, but deeper organs such as kidney, liver, and lung may be subjected to biopsy to give a tissue diagnosis. For instance, in a patient with a pneumonitis accompanied by hypogammaglobulinaemia infection with *Pneumocystis carinii* may be suspected. Lung biopsy is probably the only sure way of establishing the diagnosis of this infection, which may be responsive to therapy with pentamidine isethionate.[14 15]

EXAMINATION OF LEUCOCYTES

Total and differential white cell counts may be helpful in the diagnosis of conventional infections. On the other hand, in patients suffering from the types of disorders in which opportunistic infections are common leucocyte counts may be quite misleading.

NBT TEST

Park *et al.*[16] noted that polymorphonuclear leucocytes can spontaneously reduce the dye nitroblue-tetrazolium (NBT) and that in bacterial infections the percentage of grannulocytes reducing the dye was greatly increased. The test therefore offers a basis for distinguishing between disorders and indicating those which might have a bacterial origin. Wollman *et al.*[17] used the NBT test in a group of uraemic and renal transplant patients. They found that the dye test was not affected by large doses of corticosteroids, nor by transplant rejection and that it was useful in the differential diagnosis of infection in these patients. Freeman and King[18] found the NBT test helpful for monitoring patients with indwelling intravenous or intra-arterial catheters. Their patients were all receiving prophylactic antibiotics, which they comment appeared ineffective in prevention of infection, and when infection occurred the NBT test rapidly became positive. In some cases when the infected catheters were removed the test became negative. Thus the test can be used both to distinguish bacterial infection from other conditions causing pyrexia and also as an early warning system in those at particular risk. This test has considerable promise and may have particular relevance in the management of patients with reduced immune responses liable to produce opportunistic infections.

Treatment and Management

Treatment of opportunistic infections may be considered under the heads of preventive and therapeutic measures.

PREVENTION

The most important requirement in the prevention of opportunistic infection is to realize that it may occur, and to anticipate its arrival by careful clinical appraisal and assessment of microbiological data. Routine "preventive" bacterial monitoring by obtaining cultures from several different sites, particularly blood, even in the absence of overt clinical signs suggesting infection, is an essential part of the early warning drill. The microbiologist must be considered a member of the medical team and with his co-operation essential information may be available for early assessment. This approach to the patient will involve not only a particular physician's individual skill, but also many other facets of patient care, such as the antibiotic prescribing habits in special wards and units, the availability and use of isolation facilities, and the standard of nursing and other ancillary care. The incidence of opportunistic infection is a function of collective expertise, or lack of it, and its occurrence may be a reflexion not only of the ability of a particular individual or team but of the skill and understanding of that whole medical community.

Antibiotic Policy

In some cases the prevention of opportunistic infection may merely require the withdrawal of a particular drug; avoiding unnecessary administration may be as important as selection of the appropriate antimicrobial agents.

An established and adhered to policy in antibiotic usage may help in restricting bacterial resistance to known groups of drugs so that if blind therapy is required, appropriate selection can be made. The concept of "reserve" drugs should be encouraged—for instance, by an agreed restriction of administration of one or more antistaphylococcal drugs to exceptional circumstances such as fulminating septicaemia, or in infections due to multiply resistant strains. These methods involving discipline in antibiotic usage have been shown to reduce the incidence of infection with resistant staphylococci in a particular unit.[19]

Isolation

Probably the single most effective measure is to isolate the patient in a separate room.[20 21] The object is to protect the patient from contact with high concentrations of predominantly air-borne pathogens. This "reversed barrier" technique assumes major importance where vulnerable patients are exposed in a general hospital ward or unit, when highly resistant pathogens must be expected. The idea of *preventive* isolation to protect individual patients must be emphasized rather than the late removal to isolation of a patient heavily infected with pseudomonas or resistant staphylococci to protect other patients in the ward. Quite clearly these are two good reasons for isolation, but early preventive isolation is preferred.

Various modifications of "single cell" isolation are available. Thus plenum ventilation, with ultra-violet barriers at doorways and airlocks,[21] laminar flow ventilation systems,[22] plastic tents,[23] or isolators[24] have their uses. A useful addition is the Portable Island Ward,[25] which can be used either as a sterile unit (for example, clean filtered air is supplied) or as a simple isolation cubicle. Nevertheless, even the most sophisticated and elegant facilities are useless if the staff who work in these units have not been trained in the methods of prevention of infection.

Therapeutic Measures

In managing opportunistic infection any underlying disease, such as leukaemia, lymphoma, uraemia, or diabetes mellitus must be adequately treated and the infection dealt with at the same time. This may involve several different "firms" being actively engaged in treating acutely ill patients.

As in other infections, antimicrobial therapy should be based on adequate samples and antibiotic sensitivity tests, but this will not always be possible in ill patients. It is not within the scope of this article to list the various pathogens with appropriate therapy, but to suggest principles and indicate some special methods which may be helpful.

Prophylactic antibiotics, except in a few selected cases, should be avoided.[26–28] Bactericidal drugs or combinations of drugs should be used when possible; large doses administered parenterally, at least in the initial stages, are preferred. Impairment of renal and to a lesser extent hepatic function may demand modification in dosage; estimation of plasma concentrations of drugs particularly of aminoglycoside may be warranted.

The cidal serum concentration is a most useful estimation, especially if several antibacterial agents are administered simultaneously.

SEROTHERAPY

In some patients at special risk, such as those with severe burns, mortality may be closely associated with pseudomonas septicaemia. The work of Feller *et al.*[29] has shown that the incidence of septicaemia and the mortality due to pseudomonas can be reduced by the use of hyperimmune serum. These workers combine passive immunity with active immunization, and an extension of this approach must be considered in special units—such as transplant and dialysis units, radiotherapy centres, and possibly intensive therapy units. Likewise, the failure of penicillin to cure fulminating pneumococcal infections (especially those due to Type III pneumococcus) might prompt the reconsideration of antipneumococcal vaccines in some patients at special risk.[30]

Established opportunistic infection may be impossible to treat: prevention is therefore extremely important and such indirect therapeutic measures as we have must suffice until we can modify host response in a selective way without encouraging pathogens to exploit their opportunities.

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Any Questions?

We publish below a selection of questions and answers of general interest

Driving against Medical Advice

An epileptic patient who has minor attacks daily, and a diabetic patient who goes into insulin coma approximately once a month, both continue to drive motor cars despite strong medical advice to the contrary. What further steps, if any, should the family doctor take?

Unless the disabilities in both these patients started within the last three years, they have presumably made false declarations in applying for the first issue or renewal of their driving licences. The epileptic would have answered "No" to question 7(a) on form D.L.1 (Revised) 1971—"Do you suffer from or have you at any time had epilepsy?" and the diabetic to 7(f) "Are you suffering from any other disease or disability likely to cause the driving of a motor vehicle by you to be a source of danger to the public?" When they next apply for the renewal of their licences they will use the new application form D1(J), which includes the question 5(c) "Has a doctor ever advised you not to drive?" The patients can be warned that an applicant who, for the purpose of obtaining a licence, knowingly makes a false statement is liable to a fine of up to £100 or to imprisonment for a term of up to four months, or both.

If this step is ineffective, then the family doctor can enlist the help of the patients' families in protecting the patients and other road users by their putting pressure on the patients or communicating the circumstances to the licensing authority. The authority will always ensure anonymity of the informants in these circumstances. Finally, if the family doctor feels that, because of the amount of driving the patients do, the routes over which they drive, and the type of vehicles, and the way they drive, constitute such risks to other road users, he may consider his responsibility to the public overrides his ethical relationships with his patients. The B.M.A. and the medical defence societies recognize this dilemma and would support the practitioner if he communicated with the licensing authority after warning the patient.[1 2]

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Inoculation and Intercurrent Infection

Should routine inoculation be withheld from children with intercurrent infection or who are receiving antibiotics?

On general grounds it would be advisable to withhold immunization from children with intercurrent infection because the reaction to immunization would be superimposed on the infection and the child would be correspondingly more ill. Furthermore, if a live virus vaccine is being used there is also a possibility of interference occurring so that the effective immunological response might be reduced.

The second part of the question is not so clear cut. I think most people believe that a child ought to be completely fit when he is being immunized so that the immunological response is optimal while the risks of unpleasant reactions are reduced. So one reason for avoiding immunization if an antibiotic is being given would be that a healthy child would not be having an antibiotic.