Infectious diseases today – more questions than answers?

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ABSTRACT Antimicrobials have transformed the management of infections. The emergence of resistance, however, has become a major problem both in primary and secondary care. There is a need for new ways to deal with resistant infections, and the use of newer antimicrobials is only a small part of the solution. Suffice to say that methicillin-resistant *Staphylococcus aureus* (hospital or community acquired), virulent strains of *Clostridium difficile*-associated diarrhoea, multidrug resistant tuberculosis and invasive streptococcal infections have continued to increase in recent times, and are associated with significant morbidity and mortality. This symposium dealt with some of these issues and suggested ways to investigate and manage them.

KEYWORDS Antimicrobial resistance, antimicrobial stewardship, human immunodeficiency virus (HIV), Group A streptococcal infections, multidrug resistant tuberculosis, neutropaenic sepsis, outpatient parenteral antimicrobial therapy, pyrexia of unexplained origin (PUO), returning traveller

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SESSION 1 MAKING THINGS BETTER

We have come a long way from the old fever hospitals of the late nineteenth century. Dr Nick Beeching (Clinical Lead and Senior Lecturer, Liverpool School of Tropical Medicine) took us on a journey starting from 1880 to the present. Long gone are the fever vans which used to patrol the streets of most British cities in the early twentieth century collecting young people with scarlatina or smallpox and taking them to fever wards in city hospitals. Gone too are the open wards available for people with tuberculosis (TB). These have largely been replaced by modern infectious diseases units with separate isolation rooms. The infectious diseases physician nowadays manages different groups of people, such as intravenous drug users and travellers to exotic countries, with a variety of diseases not commonly seen in the past. To this we should add the threat of bioterrorism and emerging infections.

Antibiotic misuse is one of the main reasons for the emergence of resistant organisms. Around 80% of all antibiotics are prescribed in the community, and of these, 20–50% are prescribed unnecessarily.[1] It is thought that the main reasons for antibiotic misuse include undue pressure on doctors to prescribe antibiotics for viral infections, patients' ability to acquire and self-prescribe over-the-counter antibiotics and patients stopping treatment once symptoms have subsided.[2] Professor Dilip Nathwani (Consultant Physician and Honorary Professor of Infection, Ninewells Hospital, Dundee) discussed the concept of antimicrobial stewardship as a means of controlling antimicrobial misuse through streamlining, promoting intravenous-to-oral switch, education and audit.[3] In Scotland, the Scottish Antimicrobial Prescribing Group was launched in March 2008 with the aim of improving the quality of antimicrobial prescribing and infection management in hospitals and primary care.

Outpatient parenteral antimicrobial therapy (OPAT) is the administration of parenteral antimicrobials on different days without an overnight hospital stay.[4] This is particularly useful in cases where patients are clinically stable and either an oral agent is not readily available/appropriate or when rapid achievement of therapeutic concentration is required. OPAT has been particularly useful in cases of skin and soft tissue infections, joint/bone infections and haemodynamically stable patients with infective endocarditis. In return, patients can remain in the community and can often return to their daily activities.[5] Moreover, one of the most important advantages is the reduced risk of acquiring healthcare-associated infections.[6]

Dr Andrew Seaton (Consultant in Infectious Diseases and General Medicine, Gartnavel General Hospital, Glasgow) gave an overview of the key elements of an OPAT service. This is based on patient considerations (such as availability of home support and ease of access to hospital), antibiotic properties (such as long half-life and stability of the drug following reconstitution) and healthcare support requirements (such as clear guidelines and outcomes monitoring). A new concept is the introduction of a nurse-led OPAT service for the management of uncomplicated skin and soft tissue infections. This was shown to be associated with the same cure rates and rates of readmission but a significant reduction in the duration of outpatient intravenous antibiotic therapy.[7]

SESSION 2 NO EASY ANSWER

Whereas HIV diagnoses have increased steadily over the years, HIV-associated deaths and the incidence of AIDS have dropped dramatically.[8] In Scotland, the number of HIV-positive patients who are heterosexual is similar to that of men who have sex with men.[9] In those heterosexuals who acquire HIV, the vast majority have acquired the infection from Africa.[10] It is very difficult to estimate the number of people living with undiagnosed HIV. Some of the evidence comes from unlinked anonymous surveys of genitourinary medicine clinic attendees around the UK, which show that 3.4% of homosexuals and 0.4% of heterosexuals have undiagnosed HIV infection.[11]

Based on the above data, Dr Stephen Baguley (Consultant Genitourinary Physician, Woolmanhill Hospital, Aberdeen) argued the case for universal testing for HIV. The benefits of knowing that a patient is HIV positive are numerous. These include reducing the number of late presenters and a higher life expectancy due to earlier diagnosis and treatment.[12] Moreover, people who know that they are HIV positive report reductions in 'high-risk' behaviour. This could potentially result in a 25–50% reduction in the risk of HIV transmission.[13] There are suggestions that HIV testing in the general population should be undertaken in areas where HIV prevalence in 15–59 year olds exceeds 2 in 1,000.[14] In this scenario, testing should be carried out on all men and women registering in general practice and all general medical admissions. Until now, no health board in Scotland has reached this level of seroprevalence, and so a more selective approach to testing is recommended, reserving it for individuals identified as high risk through social/sexual factors and HIV indicator diseases.[14]

The HIV population is growing older.[15] This is partly due to the efficacy of combination antiretroviral treatment (cART). While encouraging, this development presents new challenges. Older patients are less likely to present with asymptomatic HIV and more likely to present with advanced disease or AIDS. For every ten-year increase in age at the time of seroconversion there is a 1.47-fold increase in the risk of death.[16] Dr Alisdair MacConnachie (Consultant in Infectious Diseases and General Medicine, Gartnavel General Hospital, Glasgow) discussed the effect of HIV on the body and the long-term effects of cART. HIV-positive patients are at higher risk of developing ischaemic heart disease, diabetes and metabolic syndrome, probably because of a combination of early atherosclerosis due to the HIV infection and the effect of antiretroviral therapy on lipid metabolism.[17–19] Life expectancy of people with HIV is increasing due to the effectiveness of cART. Hence, more patients are presenting with non-HIV-related neoplasms, such as anal carcinoma, head and neck neoplasms and Hodgkin's lymphoma.[20] Around half of the patients with HIV have evidence of neurocognitive impairment; this rate increases in the presence of other comorbidities and a low CD4 count.[21]

SESSION 3 OLD BUGS WITH NEW TRICKS

The incidence of TB in Scotland has been increasing in recent years.[22] New challenges include multidrug-resistant tuberculosis (MDR-TB), where the organism is resistant to both rifampicin and isoniazid, and extensively drug-resistant tuberculosis (XDR-TB), where the organism is resistant to rifampicin, isoniazid, fluoroquinolones and at least one of the injectable drugs (excluding streptomycin). Professor Peter Ormerod (Professor of Respiratory Medicine and General Physician, Royal Blackburn Hospital) gave an overview of the management of drug-resistant TB. Risk factors for MDR- and XDR-TB in the UK include history of previous treatment or treatment failure, contact with known drug-resistant TB, presence of HIV infection and residence in the London area.[23] Currently, 7% of all tuberculous mycobacteria are isoniazid resistant, while 1% is MDR-TB. Mortality can reach between 70–100% in patients with MDR-TB, especially in the presence of HIV.

It is suggested that patients with suspected MDR- or XDR-TB should be assessed and managed in negative pressure rooms by physicians with substantial experience in drug-resistant TB,[23] and that there should be close liaison with Mycobacteriology Reference Units. The principle of managing MDR-TB is to use at least five active agents, of which one should be an injectable, until the patient is culture negative. Following this, three active drugs should be continued for another nine months. Treatment of XDR-TB is even more difficult and less successful. Often the treatment has to be individualised and might include drugs with little evidence of activity against TB.

This year's Sydney Watson Smith Lecture was given by Dr Dennis Stevens (Chief of the Infectious Diseases Section, Veterans Affairs Medical Center, Boise, Idaho, and Professor of Medicine, University of Washington School of Medicine, Seattle). The topic was invasive group A streptococcal infections. Streptococcal toxic shock syndrome (STSS) is defined as any group A streptococcal infection associated with shock and multi-organ failure. Early symptoms are non-specific and include a viral-like prodrome associated with localising musculoskeletal pain and mental confusion. In 35% of cases the portal of entry is the skin, followed by the mucous membrane in 20%. In the remaining 45% of cases the portal of entry is unknown, but muscle strains, sprains or haematomas are recognised risk factors.[24] Myonecrosis (necrotising fasciitis) can develop rapidly and it is thought that vascular ischaemia contributes significantly to its pathogenesis.[25] Patients diagnosed with STSS should be treated in intensive care units. Clindamycin is probably better than penicillin because it inhibits toxin production. Combining the two antibiotics does not confer any added benefit.[26] Intravenous immunoglobulins can be used in difficult cases but the benefit in these situations has not yet been established.[27]

SESSION 4 HOT AND BOTHERED

Pyrexia of unknown origin (PUO) used to be defined as a fever of 38.3° C for >3 weeks and an uncertain diagnosis after one week of hospital investigations.[28] However, the practice of medicine has changed over the years. Investigations now include some which can be performed on outpatients. In the early 1990s the definition was changed to include a pyrexia which has not been diagnosed after three outpatient visits. In the original series of 100 patients with PUO, infection only accounted for 36% of the total diagnoses, the remainder being made up of neoplasia, multisystem disease, miscellaneous and unknown.[28] Diagnosing a PUO nowadays involves the more frequent use of transoesophageal echocardiography and nuclear medicine, such as positron emission tomography (PET) scanning. Bacterial and viral serology is rarely helpful.

Dr David Wilks (Consultant in Infectious Diseases, Western General Hospital, Edinburgh) looked at algorithms available to help the physician dealing with cases of PUO. In a systematic review of 11 series of cases with PUO from Western countries, the commonest infections were TB and intra-abdominal abscesses, whereas the commonest malignancy was lymphoma.[29] The authors of this review recommended a list of investigations before labelling a patient as having a PUO. Abdominal CT to look for abscesses, liver biopsy (even in the absence of deranged LFT and hepatomegaly) and temporal artery biopsy in the elderly are the most helpful in identifying the cause of PUO, although clinical judgement has to be taken into consideration before organising these tests. There is no evidence that bone marrow examination or a trial of treatment with anti-tuberculous drugs or steroids is helpful in identifying the cause. In a prospective multicentre study involving 73 patients presenting with PUO, the authors described an algorithm for dealing with such cases.[30] Despite this, 50% of patients did not have a diagnosis, which is not surprising since they are those patients who would have previously been investigated extensively prior to being diagnosed as PUO and included in the study.

Travelling abroad has become much more common nowadays. The risk of people developing any health problems after a stay of one month in exotic countries is 50–65%.[31] The most common symptoms encountered include fever, diarrhoea and skin rashes. Eosinophilia is frequent in travellers. Around 35–45% of those staying in such countries for at least one month will develop traveller's diarrhoea. The risk of malaria for the same period is 2%. When patients present with fever it is important to exclude tropical infection, but other non-tropical infections, neoplasms or connective tissue diseases should also be considered. Dr David Lalloo (Reader in Tropical Medicine, Liverpool School of Tropical Medicine) compared the aetiology of fever in different cohorts of returning travellers. Malaria, respiratory infections and diarrhoea are common causes. Between 10 and 25% of patients remain undiagnosed even following extensive investigations. Falciparum malaria usually manifests itself within the first five months following travel. Because of its potential to become a severe illness, it is suggested that all patients with a diagnosis of malaria should be admitted and treated in hospital where expertise in treating the disease exists.[32] Artemisinins are becoming the mainstay of treatment in many countries because of their long half-life and activity against different stages of the disease.

Typhoid fever is particularly problematic in travellers to Asia because of a high incidence of fluoroquinolone resistance. It is suggested that empirical treatment should be with ceftriaxone until full sensitivities are available. Traveller's diarrhoea is a common presenting symptom in the returning traveller, usually occurring in the first two weeks of travel. Around 1% of patients require hospitalisation. The most common causes include enterotoxigenic *Escherichia coli*, campylobacter, salmonella, shigella, entamoeba and giardia. Self-treatment is often recommended, and patients are advised to take antibiotics on first suspicion of diarrhoea. Ciprofloxacin is the drug of choice, although this is contraindicated in pregnancy and children.

Neutropaenic sepsis is becoming more common nowadays due to the increased number of transplants and more aggressive chemotherapy aimed at curing or limiting haematological malignancies. Dr Dominic Culligan (Consultant Haematologist, Aberdeen Royal Infirmary, Aberdeen) provided an overview of the empiric therapy of neutropaenic sepsis. High-risk groups include patients with a neutropaenia of >7 days in the presence of other comorbidities, such as respiratory, renal and hepatic impairment, haemodynamic instability and presence of indwelling catheters.[33] Such patients are treated empirically with broad spectrum antibiotics such as piperacillin/tazobactam plus gentamicin or carbapenems. There is no evidence that combination therapy is any better than monotherapy.[34]

Invasive fungal infections are occasionally encountered in neutropaenic patients. It can be difficult to prove the existence of a fungal infection so treatment may need to be started in probable or possible cases. Treatment of suspected fungal infection with caspofungin is associated with a better outcome when compared to liposomal amphotericin B.[35] On the other hand, in proven or probable invasive aspergillosis, voriconazole is more effective than amphotericin B.[36] Better diagnostic tests are required for invasive fungal infections; the current progress in PCR testing and antigen tests is encouraging.

CONCLUSION

This symposium covered a wide range of topics in infectious diseases. It gave a comprehensive overview of current thinking and available evidence on the investigations and management of topical infectious diseases.

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