Selected abstracts from 'Infectious diseases today: more questions than answers?'

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FROM FEVER HOSPITAL TO INFECTION CENTRE

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In the nineteenth century most cities had isolation or fever hospitals to isolate patients with infection. The prevalence and patterns of infection have changed over the ensuing 150 years, and infection centres now play a different role.

The talk outlines changes in infectious disease practice since the early twentieth century, with an emphasis on the increasing complexity and interdisciplinary nature of infection medicine. This includes the continued need for regional inpatient referral centres and the recent rediscovery of the role of isolation wards to deal with nosocomial infection such as *Clostridium difficile*. Infectious disease consultants share responsibility for antimicrobial stewardship, infection control and general infection consulting activity with colleagues in clinical microbiology and virology, and increasingly with specialist pharmacists.

Outpatient specialty practice (including specialist nurses) varies around the UK but includes networking and developing standards for clinical care for hepatitis with hepatologists, HIV with genitourinary medicine and tuberculosis with chest physicians. In some centres specialist practice includes bone infection, neurological infection, fungal infection and renal/intensive care. A subset of infectious disease doctors (usually academic appointees) specialise in imported infection and tropical medicine overseas and some have input to the growing specialty of travel medicine. Infectious disease physicians are integral to planning for disasters including pandemic influenza and deliberate release, and good liaison with local public health networks is essential.

This changing role produces tensions in training requirements, as infectious disease physicians need to be good general physicians as well as infection specialists. Integrated training with clinical microbiology is increasingly popular, but limits on training time mean that this can preclude adequate general medical training. Tropical training tracks are under threat, while travel medicine curricula are becoming better defined. About 50% of infectious disease physicians hold academic appointments and entry to specialist training at specialty registrar level remains very competitive.

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MANAGING ANTIBIOTIC USE: IS THERE ANY HOPE?

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Increasing antibiotic resistance is a global public health problem and the control of antibiotic prescribing is a crucial part of any strategy to limit the development of resistance. In Europe 16 countries have developed a national strategy to contain antimicrobial resistance and nine countries have an action plan.[1]

A core component of most of these strategies is antimicrobial stewardship, a term that has often been used interchangeably with antibiotic policies and antibiotic control programmes among others and generally refers to an overarching programme to change and direct antimicrobial use in any healthcare setting. A better definition is a set of measures delivered by a multidisciplinary team working in healthcare institutions to optimise antimicrobial use among patients in order to improve patients outcomes, ensure cost-effective therapy and reduce adverse sequelae of antimicrobial use including ecological effects such as resistance and *Clostridium difficile* infections.[2,3] Such activity would include appropriate antibiotic selection, dosing, route and duration of therapy. This stewardship combined with infection prevention measures will limit the emergence and transmission of antimicrobial resistance.

The evidence base and subsequent good practice guidelines for such stewardship programmes have recently been published by the Infectious Diseases Society of America.[4] A range of stewardship strategies are recommended and employed with variable frequency and effect depending on the clinical setting and problem. One widely employed strategy is antibiotic policies, sometimes called formularies, which aim to limit the availability of antibiotic choice and will sometimes require pre-authorisation, although this primarily is used for a smaller range of high-cost agents and those requiring specialist input. Other aspects of a policy may include intravenous–oral switch or sequential therapy, mandatory antibiotic order forms, therapeutic substitution of antibiotics and automatic stop orders.

In Europe individual countries (for example, Scotland and Sweden) or collectives such as the EU Antibiotic

Stewardship Programme (ABS International) are embarking upon either primarily hospital-based national stewardship programmes (in the case of ABS International) or those in the community and hospitals.[5–7]. The Antibiotic Resistance, Prevention and Control Concerted Action Project (ARPAC) found widespread evidence of the use of antibiotic policies and a variety of control measures in European hospitals.[8] A systematic review of the most effective interventions has also been published[9] and should offer us further insight into the most appropriate evidence-based intervention.

After a brief review of the above this presentation will describe how these measures have been implemented nationally in Scotland[10] using a multifaceted interventional strategy that embraces the core principles of stewardship combined with surveillance, education and feedback, and performance management. While the emphasis is on secondary care, primary care is also discussed.

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FROM HOSPITAL TO HOME: MANAGING SERIOUS INFECTION IN THE COMMUNITY

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Outpatient parenteral antibiotic therapy (OPAT) allows timely discharge or avoided admission for a variety of patients with serious infection. Although well established in North America, OPAT has been slow to develop in the UK, with less than half of Scottish health boards currently employing dedicated staff. Advantages of OPAT include avoidance of healthcare-associated infection and speeding return to normal activities.

In Glasgow, patients with Gram-positive infections, particularly skin and soft tissue (SSTI), and bone and joint infection are most likely to benefit from OPAT as these infections are common and frequently respond to agents which can be administered daily (ceftriaxone, daptomycin, ertapenem) or thrice weekly (teicoplanin). Patients with SSTI have benefited from a specialist nurse-led 'patient group direction' which has been associated with reduced duration of IV ceftriaxone. Experience has also grown in the management of other less common infections such as Lyme borreliosis, syphilis, enteric fever, endocarditis/bacteraemia, bacterial meningitis and drug resistant tuberculosis.

Irrespective of diagnosis or treatment type OPAT is a cost-efficient alternative to hospitalisation for many patients, and patient satisfaction is high. Current challenges include managing an expanding patient population, identifying new patient groups who may benefit from OPAT, evaluation of new agents/treatment regimens and ensuring the principles of prudence in prescribing are maintained in the OPAT setting.

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UNIVERSAL TESTING FOR HUMAN IMMUNODEFICIENCY VIRUS?

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Although still incurable, there has never been a better time to be diagnosed HIV-positive; modern treatment generally results in a near-normal life expectancy and has relatively few side effects. However, approximately 25% of people with HIV in the UK are undiagnosed and many people who are diagnosed are presenting with a low CD4 count. This is a problem. Late diagnosis carries an increased risk of death, people who are diagnosed late cost more to manage and people who do not know they are infected are more likely to transmit the infection. Earlier diagnosis can thus defer death, save money and reduce incidence.

A joint guideline on HIV testing was published in 2008.[1] This recommended various strategies to increase the number of people being tested. These included:

- Testing people with 'HIV indicator conditions', many of which are common presentations to medical admissions units, e.g. bacterial pneumonia.

- Testing all medical admissions and people registering with a GP if the HIV prevalence (diagnosed cases) in the local population exceeds 0.2%, i.e. 'universal testing'.

The guideline recommends testing in other groups and is well worth reading.

In Scotland there is no health board with an HIV prevalence (diagnosed cases) that exceeds 0.2%, so 'universal testing' would not be cost-effective. Instead, clinicians need to be mindful of the numerous HIV indicator conditions and offer tests to people with these presentations. HIV testing should be offered in the same way that tests for other conditions, such as viral hepatitis, are offered, i.e. people need to know what investigations are being recommended, but no special 'counselling' is needed.

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MANAGING DRUG-RESISTANT TUBERCULOSIS

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The epidemiology of tuberculosis (TB) in Scotland, Europe and the world will be briefly discussed. Drug resistance occurs in some 7.5% of culture-confirmed TB, but can only be confirmed by positive cultures, which is why every reasonable effort to obtain material for culture should be made. Isoniazid resistance is the most common single resistance, and isoniazid and streptomycin resistance the most common dual resistance. The management of these, and other mono-resistances, will be covered. Isolated rifampicin resistance is uncommon, comprising only some 5–10% of rifampicin resistance. Rifampicin resistance, found by culture or on polymerase chain reaction (PCR) testing, should be assumed to be due to multidrug-resistant TB (MDR-TB), and isolated and treated as such until the full resistance profile is available. Isolated rifampicin resistance is treated with 2HZE/16HE.

Prior TB treatment is the biggest individual risk factor for MDR-TB; there are also geographical 'hotspots'. Multidrug-resistant TB is resistance to rifampicin and isoniazid +/- other drugs. Extremely drug-resistent TB (XDR-TB) is resistance to rifampicin, isoniazid, quinolones and an injectable other than streptomycin. The outlook for MD and XD-RTB gets progressively worse. Multiple reserve drugs have to be used, and surgery under drug cover considered for unilateral or bi-apical disease. Isolation criteria are in national guidelines. Drug resistance is an increasing problem in TB management, with increasing complexity.

Further reading

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INVASIVE GROUP A STREPTOCOCCAL INFECTIONS

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While group A streptococcal infections have plagued homo sapiens since their early evolution, the appearance of more severe infections has been well documented throughout the world over the course of the past 20 years. Invasive infections include necrotising fasciitis, pneumonia, post-partum sepsis, meningitis and bacteraemia. Streptococcal toxic shock syndrome is defined as any group A streptococcal infection associated with the sudden onset of shock and organ failure. The incidence of invasive infections is five cases per 100,000 population/per year in both the United States and Europe. Enhanced virulence of group A streptococcal infections is reflected by the high mortality (30–70%) associated with these infections. Specific M-types of group A streptococcal infection (M1, 3, 6, 11, 18 and 28) have been most common and these harbour multiple toxins, including streptolysin O, NADase and pyrogenic exotoxins A, B, C and MF, which act as superantigens.

Fifty per cent of patients with necrotising fasciitis develop infection at the site of non-penetrating trauma, a process that is enhanced by non-steroidal anti-inflammatory drugs. Mechanisms of shock and organ failure are complex and related to both a cytokine storm orchestrated by overzealous innate immune recognition and direct effects of toxins on organ function. Profound acute cardiomyopathy occurs in some patients within 24–48 hours of clinical infection and is reversible among survivors. Rapid tissue destruction associated with necrotising processes is mediated by toxin-induced vascular injury involving platelet-neutrophil complexes. Strategies to attenuate toxin production and neutralise circulating toxin are of prime importance; however, more potent products are sorely needed.

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MY APPROACH TO PYREXIA OF UNKNOWN ORIGIN

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Patients with fever of unknown origin (FUO) have been vexing physicians for centuries. In 1961 Petersdorf and Beeson[1] published their seminal definition of pyrexia of unknown origin (PUO) as a fever greater than 38.3°C for more than three weeks, with no diagnosis after investigation for one week in hospital, and reported on a series of 100 cases. Of these cases, 37% were due to infection, 19% neoplasm, 17% multisystem inflammatory disorders, 21% due to miscellaneous causes and 7% remained undiagnosed.

Since then innumerable new laboratory and radiological techniques have become available and many series of PUOs have been reported from a wide range of clinical situations. One paradoxical consequence of improvements in diagnostic technology is that, as it is more uncommon for patients in general to remain undiagnosed, the proportion of patients who satisfy criteria for PUO and remain undiagnosed after further investigation has increased over time. Thus in one recent series from the Netherlands,[2] patients were only considered to have PUO after they had been extensively investigated, including imaging of the chest and abdomen. Despite employing the latest technology including positron emission tomography – computed tomography (PET-CT) scanning, 50% of these patients remained undiagnosed.

Mourad et al.[3] conducted a systematic review of published PUO series and conclude that imaging and biopsy remain the techniques most likely to yield a diagnosis. Liver biopsy and temporal artery biopsy are useful tests even in patients without significant localising symptoms and signs. Mourad et al state: 'The utility of empiric therapy, such as antibiotics, antituberculosis agents, or corticosteroids has not been studied in PUO. This, however, is not an uncommon practice for the frustrated physician. We believe that empiric therapy should not be given to patients with FUO because it often obscures or confuses the diagnosis.'[3]

As the diagnosis of patients with PUO is clearly not getting easier as years go by, I offer you the following thoughts as guiding principles:

- Atypical presentations of common disorders are more likely than rare diseases presenting typically.
- A careful travel, sexual, occupational and animal exposure history is essential, but the significance needs to be assessed with reference to 'denominator frequency' – most 'clues' gleaned from the history will not contribute to the final diagnosis.
- Bacterial and viral serology rarely suggest a diagnosis that has not been made clinically.
- Malignancy is as likely as infection.
- Therapeutic trial of antibiotics is rarely indicated.
- Trial of steroids is almost never indicated.
- Imaging and biopsy are always most useful.

Even in the most expert hands the diagnosis often proves elusive.

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FEVER IN THE RETURNING TRAVELLER

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The number of UK travellers to tropical regions has increased considerably over the past ten years and presentation with a febrile illness or medical problem post travel is increasingly common. All physicians need to know how to diagnose and manage travel-related illness and when to seek expert advice. This presentation describes the epidemiology of travel-related diseases and highlights the most common causes of febrile illness post travel, particularly focusing on conditions which are potentially life-threatening, such as malaria, those with public health importance, such as viral haemorrhagic fevers, and newer, emerging diseases. New developments in the diagnosis and management of malaria and other conditions are discussed and important aspects of the new UK guidelines on the management of febrile travellers are highlighted. Illnesses which often pose problems post travel, such as eosinophilia and diarrhoea are discussed.

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MY APPROACH TO NEUTROPENIC SEPSIS

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The outcome for patients with haematological malignancy treated intensively has improved considerably over the past three decades. Much of this improvement relates to better supportive care, and pivotal to this is protocol-driven management of neutropenic sepsis.

Patients considered at high risk develop neutropenia $<0.5 \times 10^9$/l for longer than seven days and are at greater risk of complications through comorbidities. Fever in such patients is treated empirically with broad spectrum intravenous antibiotics and in our unit this is as a combination of aminoglycoside and anti-pseudomonal penicillin (gentamicin and piperacillin-tazobactam). Ongoing areas of debate remain the use of a single antibiotic such as meropenem, the addition of a glycopeptide for those fever-resistant to first-line therapy and the use of oral outpatient-based therapy for low-risk patients.

Studies in the 1980s demonstrated that the empiric addition of antifungal therapy to neutropenic patients with antibiotic resistant fever provided for a significant survival advantage and as a result this became standard of care. The incidence of fungal infection varies from unit to unit and microbiological confirmation is notoriously difficult. Many patients, therefore, receive toxic anti-fungal therapy unnecessarily. The recognition of this has, in recent years, led to a move towards pre-emptive therapy with a wider range of better tolerated anti-fungals, when there is additional supporting evidence of fungal infection. However, issues relating to fungal antigen testing, fungal PCR and prompt access to CT scanning present significant challenges to successfully implementing this strategy.

Further reading

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