

Selected abstracts from Infectious diseases: problems and challenges

EPIDEMIOLOGICAL INVESTIGATION OF AN OUTBREAK OF ATYPICAL PNEUMONIA IN SCOTLAND

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Background During the summer of 2006 an outbreak of atypical pneumonia was identified in staff within a meat processing plant in central Scotland. Investigations suggested an infectious agent was responsible rather than a chemical or environmental hazard. Q fever was subsequently confirmed. Q fever is a zoonoses transmitted mainly by cattle, sheep and goats and is a rare disease in the UK.

Method or theme Based on initial investigations of the local public health team and environmental health officers, an epidemiological questionnaire was devised and administered by Health Protection Scotland. Information was gathered from staff at the factory on symptoms, work location, job, routes through the factory, hobbies and outside activities. Blood samples were also taken and a range of environmental investigations undertaken.

Results 142 of 220 staff were found to have evidence of exposure to the bacterium that causes Q fever. Statistical analysis identified two areas in the factory where staff had an increased likelihood of exposure to the Q fever bacterium.

Conclusion We believe that a contaminated aerosol from the sheep lairage infected a large proportion of the workforce.

Keywords Epidemiology, Q fever, zoonoses
Declaration of interests None declared.

HOW WOULD I MANAGE DIFFICULT FUNGAL INFECTIONS OF THE LUNG?

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Background Fungal infections are increasing in frequency and complexity. Invasive aspergillosis has increased in incidence so that it is found at autopsy in 4% of all patients dying in European teaching hospitals. Other figures from Japan and the US support this upward trend. New data suggests a high frequency (~7%) in medical intensive care unit patients, of whom >40% are chronic obstructive pulmonary disease patients. More than 500 cases have been described postoperatively in non-immunocompromised patients. High-risk groups

include allogeneic haematopoietic stem cell transplantation patients with graft-versus-host disease, acute myeloid leukaemia patients undergoing induction chemotherapy and/or corticosteroid treatment and those with chronic granulomatous disease.

Theme Aspergillosis has undergone a partial revision of the diagnostic categories: invasive aspergillosis can be divided into acute and subacute; chronic forms of pulmonary aspergillosis include chronic cavitary, chronic fibrosing aspergillosis, which must be distinguished from aspergilloma, and allergic bronchopulmonary aspergillosis.¹

Early diagnosis is critical to a good outcome in invasive aspergillosis,² in which mortality rises from 40% if treatment is given in the first 10 days of illness to 90% if delayed beyond that. In both acute and subacute forms of aspergillosis, many diagnoses are missed because the condition is not considered and diagnostic tests not ordered, or because the tests perform badly.

New diagnostic approaches are being developed and existing ones are being re-evaluated in the light of effective prophylaxis.¹ The use of computerised tomography scanning of the lung in stem cell transplant and leukaemic patients now has an established place in the early diagnosis of invasive aspergillosis. It is less useful in other patients, or if delayed. Antigen tests on blood are well established for invasive aspergillosis in haematology patients, although they perform less well with effective prophylaxis and are often falsely positive in those receiving tazocillin or ampicillin, and in children.

Bronchoalveolar lavage (BAL) antigen tests may be valuable. The *Aspergillus* antigen may be useful in cerebrospinal fluid for cerebral aspergillosis and in BAL fluid in transplant and leukaemic patients. Antigen tests do not distinguish species of *Aspergillus*, which is pertinent as *Aspergillus terreus* is resistant to amphotericin B. New diagnostic tests are required for infections caused by the Mucorales, to distinguish them from aspergillosis. Real-time polymerase chain reaction (PCR) is now entering the clinical arena and the results of PCR on respiratory samples in immunocompromised patients are excellent.³⁻⁵ These tests are being commercialised.

Voriconazole is the treatment of choice for invasive aspergillosis. The echinocandins and amphotericin are less effective, but may be useful in those with drug interactions or those who fail therapy. Itraconazole is probably less effective than voriconazole, both of which require therapeutic drug monitoring. Azole resistance in *Aspergillus fumigatus* is an increasing problem.

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Keywords Aspergillosis, *Aspergillus*, Mucorales, PCR, voriconazole

Declaration of interests Professor Denning has received research grants from a number of pharmaceutical companies, including Pfizer, Merck, Astellas, F2G, OrthoBiotech, Indevus and Basilea.

HOW TO MANAGE BLOODY DIARRHOEA AND VTEC INFECTION

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Background Bloody diarrhoea is most commonly caused by infection. Verotoxin-producing enteropathogenic *Escherichia coli* (VTEC), *E. coli* O157, is an uncommon but important cause of bloody diarrhoea, particularly in Scotland where rates of infection are higher than the rest of the UK. The early recognition of *E. coli* O157 infection is vital because it may be complicated by the haemolytic uraemic syndrome (HUS), which has severe consequences and significant mortality.¹ Many questions remain unanswered in the management of VTEC infections, particularly regarding the potentially harmful effect of antibiotics,² the role of plasma exchange in the management of HUS³ and the outcomes following HUS. Detailed clinical analyses of outbreaks⁴ and research into the pathogenesis of HUS have provided some answers but also prompted new questions. Enhanced surveillance of HUS has been active in Scotland since 2003, and the data collection is ongoing.

Method or theme

- HPA and HPS data
- Retrospective and prospective analysis of the 1996 Central Scotland Outbreak

- Data from ENSHURE (Enhanced Surveillance of HUS)
- Literature review using OVID database

Results

- Antibiotics should be avoided in VTEC infections.
- Haemolytic uraemic syndrome can and should be recognised early.
- Dialysis and filtration are central to the management of HUS. However, plasma exchange may also have a role in adults.
- ENSHURE is contributing to our understanding of the epidemiology and clinical management of HUS in Scotland.
- Verotoxin-producing enteropathogenic *Escherichia coli* infections continue to cause severe disease, and prevention is central to effective management.

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Keywords Bloody diarrhoea, *E. coli* O157, haemolytic uraemic syndrome, plasma exchange, VTEC

Declaration of interests None declared.

RABIES: THE THREAT AND THE REALITY IN THE ANIMAL POPULATION

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Background Classical rabies virus strains have a worldwide distribution, except for specific countries in Western Europe and a few island nations including the UK, New Zealand and Hawaii and the continents of Australia and Antarctica. In Western Europe, many countries are now free of terrestrial rabies. This is, however, at considerable cost and with a continual risk of re-importation. Measures aimed at preventing the disease's re-introduction and establishment have been made subject to specific legislation throughout Europe. Rabies is a notifiable disease between member states of the European Union.

The re-emergence of rabies in some regions of Europe that were previously designated 'rabies-free' has demonstrated the need for continual vigilance and strict control measures. Despite the substantial advances that have been made during the twentieth century in reducing the burden of rabies, especially in Central and Eastern

Europe, the disease remains endemic in many countries, largely as a result of financial limitations and a poor medical/veterinary infrastructure. The risk of re-importation of rabies into the UK continues to exist.

The major risk factors include:

- the release of a smuggled rabid animal into the UK from a rabies-endemic country;
- the introduction of an imported rabid dog into quarantine;
- deliberate release.

Method or theme In the event of a case of rabies being re-imported to the UK, the main objective would be to prevent the disease becoming established in wildlife species, especially the increasing urban and rural fox population.

Results The principal requirements in preventing the re-introduction of rabies to the UK will be to promote the vaccination of companion animals that are moved across national boundaries and the oral vaccination campaigns of wildlife species to control sylvatic rabies (especially in Eastern Europe). The latter objective will be to create rabies-free areas throughout Europe and to increase the number of rabies-free countries that are eligible to participate in a universal pet travel scheme. In Europe, this can only be achieved through the introduction of compulsory parenteral vaccination for domestic animals that are moved between countries. In addition, a widespread legislative system to control trade and movement restrictions of animals would be an advantage to safeguard existing rabies-free areas. Clearly, cross-border co-operation between countries of Western and Eastern Europe will be a primary goal in tackling rabies elimination.

While the control of rabies in foxes throughout Europe is applauded, the vigilance and surveillance of rabies must continue, especially in new reservoir species such as the racoon dog, and in assessing the prevalence of new and emerging variants of rabies virus in European species of bats. This can be achieved through the harmonisation of a laboratory network throughout Europe and in adopting a 'one health' approach to rabies control.

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Keywords Bat, dog, fox, lyssavirus, rabies, reservoir, vaccine, virus

Declaration of interests None declared.

RABIES: CLINICAL MANAGEMENT AND PREVENTION IN HUMANS

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Background Rabies is a neglected disease. In developing countries there is failure to prevent transmission between dogs and insufficient prophylaxis for humans. Dog rabies virus infection is universally fatal in man, but the disease is 100% preventable. All deaths from rabies are due to a failure of prevention.

In Asia and Africa, human mortality from rabies is estimated at 55,000 annually, but it has been suggested that only 3% of cases are recorded. Ten patients with rabies have been recognised in the UK since 1980, including an indigenous case in Angus, Tayside.¹

Although hydrophobia and an inexplicable feeling of terror are cardinal features of 'furious' human rabies encephalitis, there is evidence that patients with more 'paralytic' signs go unrecognised. Laboratory diagnosis is rarely attempted. Clinical rabies has been missed in organ donors with dire consequences.² The diagnosis should be considered in patients with unusual neurological, musculoskeletal, throat or psychiatric clinical features.

Conclusion No therapy has proved effective, but should the recovery of an unvaccinated teenager with bat rabies infection influence the management of all human cases in future?³

No deaths have been reported in anyone given pre-exposure rabies immunisation followed by booster vaccination after possible exposure to infection. If clinicians warned prospective travellers, wildlife enthusiasts, etc. of the risk of exposure to rabies and efficacy of prophylaxis, they could save anxiety and lives.

In Asia and Africa, human rabies mortality could be dramatically reduced if effective prophylaxis⁴ were widely available and if sufficient resources were devoted to controlling the epizootic in dogs. Rabies could eventually become truly rare.

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Keywords Encephalitis, organ donor, rabies, vaccine

Declaration of interests None declared.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS BACTERAEMIA AND ENDOCARDITIS: A CONSEQUENCE OF MEDICAL PROGRESS

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Background The frequency of *Staphylococcus aureus* bacteraemia and endocarditis is increasing, and a primary cause for this increase is healthcare contact. The classic association of endocarditis due to viridans group streptococci associated with the risk factor of rheumatic or congenital heart disease has now been largely replaced in most industrialised nations with endocarditis due to *S. aureus*, associated with the risk factor of healthcare contact.

The complexity of *S. aureus* bacteraemia and endocarditis has increased, and the primary reason for this increasing complexity is medical devices. Prosthetic implants have improved the quality and length of life of countless thousands of patients – until those devices become infected. The intersection between prosthetic material and infection is an ever-widening one for which current therapy is unsatisfactory at best.

The emergence of methicillin-resistant *S. aureus* (MRSA) as a community-acquired pathogen, and the limited pipeline of new antibiotics for MRSA, underscores the need for new treatment options.

Conclusion *S. aureus* is a serious, common and increasingly healthcare-associated cause of bacteraemia and endocarditis in most of the industrialised world. Increases in frequency, infection complexity and proportions of MRSA have contributed to an unmet medical need for new treatments for this persistent pathogen.

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Keywords Bacteraemia, endocarditis, healthcare contact, prosthetic implants, *Staphylococcus aureus*

Declaration of interests Dr Fowler has received funding from and consulted for various companies, including Cubist, Merck, Leo, Johnson & Johnson, Inhibitex, Theravance, Arpida, Nabi, Astellas, Cerexa and Ortho-McNeil.

HOW TO MANAGE TICK BITES AND LYME BORRELIOSIS

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Background With warmer winters, tick bites occur throughout the year. Ticks should be removed with tweezers and not with fingernails. All parts of the mouth must be removed from the wound. In many parts of Scotland, none of the ticks are infected with *B. burgdorferi* and where there is infection, only 1–30% of the ticks are infected. Further, if ticks are removed within 24 hours, there is no risk of Lyme borreliosis. In Scotland, Lyme borreliosis peaks in males aged 60–65 years, and in females aged 55–65 years.

Individuals with occupational or recreational exposure should only be tested for Lyme borreliosis if symptomatic. Patients with early Lyme borreliosis may have negative serology, but the classical erythema migrans rash is diagnostic. Patients with late disease nearly always have positive serology, and therefore a negative result excludes Lyme borreliosis. Patients with positive serology should be treated if clinically indicated; the presence of positive serology alone does not require treatment. Only 5% of patients with chronic fatigue syndrome will have the illness caused by Lyme borreliosis.

Further reading

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Declaration of interests None declared.

THE CLINICAL MANAGEMENT OF Q FEVER

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Background Q fever is a rare zoonotic infection caused by *Coxiella burnetii*. Acute infection is usually mild, but chronic infection can result in significant morbidity and mortality. Specific reference is made to the initial management and clinical follow-up of Scotland's largest Q fever outbreak, which occurred in the summer of 2006 at an abattoir in Bridge of Allan, near Stirling. The talk focuses on the clinical presentation, diagnosis, risk

stratification and management of Q fever. Uncertainty remains over the optimal management of Q fever due to the absence of prospective randomised trial evidence.

Conclusion Acute Q fever should be considered in febrile illnesses or community-acquired pneumonia in those with epidemiological risk factors. Diagnosis is by paired Phase II IgM titres, and treatment with doxycycline 100 mg for two weeks is preferred, although quinolones and macrolides may also be effective. Overall, the risk of chronic infection is around 1%.¹ Those at higher risk of chronic infection, including those with valvular heart disease, vascular grafts, immunosuppression and pregnancy should be offered prolonged preventative therapy.² Chronic Q fever is diagnosed by the persistent presence of phase I IgG titres >1:800 with a compatible clinical illness. Prolonged treatment with doxycycline and hydroxychloroquine is most effective.³ Observation of minimally symptomatic individuals with high Phase I IgG titre appears to be a safe strategy.

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Keywords Doxycycline, hydroxychloroquine, macrolides, Q fever, quinolones, zoonosis

Declaration of interests None declared.

HOW TO MANAGE A SEPTIC PATIENT (WHAT IS APPROPRIATE ANTIMICROBIAL THERAPY?)

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Background Appropriate antimicrobial therapy is key to the survival of the septic patient, and its urgent administration is crucial in optimising outcome. Unfortunately, this is increasingly difficult to achieve as new antibiotic development has not kept pace with the rise of multidrug-resistant (MDR) pathogens. The easiest solution, perhaps, is to use the broadest empirical regimen, such as a carbapenem and a glycopeptide. This, however, increases pressure for the selection and spread of new resistances, even if streamlining of therapy is achieved on return of positive cultures.

Method An alternative, and my favoured, approach is to risk assess each patient for carriage of MDR pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and expanded spectrum β lactamase (ESBL) producing gram negatives. Carriage of such organisms is a risk factor for subsequent infection. Recent hospital admission, nursing home residence, prior antibiotic exposure, transfer from a hospital abroad or previous carriage

should prompt inclusion of these pathogens in empiric cover for the septic patient. Carriage of one MDR pathogen makes colonisation with a second MDR pathogen more likely.

Admission screening for MRSA is likely to prove helpful in guiding empiric therapy in the future, to cover MRSA but also to avoid use of agents such as the quinolones and cephalosporins that might exacerbate MRSA virulence and transmissibility. The glycopeptides remain standard therapy for many MRSA infections, but their use should be questioned in septic patients, due to both poor outcome and creeping resistance. They also provide suboptimal treatment for methicillin-susceptible *S. aureus*.

Conclusion Although the clinical evidence base is weak and toxicity a risk, I often use a stat dose of gentamicin (7mg/kg) in those with haemodynamic instability. This may provide synergy with a β lactam and more rapid bacterial kill of most organisms than any other antibiotic. It also broadens the spectrum of empiric therapy and is likely to lessen the risk of selecting resisting strains. In this context, and to achieve maximum antibacterial action, higher doses of antibiotics than normal should be used until a clinical response is achieved or a minimum inhibitory concentration of the infecting organism is available. Then doses can be titrated according to modern pharmacokinetics/pharmacodynamics principles.

Keywords Antibiotic resistance, carbapenem, gentamicin, glycopeptide, sepsis

Declaration of interests Dr Gould is consulting for MSD, GSK, Novartis, Johnson & Johnson, Pfizer and Wyeth and several other companies involved in the treatment and diagnosis of MRSA, and has shares in several pharmaceutical companies.

GOOD ANTIBIOTICS/BAD ANTIBIOTICS – A CLINICIAN CONUNDRUM

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Background Infectious disease incidence and mortality declined steadily over the later half of the nineteenth and early twentieth centuries in industrialised nations, mainly due to public health measures. The discovery of the synthetic antimicrobial agents, the sulphonamides, and subsequent discovery of the antibiotic properties of fungi, notably *penicillium* and *cephalosporium* species, has promised the cure and potential eradication of previously fatal infectious diseases.

Antimicrobial resistance, described since the 1940s, is directly linked to prescribing pressure in the individual and in both hospital and community populations. Healthcare-associated infections, particularly *Clostridium difficile*-associated diarrhoea and MRSA, have been selected

out in hospitals where broad spectrum antibiotics are widely, and often indiscriminately, prescribed.

The clinician's conundrum is how to cure the individual while doing no harm and safeguarding future treatment options for the wider population. The role, practicality and utility of a prudent antimicrobial management programme are discussed.

Keywords Antibiotic therapy, antimicrobial management, *Clostridium difficile*, MRSA, prudent antibiotic prescribing
Declaration of interests None declared.