BEHIND THE HEADLINES

Behind the Headlines reproduces selected clinical articles which have been published online in *The Bulletin* in the preceding quarter, in order to disseminate this topical clinical information to a wider audience (including those Fellows and Members without Internet access).

The reproduced articles aim to educate and inform the wider College membership about specialist items that have been reported in the international medical and mainstream media: to the non-specialist it may not always be clear how accurately such stories – whether reporting results of scientific studies or issues of concern to health professionals – have been reported. To clarify such situations, expert clinical comments are commissioned on matters that are recurring in the international media, or about which different reports have caused conflicting messages for those practising in other specialties.

In time, it is hoped that this section will become an invaluable source of independent and authoritative advice for Fellows and Members interested in updating their knowledge of new developments in other specialties.

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- Methicillin resistant *Staphylococcus aureus* (MRSA) and its clinical impact;
- Diuretics: a risk for kidney patients?;
- Sleep apnoea and road accidents; and
- Severe acute respiratory syndrome in Hong Kong.

METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) AND ITS CLINICAL IMPACT

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Staphylococcus aureus (S. aureus) is one of the oldest known and most important of bacterial pathogens, causing a wide range of superficial and deep infections. At the dramatic beginning of the antimicrobial era, it was, like many other pyogenic bacteria, very susceptible to the sulphonamides and later to penicillin. The subsequent story of antibiotic resistance in *S. aureus* is a good example of the evolving interaction between a pathogenic organism and antibiotics. Clinically important resistance to penicillin was noted soon after its introduction[1] and spread rapidly so that, within a decade or so, penicillin resistance in *S. aureus* was the rule rather than the exception. This resistance is due to the production by the organism of a beta-lactamase enzyme, which lyses the essential beta-lactam ring of penicillin. The 1960s saw the development of a number of semi-synthetic penicillins such as methicillin, nafcillin, and cloxacillin which are more stable to the action of the beta-lactamase. These new agents seemed at first to solve the problem, but their widespread use was again followed by the emergence of resistant strains, described initially in relation to methicillin.[2] These strains produce a modified version of a bacterial cell-wall synthesising enzyme, which enables cell-wall synthesis and bacterial multiplication to continue uninhibited even in the presence of the beta-lactamase stable semi-synthetic penicillins. This confers resistance against all antibiotics based on the beta-lactam ring structure, including the cephalosporins, but for historical reasons these strains are known as Methicillin Resistant *Staphylococcus aureus* (MRSA). This resistance is also often linked to resistance to several other

BACKGROUND

This comment was commissioned following:

- The publication of a paper in the *British Medical Journal* (*BMJ*) (Crowcroft NS, Catchpole M. Mortality from methicillin resistant *Staphylococcus aureus* in England and Wales: analysis of death certificates. *BMJ* 2002; **325:**1390–1) which found that there had been a five-fold increase in mortality from methicillin resistant *Staphylococcus aureus* (MRSA) in England and Wales between 1993 and 1998. While it had been known previously that MRSA infection rates were rising in England and Wales, this paper marked the first finding of an accompanying increase in mortality.

- The publication of a report, by the Scottish Centre for Infection and Environmental Health, which highlighted an annual increase in the number of hospital in-patients in Scotland contracting MRSA.

Both these publications prompted wide-spread media coverage.

unrelated groups of antibiotics, so that treatment choices are limited. Typically, MRSA strains are resistant to all the penicillins and cephalosporins, erythromycin and ciprofloxacin. Many strains remain susceptible to gentamicin, cotrimoxazole, tetracyclines, rifampicin and fusidic acid, though there are local variations in the distribution of strains. They are almost invariably susceptible to vancomycin and the related compound, teicoplanin, but a few strains have been recently described which show a clinically significant reduction in susceptibility. Newer agents have been recently introduced into clinical use,[3] but these are best reserved for situations where there is resistance to the older antibiotics such as vancomycin, or when their use is precluded by adverse effects.

Though recognised as a significant problem by 1971, the spread of MRSA was slow until the late 1980s but accelerated in the 1990s to become a global problem. Genetic analysis has revealed much variation, but a small number of closely related strains, known as epidemic MRSA or E-MRSA strains, account for much of the recent rapid spread through healthcare facilities. Though the magnitude of the problem varies markedly, many areas of the world have seen a dramatic increase in the morbidity and mortality associated with *S. aureus* infection in recent years. Nearly all of this increase is attributable to methicillin resistant strains. Methicillin resistant *S. aureus* is now the single most common cause of serious hospital acquired infections. Bloodstream infections associated with vascular access devices, ventilator associated pneumonias, wound infections in orthopaedics, cardiothoracic surgery, solid organ transplantation and burns, and deep infections like endocarditis and blood-borne osteomyelitis are prominent areas of concern.

Nearly all cases of *S. aureus* infections, including MRSA infections, are caused by strains which have previously colonised the patient. In the case of MRSA, this colonisation is very often recently acquired, after hospitalisation, but in some patients, particularly older patients who are resident in care facilities, colonisation may have occurred before admission to hospital.

Methicillin resistant strains do not seem to posses more virulence factors than susceptible strains, but colonisation with MRSA seems more likely to be followed by invasive disease.[4] Hospitalised patients frequently receive broad-spectrum antibiotics which eliminate the patient's healthy commensal bacteria, leaving the field clear for resistant bacteria like MRSA to establish heavy colonisation rapidly. Such heavy colonisation involves the upper respiratory tract and skin, including any surgical wounds or access sites for catheters, and so predisposes to invasive infection. Other factors which increase the likelihood of significant colonisation include prolonged hospitalisation, underlying serious illness, skin diseases such as eczema or psoriasis, excessive patient-staff contact as may occur in intensive care, and the use of invasive devices for vascular and ventilatory access. Colonisation of healthy individuals is uncommon and transient, and rarely leads to invasive disease.

It is hard to eradicate MRSA colonisation from a healthcare facility where its presence has become endemic. However, transmission to new cases can be usefully prevented and controlled by everyday infection control practices and special control measures. Routine measures such as hand washing, environmental cleanliness and rational antibiotic prescribing should be vigorously promoted, since these significantly reduce the likelihood of hospital-acquired infections generally. Special control measures such as isolation, cohort nursing, screening for carriage and eradication of carriage in patients and staff are expensive, disruptive and difficult to implement, but have their place during outbreak situations or in special clinical areas. Hospital and community infection control teams should make careful risk assessments of their local situations and recommend special control measures as appropriate. Measures such as pre-admission screening of patients, screening of staff and treatment aimed at eradication of carriage may be appropriate in an organ transplant or prosthetic joint implantation setting, but not in an acute admissions unit or a long-term elderly care facility. One policy does not fit all.

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DIURETICS: A RISK FOR KIDNEY PATIENTS?

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BACKGROUND

This comment was commissioned following the publication of a paper, and accompanying supportive editorial, in the *Journal of the American Medical Association* (*JAMA*) which found that the use of diuretics in critically ill patients with acute renal failure was associated with an increased risk of death and non-recovery of renal function. Given the widespread use of diuretics in renal medicine the publication of this paper also attracted extensive media coverage worldwide.

The incidence of acute renal failure requiring renal replacement therapy is rising and now exceeds that of chronic renal failure.[1] Ischaemic (poor renal perfusion) and nephrotoxic causes account for most cases, but obstructive renal failure, multi system disorders, chronic renal failure presenting acutely and multi factorial causes are also important. Patients are either dry or wet when first seen, and may have single-organ or multi-organ failure.

A dry patient with single-organ failure (the kidney) poses a completely different challenge from a wet one with multi organ failure. The priority for the dry patient is fluid. Many are still prescribed intravenous fluid infusions of 500 ml/four hours by junior doctors when in fact what they need is at least one litre over the first hour, one litre over the next two hours, a further one litre over the next four hours (i.e. three litres over seven hours), and possibly more than this until they start passing urine or their central venous pressure (CVP) is 12–16 cm. The message here must be 'fill, fill, fill'.

The wet patient with multi-organ failure, by contrast, is a much sterner test. Wetness in this context means peripheral oedema (or ascites in patients with chronic liver failure) which is usually due to leaky capillaries and hypoalbuminaemia, or pulmonary oedema as a result of co-existent left ventricular systolic dysfunction or renal vascular disease.[2] The priority here is to load the intravascular space with colloid and saline, then provide circulatory support with inotropes in order to achieve an effective cardiac output. Most of these patients will require ventilation and many will have other organ failures either as a cause or consequence of their illness.

Against this complex background a number of investigators have attempted to evaluate the influence of other supportive treatments including low-dose dopamine and intravenous diuretic. Although there are theoretical reasons for believing these might benefit patients with acute renal failure, neither form of therapy has been shown to improve hospital mortality rates or recovery of renal function when subjected to prospective randomised controlled trials.[3, 4]

The latest analysis of intravenous diuretic in acute renal failure, published in the *Journal of the American Medical Association* (*JAMA*) in November last year, goes one step further and concludes that the use of frusemide and other loop diuretics in critically ill patients might actually increase the risk of death and failure of recovery of renal function.[5] Predictably the risks have been sensationalised in the mainstream medical press with headlines syndicated around the world which include 'Diuretics commonly prescribed to boost the urine output of patients suffering kidney failure may instead prove deadly.'[6] So where does the truth lie, and what exactly does this new study tell us?

A total of 552 critically ill patients with acute renal failure in four US academic medical centres were categorised by the use of diuretics on the day they were seen by a nephrologist and also during the next week. After some fairly sophisticated statistical adjustments were made, the authors concluded diuretic use was associated with a 68% increase in in-hospital mortality and a 77% increase in the odds of death or failure of recovery of renal function. One interpretation of these data is that patients with acute renal failure who receive diuretics do worse because they are given diuretics. Another possibility, of course, is that these patients were given diuretics because they were more ill and that diuretics were the consequence, not the cause, of their precarious clinical state.

In support of the latter view we are told that the patients who received diuretics were more likely to be older, have acute respiratory failure and a history of congestive heart failure. A further observation against a causal relation between diuretics and mortality in this paper was that the increased risk of death was limited to patients who did not respond to diuretics, where diuretic responsiveness was defined *a priori* as a frusemide dose per ml of urine output per day of <1. In practical terms this means that patients who were given 100 mg frusemide per day and passed more than 100 ml urine (ratio <1) experienced no increase in risk (odds ratio 1·15, 95% CI 0·65–1·45). By contrast, those who were unresponsive to diuretics (diuretic responsiveness ratio >1) had significantly increased risk of death or failure of recovery of renal function (odds ratio 2·94, 95% CI 1·61–5·36). Somewhat tantalisingly the authors did

not analyse their results by dose of frusemide alone, which is a pity because if diuretics are indeed harmful then it would not be unreasonable to suppose that larger doses might be associated with greater mortality or failure of recovery of renal function than smaller doses.

Where does this new analysis leave us? The media claim that diuretics may prove deadly in patients with acute renal failure seems somewhat exaggerated. I suspect that a more in-depth quality newspaper report would have tackled this differently by quoting from the conclusions drawn by the authors of the paper in *JAMA*, that 'in the absence of compelling contradictory data from a randomised controlled trial, the widespread use of diuretics in critically ill patients should be discouraged'. The author of the editorial accompanying the *JAMA* article was clearly of the same opinion, suggesting that 'a trial of high dose loop diuretics in an oliguric patient should only be attempted after careful correction of the volume status, should be limited in time, and, more important, should not postpone a consultation with a nephrologist experienced in acute renal failure'.[7] These are more measured responses with which all nephrologists are likely to agree.

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SLEEP APNOEA AND ROAD ACCIDENTS

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BACKGROUND

This comment was commissioned following media coverage of the publication of a report, of a Task Force of the European Respiratory Society, which highlighted the need to improve detection and speed of treatment of sleep apnoea patients in Europe and the disparity between countries in reporting the diagnosis to the driving authorities.

Sleepiness and difficulty concentrating are the dominant symptoms of the obstructive sleep apnoea/hypopnoea syndrome (OSAHS). These symptoms are worst in monotonous situations such as driving on major roads and motorways; consequently drivers with OSAHS have an increased risk of road accidents. As OSAHS affects 1–4% of drivers this is a significant public health issue. This was highlighted in a recent report by a working party of the European Respiratory Society.

Although OSAHS patients tend to under-report driving difficulties, over one-third report having had an accident or near accident due to falling asleep at the wheel.[1] Falling asleep while driving is also common in the general population, with 19% of men admitting to doing so in one study.[2]

Objective evidence indicates raised accident rates in sleep apnoeics. A study of all drivers presenting to an accident department showed that those with frequent apnoeas were six times more likely to be road accident drivers than subjects without sleep apnoea.[3] Retrospective studies in patients prior to the diagnosis of OSAHS being established suggest a three-fold risk of road accidents compared to other drivers.[4]

There is also convincing evidence from vigilance tasks and driving simulators that driving performance is impaired in patients with OSAHS.[5] Indeed, drunk normal subjects perform better on a driving simulator than sober OSAHS patients.[6] Interestingly the impairment is not just limited to periods when patients actually fall asleep; their response is also impaired when they are awake, reflecting impaired vigilance and delayed reaction times.[7]

Treatment of OSAHS significantly improves driving performance. Prospective studies have found that therapy with continuous positive airway pressure (CPAP) improves OSAHS patients' performance on driving simulators[8, 9] and decreases the frequency and severity of road accidents. A recent analysis[10] showed that CPAP not only returned OSAHS patients' accident rates to the population norm, but also that treating 500 patients with CPAP for five years saved £4·9 million when the expenditure on treatment and follow-up were set against the savings on accident related costs. This is in addition to other well-documented benefits of CPAP in terms of sleepiness, quality of life, mood, work performance and blood pressure.

This article was stimulated by the report[11] of a Task Force of the European Respiratory Society, which pointed out the need to improve detection and speed of treatment of OSAHS patients in Europe and highlighted the disparity between countries regarding reporting the diagnosis to the driving authorities.

There is clearly a need to identify and treat individuals with OSAHS to reduce accident risk and to allow them to return to driving safely. This must be done sympathetically and quickly, however. Otherwise, if it became apparent that individuals with suspected OSAHS had lost their licence for months or years while waiting for investigation and treatment, many would not come forward for diagnosis. This would perpetuate the current situation where around 90% of patients with possible OSAHS remain undiagnosed and untreated to the detriment of themselves and other road users. Ideally patients with a clinical picture suggestive of OSAHS should be warned of the dangers of driving when sleepy – preferably in writing – and should be advised not to drive while their investigations and treatment are fast-tracked.

Unfortunately, current waiting times for investigation and treatment can range up to four years in the UK. Such delays are driven by erroneous concepts of economies of healthcare delivery, rather than looking at the wider benefits of offering cheap and effective treatment quickly. The publication of a Scottish Intercollegiate Guidelines Network Guideline on the Management of OSAHS in spring 2003 should improve service delivery.

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SEVERE ACUTE RESPIRATORY SYNDROME IN HONG KONG

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In the past couple of months, the severe acute respiratory syndrome (SARS) epidemic has hit the headlines around the world;[1] Hong Kong, unfortunately, appears to be the epicentre of the outbreak.

In November 2002 clusters of cases of a severe atypical pneumonia of unknown cause were reported in Guangdong Province in southern China (just north of Hong Kong). It was described as highly contagious, especially among medical and nursing personnel attending patients and their household members. Many patients have died. Similar cases were then seen in Hanoi, Vietnam, in February 2003. Sadly, Dr Carlo Urbani, a World Health Organisation (WHO) infectious disease expert, who attended a patient in Hanoi, caught the disease and died in Bangkok on 29 March 2003. His work helped to define SARS.

On 21 February 2003, a doctor working in a hospital in southern China travelled to Hong Kong and stayed in a hotel. He had developed symptoms a few days earlier, but was well enough to go shopping for a day before falling sick and being admitted to a hospital. His pneumonia deteriorated rapidly and he died ten days later. His journey to Hong Kong developed into a nightmare spread of infectious disease; guests in the hotel where he stayed (some of whom had returned to their home countries including Singapore and Canada), the healthcare workers attending him, and other patients and visitors in the wards to which he was admitted, rapidly became infected.[2] On 11 March 2003, two patients presented with SARS in Hong Kong, but this number increased to 197 (with six deaths) by 21 March 2003. 'Hong Kong bears brunt of latest outbreak,' commented *The Lancet*.[3] On 15 April 2003, the number of cases rocketed to 1,232 (with 56 deaths); all schools were closed temporarily while a housing block (accounting for over 300 cases) was quarantined for ten days. On the same day, the WHO recorded a total of 3,235 cases of SARS in 24 countries/regions worldwide with 154 deaths. It is clear that SARS is rapidly becoming a truly worldwide epidemic.[4–6] The worst hit areas are in Asia (Mainland China 1,418 cases with 64 deaths, Hong Kong 1,232 cases with 56 deaths, Singapore 162 cases with 13 deaths, Vietnam 63 cases with five deaths); the West is not exempted – Canada 100 cases with 13 deaths, the US with 193 suspected cases, and the UK, Germany, France, Italy, Switzerland, Ireland, Belgium, Spain and Romania have a total of 24 patients with no deaths.

BACKGROUND

On 12 March 2003 the World Health Organisation (WHO) issued a global health alert regarding cases of atypical pneumonia. This followed the outbreak of cases of a severe acute respiratory syndrome (SARS), of unknown origin, in Vietnam, Hong Kong and mainland China which then spread globally as travellers, who had been exposed to a carrier of this virus, returned to their home countries. The spread of this virus escalated into an epidemic and by 2 April 2003 WHO had reported 2,223 cases of SARS in 18 countries and regions, resulting in 78 deaths. The rapidity with which this virus spread around the world, coupled with the knowledge that its causative agent and mode of transmission are unknown, has resulted in global media coverage and medical interest. To inform our membership about this important, and topical, issue this commentary was commissioned from the College's Regional Adviser in Hong Kong, Professor W-K Lam, Professor of Respiratory Medicine, University of Hong Kong, who has co-authored a paper on this subject which has recently received an advance online publication in the *New England Journal of Medicine*.

Initial experience in Hong Kong showed that most patients are middle aged (1–86 years old) with an equal sex ratio. High fever, with or without chills and rigors, and malaise are universal presenting features.[2,7] Most patients also have headache, myalgia, dizziness, dry cough and shortness of breath. Some patients have diarrhoea. Interestingly, sore throat and running nose occur in less than 30% of our patients. History of contact (either history of attending to patients or household members of patients) or of travel to southern China is characteristic. The incubation period is thought to be about two to ten days. Commonly observed blood test findings include lymphopenia, elevated aspartate and alanine aminotransferase, and sometimes hyponatremia. The most commonly seen chest radiograph abnormalities on presentation are air-space shadowings, predominantly in the lower lung zones (ground-glass opacities, focal consolidation or patchy consolidation).[2,7] Pleural effusion is very uncommon. In some 10–15% of patients, rapid deterioration of chest radiographs occur within one or two days, with the development of diffuse bilateral consolidations coincidental with hypoxemia and marked shortness of breath, requiring intubation and mechanical ventilation. The lung pathology shows histological changes of adult respiratory distress syndrome (ARDS)

with diffuse alveolar damage, hyaline membrane formation and minimal mononuclear cell infiltration.[7]

All standard microbiological investigations for bacteria, mycoplasma, chlamydiae, fungi, legionella, influenza and other common respiratory viruses have either been negative or uninformative. Initially, paramyxovirus (Chinese University of Hong Kong, unpublished data), metapneumovirus[8] and coronavirus[1, 8–11] have been described as likely causative agent(s) for this SARS epidemic. The coronavirus identified appeared to be a novel virus that is not closely related to the known coronaviruses. In mid-April 2003, the CDC and Canadian scientists independently announced that the genome for the coronavirus had been sequenced.[1] On 16 April 2003, the WHO announced that a coronavirus never before seen in humans is the cause of SARS, which has been named as 'SARS virus.'[12] An RT-PCR diagnostic method is being developed which is potentially a specific and rapid test for this infection. That SARS is caused by a co-infection with more than one virus remains a possibility.

The lung pathology of ARDS, the lymphopenia despite high fever, and the rapidity of deterioration in chest radiographs suggest that at least part of the damage is due to a cytokine storm triggered by a microbial agent. Hence immunomodulation by steroid treatment appears to be indicated. But to use steroid in the absence of effective anti-microbial agent can be dangerous. Hence, an empirical regimen consisting of early and aggressive corticosteroid (intravenous methylprednisolone) plus intravenous ribavirin, a broad-spectrum antiviral agent (plus antibacterial agents as indicated), has been used in our patients with severe or deteriorating clinical conditions.[2] There are no randomised placebo-controlled trials, but the clinical responses have appeared to be very encouraging. For non-responding or relapsed patients, immunoglobulins have been tried with variable results. All nebulisation therapies, BiPAP ventilation and sputum induction procedures should be avoided in SARS patients to prevent droplet or aerosolized spread of the virus.

A major problem facing infectious disease and public health experts is the method of controlling this epidemic. The mode of transmission is thought to be by droplets and close contacts, but airborne and other modes of transmission cannot be excluded. The Hong Kong hotel and housing block stories indicate that this infection is highly contagious, and universal precautions, and control and quarantine measures, need to be quick and thorough, and contact tracing similarly so. Visitors should not be allowed in the SARS isolation ward to prevent spread to the community.

It is hoped that the mode of transmission of SARS virus will soon be delineated and confirmed, and knowledge of its gene sequence would enable development of rapid diagnostic tests, specific therapies and vaccinations. We wish that the concerted efforts of all healthcare workers, research workers, governments and citizens, together with organisations and institutes such as the WHO and the Centres for Disease Control (CDC), will soon be able to control this new worldwide epidemic of SARS.

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